90D0130: LifeVest Safety and Efficacy in Real Life Settings in France

NCT03319160

10/2016

WEARIT France Protocol

Structured according to EN ISO 14155:2011/AC:2011

Study Title:	Post-market clinical follow-up study evaluating the efficacy and safety of LifeVest in real-life settings in France
Reference code	WEARIT France
Study type	This post-market study is an observational study evaluating the efficacy and safety of the LifeVest in real-life settings.
Investigators:	Multicenter in France
Sponsor:	ZOLL 121 Gamma Drive Pittsburgh, PA, 15238 USA
Coordinating Investigators:	Dr. Nicolas Combes, Clinique Pasteur, Toulouse, France (Chief investigator) Dr. Eloi Marijon, Hôpital Georges Pompidou, Paris, France
Contract Research Organisation:	ClinSearch, Malakoff, France wearit-france@clinsearch.net

Version control:

Amendment 2 version, dated October 10th, 2016

This study protocol has been written in accordance with current applicable guidelines, in particular the ISO 14155:2011/AC:2011 was used as guidance for the structure of the protocol.

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1. General

1.1 Introduction

Sudden cardiac death (SCD) is a major cause of mortality throughout the world, accounting for approximately 300,000 deaths per year in the United States.[1] SCD accounts for about 50% of all heart related deaths. Studies of patients who suffer SCD suggest that ventricular tachyarrhythmias are the dominant cause of this rapid terminal event although asystole due to heart block or sinus arrest can account for approximately 10-15% of the sudden deaths. However, these are most often electrical signs of a dying heart or electro-mechanical dissociation. The introduction of the implantable cardiac defibrillator (ICD) in the 1980s resulted in subsequent clinical trials showing a significant reduction in SCD with ICD therapy in at-risk cardiac patients.

However,[2-4] not all high-risk patients are candidates for the ICD for a variety of reasons. These are: transient nature of the high-risk for SCD; patients who do not meet current guideline indications for an ICD;[5] high-risk cardiac patients who had previously received an ICD but had it removed because of complications or malfunction; patients who refuse an ICD; age-related factors; and a variety of other medical and ethical considerations.

The use of automatic external defibrillator (AED) in acute cardiac arrest in the home, school, workplace, airplanes, and locations where there is a high density of people such as airports and sporting events has limited effectiveness in saving lives.[6] Successful resuscitation with utilization of the AED is dependent on a short time-interval of just a few minutes between the witnessed cardiac arrest and the AED intervention. The rate of successful resuscitation for out-of-hospital cardiac arrest with the AED with full recovery to a normal neurologic state is not more than 8%.

The Wearable Cardioverter-Defibrillator (WCD) gives the patient's physician time to assess the long-term arrhythmic risk in cases when the risk of life-threatening arrhythmias may only be temporary and to make appropriate plans. Thus, the WCD can be used as a risk stratification tool. It provides continuous arrhythmia monitoring, detection of life-threatening ventricular arrhythmias, and provides automatic defibrillation within a minute of detection of the potentially fatal ventricular tachyarrhythmia, unless the patient withholds the shock delivery. The safety and effectiveness of the WCD in saving lives has been documented in several publications including the first report in 1998,[7] WEARIT/BIROAD study in 2004,[8] and the US and German experience report in 2013.[9-12]

Currently, there is only one approved WCD device on the world-wide market. This is the LifeVest®, produced by ZOLL, Pittsburgh, PA, USA. During the past few years, there has been an increased use of the WCD to more than 100.000 patients (personal information from ZOLL, Pittsburgh, PA, USA) having a spectrum of at-risk cardiac conditions, with use of the WCD averaging over 21 hours per day for periods of 1 to 6 months, or even longer.

The WCD is a therapeutic option, listed along with implantable cardioverter-defibrillators (ICDs), in the ACC/AHA/ESC Guidelines for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death[13]. It is also a Class I recommendation in the International Society for Heart and Lung Transplantation Guidelines for the Care of Cardiac Transplant Candidates[14].

1.2 Sponsor

ZOLL
121 Gamma Drive
Pittsburgh, PA 15238
USA

1.3 Coordinating investigators and investigation site(s)

a) Name and address of the coordinating investigators.

Dr. Nicolas Combes (Chief investigator)
Clinique Pasteur, Toulouse, France

Dr. Eloi Marijon (Coordinating investigator)
Hôpital Georges Pompidou, Paris, France

b) Name and address of the investigation site(s) in which the clinical investigation will be conducted.

A list of investigational sites is maintained in the Trial Master File.

c) Name(s) and address (es) of other institutions involved in the clinical investigation.

N.a.

1.4 Rationale and Aims of the study

LifeVest is a wearable cardioverter defibrillator (WCD) that has been recently approved for reimbursement by the HAS. LifeVest has obtained coverage for 4 indications: (i) implantable cardiac defibrillator (ICD) removal due to cardiac device infections, (ii) a bridge to heart transplantation, (iii) in the early post-MI period with left ventricular (LV) dysfunction (LVEF <30%), (iv) and a recent coronary revascularization with LV dysfunction (LVEF < 30%). There is no current comparator to LifeVest. In France, patients at high risk for sudden cardiac arrest (SCD) and waiting for heart transplant or ICD are hospitalized or discharged home without any particular ECG monitoring. LifeVest has been demonstrated to automatically detect and terminate rapid ventricular arrhythmias. Introduction of LifeVest into the current patient management would definitely improve the clinical outcomes and benefit the patients with temporary risk of SCD. The use of LifeVest was shown to be effective in protecting patients against SCD in the United States. However, the clinical impact of using LifeVest in France remains unassessed. Therefore, this post-market study in France will provide efficacy and safety data for the reimbursement dossier renewal before September 2018.

Identification and description of the investigational device

The Wearable Cardioverter-Defibrillator (WCD) [LifeVest ®] is an external defibrillator, guided by an algorithm to detect ventricular tachyarrhythmic events, recorded by non-adhesive ECG electrodes (two leads). The WCD delivers up to 5 biphasic, high-voltage electrical shocks unless shock delivery is withheld intentionally by a conscious patient. The WCD comprises also a continuous ECG monitoring system, which transmits ECG data and other information (such as recorded arrhythmic events and alerts, details of the shock delivery episode, appropriate WCD use, daily wearing time, correct ECG monitoring,

battery charging and electrode connection/electrode noise) directly from the LifeVest to a central ECG and data server in the USA, Pittsburgh. The patient's physician is able to check the history of recorded arrhythmic events, details of the shock delivery episode, appropriate WCD use, daily wearing time and correct ECG monitoring via a password protected web-accessed to the ECG and data server.

The WCD has CE certification and is FDA approved since 2002.

2. Justification for the design of the investigation

In general, patients considered having high, long term risk of sudden arrhythmic death (SCD) receive implantable cardioverter-defibrillators (ICD).

