Heart Sounds Measurement Using the Wearable Cardioverter Defibrillator (HS-WCD) Study
NCT#02825966
February 3, 2016

DOCUMENT APPROVAL PAGE

Document Number:	Rev:	Page:
90D0153	A	1 of 17

Title:
Heart Sounds Measurement Using the Wearable Cardioverter Defibrillator (HS-WCD): Study Protocol

Author: Ramu Perumal **Date:** 3-February-2016

Approvals

("☒" indicates approval signature required)

☒ Medical Affairs:	Date: 03-Feb-2016	☒ Marketing: Michelle Simon 2-5-16	Date:
☒ Clinical Operations:	Date: 3 Feb 2016	☐ Billing/Reimbursement:	Date:
☐ IE/QE Engineering:	Date:	☐ Support Service:	Date:
☐ Service Operations:	Date:	☐ Technology Applications:	Date:
☒ OEM Regulatory:	Date: 2/3/16	☐ OEM Engineering:	Date:

Documentation Control:	Date Archived:
Kimberly Albeter	2/11/16

Electronic File info: (if applicable) *If multiple files (such as multiple sheets of a drawing) list file info separately

File name:	Size (in bytes)	Time & Date (or Date & Time)
90D0153_revA.docx	3316 KB	KA 2/11/16 ~~2/11/16~~ 2/3/16 12:34pm

Transferred File info: (To be completed by Documentation Control)

File name:	Size (in bytes)	Time & Date (or Date & Time)
90d0153_reva.doc 90d0153_reva.pdf	33115 KB	2/11/16 2:19pm

ZOLL Services Form Number: 90A0001-A01
Form REV Level: A

DOCUMENT REVISION HISTORY PAGE

Document Number:	Rev:	Page:
90D0153	A	2 of 17

Title: Heart Sounds Measurement Using the Wearable Cardioverter Defibrillator (HS-WCD): Study Protocol

Revision History Of Document

Rev	CO Number	Description of Change	Author	Effective Date
FI	NA	First issue	RP	1/15/16
A	0182	Exclusion criteria were expanded to include subjects with pacemakers; implanted defibrillators, and cardiac resynchronization therapy devices; and subjects with a previous history or current diagnosis of atrial fibrillation. Added a note that subject's blood pressure and heart rate will be measured once the subject is eligible to participate in the study.	RP	2/11/16

Heart Sounds Measurement Using the Wearable Cardioverter Defibrillator: Study