Risk assessment in patients that are candidates for ICD therapy is difficult and time consuming, though. In order to bridge the time period necessary to identify the patient who will need an ICD or in whom ICD therapy is unnecessary, a tool is mandatory that protects the patient during this time period from dying suddenly and to provide continuous ECG monitoring which is necessary for the risk assessment.

The device that is able to fulfill these characteristics is the wearable cardioverter-defibrillator (WCD). The WCD has CE certification and is FDA approved since 2002. Currently, only observational studies with the WCD are available. Prospective randomized studies in patients that are already considered carrying a high risk of sudden death are difficult, if not impossible to perform, mainly due to ethical reasons.

Currently available data with the WCD demonstrate that the WCD is safe and effective. Detected ventricular tachyarrhythmias are terminated with the first shock in 98% of all cases; inappropriate defibrillator discharges (not occurring on sustained VT or VF) may occur in <1% per month of WCD wearing[9].

3. Risks and benefits of the investigation

Patients participating in the post-market clinical follow-up study in France will have neither additional risks due to participation in the study compared to clinical routine care nor individual benefits, because of its purely observational character.

4. Objectives and hypotheses of the investigation

4.1 Objectives

a) Primary Objective:

1. **Appropriate shocks** as measured by shocks delivered for adjudicated sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) episodes.

2. **Inappropriate shocks** as measured by shocks delivered for all episodes that are not adjudicated sustained VT or VF episodes.

The frequency and rate of appropriate and inappropriate shocks will be measured. The risk of receiving an inappropriate shock will be analyzed. The risk of not receiving appropriate shocks when necessary will also be analyzed.

b) Secondary Objectives

1. **Overall survival** as measured by the ratio of the number of patients that are alive at the end of the use of the WCD to the total population of patients prescribed the LifVest.

2. **Quality of life relative to health state** as measured through the administration of a patient quality of life survey. This survey has been used previously in a published study of patient quality of life.

5. Design of the investigation

5.1 General

5.1.1 Description of investigation

France post marketing protocol is an observational study of patients with a prescribed WCD during the time of risk assessment for future potential ICD therapy. Patients who are prescribed a WCD will be asked to participate in the prospective cohort of the study. Patients who have already completed use of LifeVest before start of the study in the corresponding study site can also be asked to consent for use of their clinical data to be included in the retrospective cohort of the study. The retrospective cohort of patients will be analysed separately compared to prospectively included study patients for any variables that are not available for both cohorts, such as the patient survey. Mean WCD wearing time is anticipated to be three months. However, some indications for wearing the WCD may be longer (up to 6 months) or shorter (only one month). For patients who are listed for heart transplantation, the wearing time is scheduled until heart transplantation is performed, or an ICD will be implanted.

5.1.2 Description of the measures to be taken to minimize or avoid bias, including randomization and blinding/masking

There is no randomization of patients enrolled into the study. All consenting patients with a routinely prescribed WCD in the study participating centers will be evaluated, regardless of the length of WCD wearing, including patients who have already completed use of LifeVest before start of the study in the corresponding study site.

The selection bias is limited by the protocol comprehensiveness. There will be no selection, the study will be proposed to all patients receiving LifeVest. In addition, all centres performing implantation of the device will be asked to participate. “Non-participants” will be described.

The attrition bias is also limited (non-existent) as at the end of LifeVest utilization, all material provided to the patient should be returned systematically. Furthermore, the patients follow- up is completely identical to the routine clinical practice. This means that we don’t expect to have any difference between the data collected retrospectively and those collected prospectively. However, only patients included prospectively will be asked to complete the quality of life questionnaire.

The prospective cohort of patients will be analysed separately for variables not available for the patients in the retrospective cohort, such as the patient survey.

Patients who have worn WCD for at least 8 days (i.e. longer than 1 week) will be evaluated separately in an “on-treatment” efficacy analysis, because it is assumed from clinical experience that the WCD wear-

ing time will only for those patients be long enough to reliably compare their long-term outcome in a cohort of patients who have had the WCD for several months (even six or more months in some indications).

5.1.3 Main Definitions and criteria for evaluating efficacy and safety

Efficacy will be evaluated using the success rate of appropriate shocks. In order for a shock to be appropriate, it must be administered while a patient is experiencing either sustained VT or VF. Otherwise, the shock is inappropriate.

The risk associated with the use of LifeVest will be assessed in terms of inappropriate shocks. Any shock administered to a patient who is not experiencing either VF or sustained VT at the time of administration is an Inappropriate Shock. Even if the patient experiences VT or VF and the condition resolves by itself or bystanders intervention just prior to administration of the shock, it would be classified as Inappropriate.

The classification of individual shocks into the categories of Appropriate and Inappropriate is quite unambiguous, so long as the ECG signal is of sufficient strength to be able to accurately determine the heart rhythm. If the signal is obscured by noise and it is not possible to unambiguously determine the rhythm the shock is generally categorized as Inappropriate, because the noise is generally the cause of the false detection.

All appropriate and inappropriate WCD shock deliveries, as well as VT/VF events will be recorded and analyzed by means of precise ECG recording, provided the VT/VF exceeds the programmed rate threshold for event detection by the WCD. ECG recordings are retrievable from a central server to which all WCD data and ECGs will be transmitted automatically. Similarly, all shock-withhold VT/VF events or VT/VF events that terminated spontaneously will be recorded and counted. All potential bradyarrhythmic or asystole events will be recorded. The device is programmed to record events which are slower than 20 beats per minute or have a QRS amplitude less than 200 microvolts (peak to peak), provided the patient does not respond to alarms.

There will be assessment of all ventricular tachyarrhythmic events, either treated by WCD-shock or with shock withheld by the patient. Furthermore, the assessment of the overall outcome (death) and of clinical events (cardiac and non-cardiac), such as hospitalization, heart failure status, ischemic events, ICD implantation, Pacemaker implantation, surgical interventions (CABG or valve replacement) during the period of WCD wearing.

The assessment and classification of the type of arrhythmic events will be carried out by an independent Clinical Event Committee (CEC) by evaluating the ECG data provided by the WCD during wearing and recorded on the central ECG and WCD data server. Members of the CEC are listed in Appendix A. Events will be separately reviewed by at least two CEC members. A third reviewer will review events for which there is not agreement between the first two reviews.

Primary parameters to be assessed during follow-up:

1. *Arrhythmic (VT/VF) events and type of event*
2. *Appropriateness of shock delivery*
3. *All-cause mortality*

4. *Hospitalization*
5. *Cardiac events*
6. *Non-cardiac events (e.g. stroke, renal failure)*

Secondary parameters to be assessed:

1. *Analysis of primary outcome parameters (see above) in sub-groups according to their clinical profile at baseline (age, gender, disease etiology, type of inherited arrhythmia syndrome, etc.)*
2. *LV-EF at time of WCD end of use*
3. *Type and character of arrhythmic events*
4. *Type and character of cardiac events*

5.1.4 Methods and timing for assessing, recording, and analysing variables.

During wearing of the WCD the responsible physician in the participating centers is able to check the event history, appropriate use of the WCD, compliance of the patient and potential complications of the WCD by means of a password protected access to the central server. The patient's ECGs in case of detection of arrhythmias and all wearing data are automatically transmitted from the WCD to the server. After an arrhythmic event, the patient is instructed to inform not only the emergency ambulance but also the responsible physician and the ZOLL Company about the event. The responsible physician is able to analyze the event and will document all available data in the e-CRF system. The ECG recording during the event is also stored and retrievable from the server.

All arrhythmia and clinical events as well as the clinical status (including measurement of LV-EF) of the patient during the WCD wearing period are documented in the e-CRF by the responsible physician. All arrhythmia episodes detected by the WCD will be reviewed and evaluated by an independent Clinical Event Committee. All patient data from France post marketing study will be gathered by CRI on e-CRFs.

After the first month of use, all participating patients will be surveyed confidentially to assess their quality of life related to their health status and use of the WCD. Because patients who are prescribed a LifeVest are typically in an acute episode of care involving a hospitalization (e.g., ICD explant procedure due to infection, post-MI,etc.), the Science Committee felt that a general population QoL survey, such as the SF-12 or EQ5D would not be as useful in this study. Other more relevant QoL instruments that have been validated are generally condition-specific are not applicable across the entire study population. Therefore, a patient survey developed specifically for LifeVest patients will be used for this study. This instrument has been used in published, peer reviewed research.[16] Specific detail on survey content can be found in Section 6.2 of the analysis description. Study coordinators will administer the survey. Patients who have not responded to the initial survey request will be reminded to participate approximately seven days after the initial invitation.

5.1.5 Any procedures for the replacement of subjects.

The investigator is encouraged to try to enrol all patients to whom the WCD has been prescribed (provided informed consent is given by the patient). This includes also those patients who have already com-

pleted use of LifeVest before start of the study in the corresponding study site. No replacement of patients is planned because of the observational nature of the study.

5.2 Subjects

Study population will consist of patients at high risk for SCD and receiving LifeVest as a bridge therapy to heart transplantation, to ICD or to improvement of LV function.

5.2.1 Inclusion criteria for subject selection.

- Patients receiving a LifeVest prescription in clinical routine for the following indications:
  a) implantable cardiac defibrillator (ICD) removal due to cardiac device infections,
  b) a bridge to heart transplantation,
  c) in the early post-MI period with left ventricular (LV) dysfunction (LVEF <30%),
  d) a recent coronary revascularization with LV dysfunction (LVEF < 30%).
- Patients who have given their consent to participate.

This includes also those patients who have already completed use of LifeVest before start of the study in the corresponding study site (retrospective inclusion).

5.2.2 Exclusion criteria for subject selection.

There are no exclusion criteria for this study other than if the patient does not provide informed consent to participate. All patients prescribed a LifeVest will be invited to participate. All patients that were previously prescribed a LifeVest before the start of this study will also be invited to participate by allowing access to their retrospective medical information.

5.2.3 Criteria and procedures for subject withdrawal or discontinuation.

A low rate of lost-to-follow up is expected since the LifeVest is rented to patients and should be returned to ZOLL by the end of the prescription. In case a patient is lost to follow up, the CepiDC a French database for automated coding of causes of death, will be interrogated to report if the patient is dead or alive, and if dead the cause of death.

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 have given consent to participate in the study but had the WCD for less than 8 days will be evaluated separately, but not withdrawn.

5.2.4 Participating centers and point of enrolment:

Participating centers: The study will start along with the early-stage marketing of LifeVest. All approved ICD implant centers in France, who are using LifeVest in their routine practice, will be invited to participate to the study. A registry will be created to collect geographic information and type of centers (public/private) refusing to participate. The reason for refusal will be reported in the registry. This registry will

be maintained by ClinSearch. Approved ICD implant centers in France who are not using LifeVest in their routine practice will be documented in the registry by ZOLL.

Participating patients: All patients in participating centers receiving LifeVest, satisfying the inclusion and exclusion criteria and consenting to participate will be consecutively included in the study. ZOLL will maintain a registry of all patients screened but not included in the study, to verify the representativeness of patients by the end of the study. It will be listed in this registry all patients meeting the selection criteria and having received a LifeVest. Demographics, indication and the reason for non-inclusion will be collected.

Start of documentation is at the time when the patient signs and dates the informed consent form. Data from medical history will be documented.

5.2.5 Personal Data and Data Protection

All data obtained in the context of the observational study are subject to data protection. This applies to patients' data as well as to investigators' personal data which may be included in any database of the sponsor or the CRO.
The investigating physicians shall take care that patient documents (e.g. copies of reports on special findings) transmitted to the CRO or the sponsor contain no names, but only the year of birth and a relevant patient study number. The storage of data for statistical analysis shall likewise be performed only under the patient's study number.

5.2.6 Data Handling and Record Keeping

a) Completion of Case Report Forms

All medical data in this observational study are to be recorded directly in the e-CRFs. Documentation on paper will be restricted to exceptional circumstances only.
The investigator must ensure the accuracy, completeness and timeliness (and legibility in case of documentation on paper) of data.

b) Archiving

The investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents. The investigator has to retain the study documents (i.e. investigator site file) after the completion or discontinuation of the study for the time period as required by national legislation. This especially applies to patients' signed informed consent forms and the patient identification list. The patient identification list will be destroyed at the end of the archiving period which is mandatory by national law as stated above.

The investigator must notify the sponsor prior to destroying any essential study documents within the specified period following completion or discontinuation of the study.

c) Confidentiality

All information disclosed or provided by the sponsor (or any company / institution acting on his behalf), or produced during the study, including, but not limited to, the clinical study protocol, the e-CRFs and the results obtained during the course of the study, is confidential. The investigator or any person under his/her authority agrees to undertake to keep confidential and not to disclose the information to any third party without prior written approval of the sponsor. The sub-investigators shall be bound by the same obligation as the investigator. The investigator shall in-

form the sub-investigators of the confidential nature of the study. Both, the investigator and the sub-investigators shall use the information solely for the purposes of the study, to the exclusion of any use for their own or for a third party's account.

5.2.7 Total expected duration of the clinical investigation:

The patient recruitment period will start along with the early-stage marketing of LifeVest. The inclusions will last for 2 years. The whole study duration will be of 24 months. Collected data will be analyzed and made available for the reimbursement dossier renewal (before April 2019). And final results will be submitted by the end of the study.

5.2.8 Expected duration of each subject's participation

The patient will be included after being prescribed a LifeVest, and will be participating until LifeVest withdrawal. According to published data, the mean duration of participation will be about 3 months, depending on the indication. Accordingly patient participation will be about 3 months according to the indication.

5.2.9 Number of subjects required to be included in the clinical investigation.

It is estimated that approximately 1,700 patients will receive LifeVest in clinical routine between May 2015 and April 2018 (300 patients first year, 520 patients second year and 880 patients third year of marketing) in France. After obtaining all regulatory approvals, the study is expected to start in August 2016. Between August 2016 and April 2018, 1,110 patients would receive LifeVest in clinical routine. Considering a participation rate of 50% related to centers participating in the study and consent given, around 550 patients will participate in this study.

5.2.10 Estimated time needed to select this number (i.e. enrolment period).

Enrollment period will last 20 months from March 2017 to December 2018. The period of clinical follow-up will take about 3 months of wearing the WCD, depending on several factors, e.g. on the indication.

5.3 Procedures

5.3.1 Description of all the clinical-investigation-related procedures that subjects undergo during the clinical investigation

Patients will not experience any particular tests or procedures that are not part of the clinical routine of adequate patient treatment according to their underlying disease. Participation in France Post Marketing Study does not require additional laboratory testing.

5.3.1.1 Informed Consent

Before entering data into the clinical study, each patient shall be informed about the use of their data in the clinical study according to the requirements of data privacy regulations, i.e. consent to processing medical data of the patient to a central scientific database. Sufficient time will be allowed for the infor-

mation to be read and for questions to be asked. The patient must be told that withdrawal of informed consent to use their data in the clinical study is possible at any time, without stating a reason and without prejudice, and does not cause any disadvantages.

5.3.1.2 Medical History

- Baseline demographic data
- Medical history of:
  - Coronary artery disease (CAD)
  - Myocardial infarction
  - PCI
  - CABG
  - Dilated Cardiomyopathy
  - Hypertrophic Cardiomyopathy
  - Heart Failure (NYHA II-IV)
  - Hospitalization for congestive heart failure
  - Cardiac arrest (CA)
  - Valve disease (aortic and mitral)
  - Stroke
  - Syncope
  - Atrial Fibrillation (A-Fib)
  - Inherited Arrhythmia Syndrome
  - Pacemaker Implantation
  - ICD Implantation
  - Congenital Heart Disease
  - Renal Disease

5.3.1.3 Symptoms and current status

- Comorbidities
- Concomitant treatments
- Physical examination
- Current cardiovascular symptoms
- Estimation of the degree of heart failure (NYHA Class I-IV)
- LV-EF at time of enrolment
- Indication for LifeVest and duration of prescription

5.3.1.4 At LifeVest end of use

- The reason for end of use (death, ICD implantation, heart transplantation, LV function improvement, patient's wish, etc)
- Reports on serious adverse events since the inclusion (ie: cardiac and non-cardiac death, hospitalization, heart surgery/revascularization, arrhythmic events and other cardiac events)

5.3.1.5 Data extracted from the LifeVest Network

- Wear time (hours per day)
- Description of all delivered treatments and associated ECG
- Description of asystole, detected arrhythmia with no treatment (e.g., short run of VT) and associated ECGs
- Information about any technical malfunctions and misuses, if applicable

5.3.1.6 Clinical Laboratory Tests

Only data of laboratory tests will be documented that have been performed as routine procedures according to clinical routine indications. All laboratory tests will be performed independently from participation in the France post marketing study.

5.3.2 Description of activities performed by sponsor representatives (excluding monitoring)

Personnel of the ZOLL company will instruct and train the patients in the correct use of the WCD. ZOLL personnel are continuously controlling the correct use and function of the WCD during WCD wearing time. They automatically replace the WCD in case of technical problems with the device. These activities by ZOLL company personnel are part of their routine obligations accompanying the use of the WCD (LifeVest ®), and are independent of this study.

5.3.3 Any known or foreseeable factors that may compromise the outcome of the clinical investigation or the interpretation of results

Only patients will receive the WCD if they are considered by their physician to be able to handle and use the WCD correctly.

5.4 Monitoring plan

Authorized, qualified representatives of the sponsor will accomplish on-site monitoring during the study. The accuracy and completeness of core CRF data of a sufficient number of patients will be checked on site against source documents. Details will be given in a risk based monitoring plan.

Quality management will assure that medical data are subject of continuous plausibility checks and data cleaning. The primary outcome parameters consist of follow-up and arrhythmic event raw data which are directly transmitted in clinical routine from the WCD device to a central database to which the treating physician has access via an internet platform enabling him to review any potential arrhythmic event

detected by the device. These data are not modified by human interactions, thus being *per se* valid and do not require source data verification.

6. Statistical considerations and methods

This is a nonrandomized, multicenter observational study. All consecutive LifeVest patients will be asked to participate. Demographic data will reported on all consenting patients. Thus, all patients in this study will receive LifeVest treatment. Descriptive statistics will be used to report major clinical characteristics of consenting patients, and incidence and frequency of appropriate and inappropriate shocks.

For the overall survival rate calculation, the population of reference will correspond to the total number of patients enrolled who were prescribed the LifeVest.

Standard methods will be used to calculate adjusted survival rates. Kaplan Meier survival curves will be used to report total mortality and wear time. The time to event and census are defined here after.

All reasons for therapy discontinuation will be reported in tabular form.

Event	Decision	Event date or census date
Occurrence of the event	Not censored	Date of the event occurrence
No event and patient followed until the study end	Censored	Date of WCD withdrawal
Lost-to-follow-up	Censored	Date of the last visit or last contact

It is common to use a significance threshold of 5%. This will be applied in this study.

6.1 Sample size

This study is a post-inscription study designed to describe all patients treated by LifeVest in a comprehensive way. Thus this study will be proposed to all patients receiving LifeVest.

No sample size calculation has been planned. All patients accepting to participate will be included.

The LifeVest device is commercialized in France since approximatively 1 year, the number of subjects has been estimated based on the sales and the foreseen participation rate.

It is estimated that approximately 1,700 patients will receive LifeVest in clinical routine between May 2015 and April 2018 (300 patients first year, 520 patients second year and 880 patients third year of marketing) in France. After obtaining all regulatory approvals, the study is expected to start in August 2016. Between August 2016 and April 2018, 1,110 patients would receive LifeVest in clinical routine. Considering a participation rate of 50% related to centers participating in the study and consent given, around 550 patients will participate in this study.

According to most recent data, the frequency of shock delivery is expected to be between 1% and 5 %. In this present study, 550 patients will allow for assessing a treatment rate ranging between 1%-5% with

an absolute precision < 2% (0.8 for 1% and 1.8 for 5%). Therefore, this sample size would be sufficient to answer the research questions.

6.2 Patient Survey

All survey data will be included in the analysis as long as the patient answered at least one item on the survey. In other words, no exclusion criteria will be used based on survey response completeness. Overall survey statistics will be presented for the survey data results including overall response rate, item level response rate, Survey responses for all items will be analyzed and reported. The majority of the items on the survey ask the patient to indicate their agreement using the 5-point Likert agreement response scale (Strongly agree, Agree, Neither agree not disagree, Disagree, Strongly disagree) with the following topics regarding their use of the LifeVest:

- Ease of use
- Peace of mind
- Worry
- Worry about being alone
- Confidence in physician knowledge about managing condition
- Sleep quality
- Confidence returning to activities of daily living (screened)
- Confidence to exercise or perform cardiac rehabilitation (screened)
- Improved self-care
- Taking condition seriously
- Family and caregiver peace of mind
- Family and caregiver sleep quality

Patient information collected on the survey will include basic demographic information for subgroup analyses as well as patient self-reported health status from the SF-12. Consistent with previous publication, survey responses for items using the 5-point Likert agreement response scale will be presented as the top two box or the percentage of patients that either Strongly agree or Agree with the statement in the survey item.

7. Procedures used for data review, database cleaning, and issuing and resolving data queries

All medical data in this study are to be recorded directly in an e-CRF system (MARVIN) running on a single central server. The e-CRF system is available for all participants based on individual access codes (numerical code) according to their duties and responsibilities in the project 24 hours/7 days. The investigator must ensure the accuracy, completeness and timeliness of data.

Plausibility rules and alert levels for parameters are programmed in the e-CRF system ensuring an optimized level of first-line data quality. Manual data queries based on repetitive statistical analyses will additionally improve data completeness and quality.

7.1 Procedures for verification, validation and securing of electronic clinical data systems, if applicable.

The e-trial management system MARVIN used in this study is a GCP and 21 CFR 11 compliant EDC and CDM system based on the CDISC ODM data standard.

Any change or correction to an e-CRF will automatically be tracked (Audit Trail), recording the account ID of the person being logged in as well as the time stamp of the change. The e-CRF system will not accept changes without given reason. The history of changes to a single item including original entries is always available.

8. Amendments to the study protocol

Any amendment to the study protocol must be approved by the Sponsor. A study protocol amendment may not be implemented until after it has been sent for comment to the IEC responsible for the principal investigator. Since the study comprises only procedures routinely undertaken, no immediate implementation of changes necessary for patient safety are expected.

9. Deviations from study protocol

Deviations from the study protocol are not to be expected, because this is only an observational study without predefined procedures:

10. Statements of compliance

10.1 Statement specifying that the clinical investigation shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki

The procedures set out in this study protocol are designed to ensure that the Sponsor and the Investigator abide by the principles of ISO 14155:2011 and the Declaration of Helsinki (latest version) concerning the conduct, evaluation and documentation of the clinical investigation.

10.2 Statement specifying compliance with this International Standard and any regional or national regulations, as appropriate.

The study procedures will also be performed adhering to the local legal conditions and regulations and to the applicable regulatory requirements Each Investigator must confirm this by signing the study protocol. The text of the applicable version of the Declaration of Helsinki will be provided by the Sponsor.

This study is within the scope of Chapter IX, relating to the treatment of personal data for research purpose in the field of health, of the French Law No. 2004-801 of 6 August 2004 amending laws No. 78-17 of 6 January 1978 and No. 94-548 of 1 July 1994 relating to information technology, files and freedoms.

The protocol will be submitted for review to the Advisory Committee on Information Processing in Research in the Field of Health (Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans le Domaine de la Santé - CCTIRS), then for approval to the French Data protection Authority (Nationale Informatique et Liberté - CNIL) before any data collection.

The participating investigators receiving financial compensation for the conduct of the study, the protocol and the financial agreement will be sent for review to the French Medical Council (Conseil National de l'Ordre des Médecins - CNOM) in accordance with the Article L.4113-6 of the French Code of Public Health.

10.3 Statement specifying that the study protocol will be sent for comment to the EC

In accordance with the French legislation (Articles L.1121-1 and following of the French Code of Public Health), given that the physician-patient relationship is not changed and that no examination or consultation is specific to the observatory, the study will not be subject to the opinion of a French Ethics Committee (Comité de Protection des Personnes, CPP).

10.4 Statement specifying the type of insurance that shall be provided for subjects, if appropriate.

No insurance is required because this study is purely observational. All medical treatment is decided and provided in clinical routine. The clinical routine insurance of the product will therefore cover all risk.

11. Informed consent process

Before entering into the study, information about the intention and nature of the study will be provided to each potentially eligible patient by the prescribing responsible physician of each participating center. Each patient will be informed about the use of his medical data in the clinical study according to the requirements data privacy regulations, i.e. consent to processing medical data of the patient to a central scientific database. Sufficient time will be allowed for the information to be read and for questions to be asked. Only subjects able to give their informed consent will be enrolled in this clinical study.

The patient must be told that withdrawal of informed consent to use their data in the clinical study is possible at any time, without stating a reason and without prejudice, and does not cause any disadvantages.

The patient will in any case receive detailed training on the use of the WCD by the ZOLL Company personnel. This will give the patient the opportunity to raise further questions about the device and data handling to the ZOLL personnel and the responsible physician.

12. Adverse events, adverse device effects and device deficiencies

Serious adverse events, i.e. cardiac and non-cardiac death, hospitalization, heart surgery, will be documented in the e-CRF. Adjudication of SAEs and second assessment of safety aspects will be performed by the sponsor.

Non-serious adverse events and adverse device effects as well as serious adverse device effects and other device deficiencies, as defined by good clinical practice and other relevant regulations, will be reported according to clinical routine procedures. For all legal reporting requirements, the sponsor remains fully responsible in the frame of his regular routine processes of reporting concerning his market authorization. Therefore, the sponsor's assessment and reporting responsibilities are not affected by this study.

13. Clinical Event Committee

The Clinical Event Committee will be composed of three experts. These experts will adjudicate, in an independent blinding manner, the occurrence of treatments and their classification (appropriate/inappropriate shocks), and will review the detected arrhythmia where no treatment was given.

14. Study limitations

Study limitations include mainly the observational nature of the design and the lack of control group.

The number of included patients could also be a limitation. As the study will start along with the early-stage launch of LifeVest, the number of patient inclusions will depend on the commercialization activities and is expected to increase over time.

15. Quality control & Quality assurance

The accuracy and completeness of the CRF entries will be monitored and checked against source documents according to a risk based monitoring plan.

Quality control procedures will be implemented to ensure the relevance and consistency of datasets.

16. Publication policy

16.1 Statement indicating whether the results of the clinical investigation will be submitted for publication.

The results of the study will be published by the principal investigator and other co-authors. The principal investigator will communicate the results of the observational study to the investigators. Prior to the communication or any publication, the sponsor will have the opportunity to have complete insight into the results and publication and to issue a statement. All relevant measures for transparency of clinical trials, and especially the recommendations of the editors of the major medical journals, will be met.

16.2 Statement indicating the conditions under which the results of the clinical investigation will be offered for publication.

The results of this study will be published by the principal investigator, but are the property of the sponsor. All publications (manuscripts, abstracts or other modes of presentation) shall be published freely but not before the sponsor had the opportunity to review and issue a statement, in advance of submission. Co-authorship with any sponsor personnel will be discussed and mutually agreed upon before submission of a manuscript to a publisher.

17. Bibliography

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3) Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med 1996;335:1933-40.

4) Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877-83.

5) Epstein AE, Dimarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities. Heart Rhythm 2008;5:e1-62.

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11) Adler A, Halkin A, Viskin S. Wearable Cardioverter-Defibrillators. Circulation 2013;127:854-860

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18. Signatures

Study Title:Post-market clinical follow-up study evaluating the efficacy and safety of LifeVest in real-life settings in France – WEARIT France.

This study protocol was subject to critical review and has been approved by the Sponsor.

Signed: _____ Date: DEC 8, 2016
Kent Volosin, MD
Vice President, Medical and Clinical Affairs ZOLL,
Legal representative of the sponsor

The undersigned have read this protocol and agreed to conduct this study in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

Signed: _____ Date: 6/12/16
Dr. Nicolas Combes, Chief investigator

Signed: _____ Date: - Dec 09. 2016
Dr. Eloi Marijon, Co-ordinating investigator

Signed: _____ Date: _____
Signature Principal investigator

_____
Name Principal investigator, in printed letters

APPENDIX A. Clinical Evaluation Committee Members

Pr Pascal Defaye
pdefaye@chu-grenoble.fr
Responsable de l'Unité de Rythmologie
Clinique de cardiologie
CHU de Grenoble site Nord - Hôpital Albert Michallon
Boulevard de la Chantourne - CS10217
38043 GRENOBLE CEDEX 9
FRANCE

Dr. Daniel Gras
DANGRAS@aol.com
Nouvelles Cliniques Nantaises,
Rue Eric Tabarly, 44277 Nantes
FRANCE

Pr Nicolas Sadoul
n.sadoul@chu-nancy.fr
Service de cardiologie
CHU de Nancy - Hôpital de Brabois
Rue du Morvan
54511 VANDOEUVRE-LÈS-NANCY CEDEX
FRANCE

STATISTICAL ANALYSIS PLAN

OF

WEARIT France

Post-market clinical observational study evaluating the efficacy and safety of LifeVest in real-life settings in France.

Authors: D. Schmidbauer, M. Wolf

Reviewed by: T. Fetsch

Version: November 13th, 2018

CHIEF INVESTIGATORS

Dr. Nicolas Combes, MD, Toulouse, France

Pr. Eloi Marijon, MD, Paris, France

SPONSOR

ZOLL,
121 Gamma Drive,
Pittsburgh, PA, 15238,
USA

CONTRACT RESEARCH ORGANISATIONS (CROs)

ClinSearch,
110 Avenue Pierre Brossolette,
92240 Malakoff,
France

Email: tony.toulorge@clinsearch.net

Tasks:

- Lead CRO
- Management of study sites
- Clinical monitoring and source data verification

CRI – The Clinical Research Institute GmbH
Arnulfstr. 19
80335 Munich,
Germany
Email: wearit-france@cri-muc.eu

Tasks:

- Setup and technical management of MARVIN CTMS and eCRF
- Data cleaning and data management
- Statistical analyses

STATISTICS

CRI – The Clinical Research Institute GmbH
Xiaoling Zhang, Statistician
Arnulfstr. 19,
80335 Munich,
Germany
Email: x.zhang@cri-muc.eu

Table of Content

1. Abbreviations

ARA2	Angiotensin receptor II antagonist
BMI	Body Mass Index
DCM	Non-ischaemic dilated cardiomyopathy
EOS	End of study
HCM	Hypertrophic cardiomyopathy
ICD	Implantable cardiac defibrillator
IEC	Inhibitor of Angiotensin converting enzyme
ITT	Intention-to-treat
LifeVest	External wearable cardioverter defibrillator
LV-EF or LVEF	Left ventricular ejection fraction
LPLV	Last patient last visit
NYHA	New York Heart Association
PCI	Percutaneous coronary intervention
SAP	Statistical analysis plan
SCD	Sudden cardiac death
SD	Standard deviation
VF	Ventricular fibrillation
VT	Ventricular tachycardia
WCD	Wearable Cardioverter-Defibrillator

2. Signature page

Date	Signature
_____	_____ Dr. Nicolas Combes (Chief Investigator)
_____	_____ Pr. Eloi Marijon (Chief Investigator)
2018-12-20 | 10:15:36 AM PST _____	DocuSigned by: Kent J. Volosin MD FACC FHRS CC2C50257BC742A... Kent Volosin (Sponsor representative)
_____	_____ Xiaoling Zhang (Study statistician, CRI)

3. General Information

This Statistical Analysis Plan (SAP) is based on the study protocol version 05.10.2015, amended on 10.10.2016 (Amendment No. 2).

This SAP aims to specify definitions, procedures and statistical methods to be applied for the final analysis of the study data.

4. Principles of the study

Sudden cardiac death (SCD) is a major cause of mortality throughout the world, accounting for approximately 300,000 deaths per year in the United States [1]. SCD accounts for about 50 % of all heart related deaths. Studies of patients who suffer SCD suggest that ventricular tachyarrhythmias are the dominant cause of this rapid terminal event although asystole due to heart block or sinus arrest can account for approximately 10-15 % of the sudden deaths. However, these are most often electrical signs of a dying heart or electro-mechanical dissociation. The introduction of the implantable cardiac defibrillator (ICD) in the 1980s resulted in subsequent clinical trials showing a significant reduction in SCD with ICD therapy in at-risk cardiac patients.

However, not all high-risk patients are candidates for the ICD for a variety of reasons [2-4]. These are: transient nature of the high-risk for SCD; patients who do not meet current guideline indications for an ICD; high-risk cardiac patients who had previously received an ICD but had it removed because of complications or malfunction; patients who refuse an ICD; age-related factors; and a variety of other medical and ethical considerations [5].

The Wearable Cardioverter-Defibrillator (WCD) LifeVest by ZOLL, Pittsburgh, PA, USA is an external defibrillator, guided by an algorithm to detect ventricular tachyarrhythmic events and gives the patient's physician time to assess the long-term arrhythmic risk in cases when the risk of life-threatening arrhythmias may only be temporary and to make appropriate plans.

4.1 Primary study objectives

1. **Appropriate shocks** as measured by shocks delivered for adjudicated sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) episodes.
2. **Inappropriate shocks** as measured by shocks delivered for all episodes that are not adjudicated sustained VT or VF episodes.

The frequency and rate of appropriate and inappropriate shocks will be measured. The risk of receiving an inappropriate shock will be analyzed. The risk of not receiving appropriate shocks when necessary will also be analyzed.

4.2 Secondary study objectives

1. Overall survival as measured by the ratio of the number of patients that are alive at the end of the use of the WCD to the total population of patients prescribed the LifeVest.
2. Quality of life relative to health state as measured through the administration of a patient quality of life survey. This survey has been used previously in a published study of patient quality of life.

LifeVest has been recently approved for reimbursement by the HAS. LifeVest has obtained coverage for 4 indications: (i) implantable cardiac defibrillator (ICD) removal due to cardiac device infections, (ii) a bridge to heart transplantation, (iii) in the early post-MI period with left ventricular (LV) dysfunction (LVEF <30 %), (iv) and a recent coronary revascularization with LV dysfunction (LVEF < 30 %). There is no current comparator to LifeVest. In France, patients at high risk for sudden cardiac arrest and waiting for heart transplant or ICD are hospitalized or discharged home without any particular ECG monitoring. LifeVest has been demonstrated to automatically detect and terminate rapid ventricular

arrhythmias. Introduction of LifeVest into the current patient management would definitely improve the clinical outcomes and benefit the patients with temporary risk of SCD. The use of LifeVest was shown to be effective in protecting patients against SCD in the United States. However, the clinical impact of using LifeVest in France remains unassessed. Therefore, this post-market study in France will provide efficacy and safety data for the reimbursement dossier renewal before September 2018.

5. Sample size and Power

This study is a post-inscription study designed to describe all patients treated by LifeVest in a comprehensive way. Thus this study will be proposed to all patients receiving LifeVest.

No sample size calculation has been planned. All patients accepting to participate will be included.

The LifeVest device is commercialized in France since approximatively 3 years, the number of subjects has been estimated based on the sales and the foreseen participation rate.

It was estimated that approximately 1,700 patients will receive LifeVest in clinical routine between May 2015 and April 2018 (300 patients first year, 520 patients second year and 880 patients third year of marketing) in France. After obtaining all regulatory approvals, the study started in August 2016. Between August 2016 and April 2018, 1,110 patients were expected to receive LifeVest in clinical routine. Considering a participation rate of 50 % related to centers participating in the study and consent given, around 550 patients were considered to participate in this study.

Due to an observed recruitment rate exceeding the initial expectations, the recruitment goal was reached prematurely with an estimated enrollment of about 1,200 patients until 31st March 2018. After the end of recruitment, follow-up of patients is planned until 31st march 2019 (LPLV).

According to most recent data from literature, the frequency of ventricular tachyarrhythmic events with shock delivery within the spectrum of indications for the LifeVest device and within the associated wearing periods was estimated between 1% and 5% [6]. In this present study, a population of 550 patients was expected as primary assumption, allowing to observe a shock delivery rate ranging between 1%-5% with an absolute precision below 2% (0.8 for 1% and 1.8 for 5%). This sample size was considered to be statistically sufficient to answer the pre-defined research questions, however, the expected final population in the study of about 1,200 patients will increase the level of precision.

6. Analysis populations

6.1 Intention to treat population (ITT)

ITT analysis in general includes every subject who is randomised according to randomised treatment assignment [7]. Since this is an observational study without randomisation, the equivalent, fundamental claim of “intention-to-treat” is the fulfilment of in- and exclusion criteria after giving informed consent on the use of medical data.

All consenting patients with a routinely prescribed WCD in study participating centers will be evaluated, regardless of the length of WCD wearing. This may include patients who have already completed use of LifeVest before start of the study in the corresponding study site.

Patients with missing outcome data are not considered in the outcome analysis [8].

The retrospective cohort of patients will be analyzed separately compared to prospectively included study patients for any variables that are not available for both cohorts, such as the patient survey.

6.2 On-treatment population

Patients who have worn WCD for at least 8 days (i.e. longer than 1 week) will be evaluated separately in an “on-treatment” efficacy analysis, because it is assumed from clinical experience that the WCD wearing time will only be long enough for those patients to reliably compare their long-term outcome in a cohort of patients who have had the WCD for several months (even six or more months in some indications).

7. Analysis datasets

7.1 Final dataset

Dataset at time of study database closure (= after date of last visit and end of data cleaning = date of end of study EOS). No further changes of clinical data will be possible, neither by sites nor by CROs.

7.2 Dataset for interim analysis

An interim analysis is planned for reimbursement dossier renewal latest in September 2018. For this purpose a dataset for interim analyses will be generated at a specific point in time defined by the sponsor. The dataset for interim analysis is a data snapshot and will partially consist of uncleaned data because data documentation and cleaning are ongoing at this point in time.

8. General methodology

Continuous variables will be summarized as means (standard deviations [SDs]), quartiles (25 %, 50 % and 75 %), and minimum and maximum value. The number and percentage of patients in each category will be presented for nominal variables. For graphical representation distribution plots, histograms, boxplots and bar charts will be used, as appropriate.

Comparisons of continuous variables will be performed using the Student´s t-test and if assumptions are not met Wilcoxon rank-sum test, and comparisons of nominal variables will be performed using the Pearson’s chi-square test or Fisher’s exact test, as appropriate.

For time-to-event data, the Cox proportional hazards model will be used unless specified otherwise. Survival estimates will be illustrated in Kaplan-Meier plots.

For comparing groups with respect to binary outcomes, logistic regression or analysis of covariance (ANCOVA) will be used as specified.

Statistical comparisons will be performed using two-sided significance tests with alpha=0.05 unless otherwise noted.

9. Demographics and characteristics of ITT population

9.1 Baseline

The following demographic and baseline characteristics will be described:

- Patient characteristics, additionally subgrouped by WCD indication:
  - Gender
  - Age
  - BMI

  - Heart rate at rest
  - Most recent LV-EF value
  - LV-EF in groups
    - ≤ 25%
    - > 25% ≤ 35%
    - > 35% ≤ 45%
    - > 45%
  - and
    - < 30%
    - >= 30 – 35%
    - > 35%
  - NYHA classification for heart failure
  - ICD removal
  - Currently implanted cardiac pacemaker
  - WCD indication
- Medical history, additionally subgrouped by WCD indication
  - Documented atrial fibrillation
  - Coronary heart disease
  - Myocardial infarction
  - PCI (intervention e.g. balloon, stent, not only angiography)
  - Bypass surgery (CABG)
  - Heart failure (ever classified as NYHA II - IV)
  - Cardiomyopathy, divided into dilated, non-ischemic cardiomyopathy (DCM) or hypertrophic cardiomyopathy (HCM)
  - Congenital heart disease
  - Cardiac valve disease, divided into aortic or mitral valve disease
  - Hospitalisation during the last year due to aggravation of heart failure
  - Cardiac arrest or resuscitation
  - Inherited arrhythmia syndrome by type
  - Previous renal disease requiring therapy
  - Stroke
  - Syncope
- Current cardiovascular symptoms, additionally subgrouped by WCD indication
  - Angina pectoris
  - Chest pain
  - Increased heart rate
  - Nausea
  - Palpitations

  - Shortness of breath
  - Sweating
  - Weakness, dizziness
  - Other current cardiac symptoms
- Current medication:
  - Antiarrhythmics (amiodarone, flecainide, sotalol, other)
  - Oral anticoagulants
  - Antiplatelet agents
  - Beta blockers
  - Diuretics
  - IEC/ARA2
  - Statines
- WCD activation/programming, additionally subgrouped by WCD indication
  - WCD activation
  - Prescription period
  - Shock energy of first shock
  - VF threshold heart rate
  - VT shock delay
  - VT threshold heart rate
- Patient questionnaires:

  All patient questionnaire data will be included in the analysis as long as the patient answered at least one item on the survey. In other words, no exclusion criteria will be used based on survey response completeness. Overall statistics will be presented for survey data results including

  - overall response rate, i.e. availability of surveys of prospective patients in %
  - item level response rate, i.e. availability of items in % and
  - survey responses for all items, i.e. frequency of answers per item in %

  For the majority of items in the questionnaires patients were asked to indicate their agreement using the 5-point Likert agreement response scale (strongly agree, agree, neither agree nor disagree, disagree, strongly disagree) with the following topics regarding their use of the LifeVest:

  - Peace of mind
  - Worry
  - Sleep quality
  - Confidence returning to activities of daily living (screened)
  - Confidence to exercise or perform cardiac rehabilitation (screened)
  - Taking condition seriously
  - Improved self-care
  - Confidence in LifeVest.

9.2 Follow-up data (wearing period) of ITT population

The following follow-up data will be described:

- Serious adverse events since inclusion by number of events in groups of
  - Type of event
    - Cardiac arrhythmic
    - Cardiac non-arrhythmic
    - Vascular non-cardiac (including stroke)
    - Cardiovascular without clearly defined other cause
    - Non-cardiovascular
  - Related hospital stay/prolongation of existing hospital stay
  - Causal relationship to WCD
  - Intensity
  - Outcome
  - Criteria for seriousness
- Time to first hospitalization
- Death
  - Cardiovascular
    - Cardiac
    - Vascular non-cardiac (including stroke)
    - Cardiovascular without clearly defined other cause
  - Non-cardiovascular
  - Death during prescription duration
  - Death while wearing the WCD
  - Death related to arrhythmic event
  - Death related to WCD dysfunction
- WCD events

  WCD events/patients with WCD events with following event parameters:
  - Type of event
  - Termination of event
  - Response button pressed
  - Shock delivered
  - Shock appropriate/inappropriate
- Occurrence of technical and non-technical problems during the wearing period
- Return of WCD device (end of therapy) due to:
  - Death
  - ICD implantation
  - Heart transplantation

- LV function improvement
- Patient's wish
- Other reason

- Clinical status on WCD return: Most recent LV-EF value, NYHA classification, risk assessment and if patient is still listed for heart transplantation
- Planned therapy after wearing period:
  - ICD implantation
  - PCI (Angioplasty, Stent)
  - Bypass surgery
  - Implantation of cardiac pacemaker
  - Heart transplantation
  - Implantation LVAD (left ventricular assist device)
  - Therapy with anti-arrhythmic agents
  - Other planned cardiac therapy
- Medication on WCD return

10. Primary analysis on ITT population

1. **Appropriate shocks** as measured by shocks delivered for adjudicated sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) episodes.

- Quantitative analysis of appropriate shocks
- Analysis of the risk of not receiving appropriate shocks when necessary, calculated as number of non-terminated VT/VF events without shock delivery and without response button pressed/ number of VT/VF events

2. **Inappropriate shocks** as measured by shocks delivered for all episodes that are not adjudicated as sustained VT or VF episodes.

- Quantitative analysis of inappropriate shocks
- The risk of receiving an inappropriate shock, calculated as number of inappropriate shocks/ non VT/VF events

11. Secondary analysis on ITT population

Overall survival as measured by the ratio of the number of patients that are alive at the end of the use of the WCD compared to the total ITT population.

Survival analysis using Kaplan-Meier curves and cox proportional hazard models will be performed to identify impacts on survival and the occurrence of WCD events will be displayed in tables in the following subgroups :

- indication for the WCD,
- medical history, and
- disease etiology: heart failure according to ESC guidelines
  - no HF (LV-EF >= 50%)

- intermediate HF (LV-EF >= 40 – < 50%)
- HF (LV-EF < 40%)

12. Efficacy and safety analysis on ITT population

12.1 Primary parameters

- Arrhythmic (VT/VF) events and characterization of event:
  - Number of WCD shocks until termination of the tachycardia event
  - Cardiac arrest immediately after shock delivery
  - Asystole after VT/VF event
  - Maximum heart rate during ventricular tachycardia
  - Polymorphic VT event
  - Immediate ventricular fibrillation (VF)
  - Ventricular tachycardia degenerating into ventricular fibrillation (VF)
- Efficacy will be evaluated using the success rate of appropriate shocks: Number of VT/VF events terminated by shocks/VT/VF events with shock delivery
- Rate of treated VT/VF episodes calculated as shocked VT and VF events/ all VT and VF events
- Cumulative probability of sustained VT/VF, determined according to the Kaplan-Meier method in function of time
- Number of arrhythmic events and shocked events
  - Within 30 days from activation date
  - Within 90 days from activation date

12.2 Secondary parameters

- Analysis of primary outcome parameters (section 12.1) in sub-groups according to their clinical profile at baseline:
  - Age:
    - < 40 years
    - >= 40 - < 65 years
    - >= 65 - < 75 years
    - >= 75 years
  - Gender
  - Indication of WCD:
    - implantable cardiac defibrillator (ICD) removal due to cardiac device infections,
    - a bridge to heart transplantation,
    - in the early post-MI period with left ventricular (LV) dysfunction (LVEF <30%),
    - a recent coronary revascularization with LV dysfunction (LVEF < 30%).
  - Type of inherited arrhythmia syndrome:
    - Long-QT syndrome (LQTS)
    - Brugada syndrome
    - Catecholaminergic polymorphous ventricular tachycardia (CPVT)

- Arrhythmogenic right ventricular cardiomyopathy
- Other
- Unknown

In addition the following parameters will be analysed in the mentioned subgroups:

- Cause of death (as assessed by CEC)
- Hospitalization
- Type of SAE

LV-EF at baseline and at time of WCD end of use

13. On-treatment efficacy analysis

For on-treatment efficacy analysis, tables on baseline characteristics and outcome will be shown comparing patient group on-treatment to not on-treatment (for definitions refer to 6.3).

14. Analysis of WCD usage on ITT population

Analysis of usage patterns will be done by:

- Description of WCD wearing profile:
  - Average prescription period
  - Average wearing period (date of activation to date of end of use)
  - Average wearing period by gender
  - Description and analysis of compliance of WCD wearing: WCD device in use during wearing period (days in use / number of days of wearing period) Average daily WCD usage (hours)
- Regression model/ANOVA evaluating factors influencing the non-compliance of patients with prescribed WCD (age, gender, neurologic function, co-morbidities etc.)
- Distribution of reasons for end of WCD usage
- Kaplan-Meier curves for time to end of WCD usage.

15. Missing values

Missing data will not be replaced by any algorithm.

16. Applied software

R (version 3.3.3 or later)

17. Literature

1) Myerburg RJ. Sudden cardiac death: exploring the limits of our knowledge. J Cardiovasc Electrophysiol 2001; 12:369-81.

2) Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005; 352:225-37.

3) Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med 1996; 335:1933-40.

4) Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002; 346:877-83.

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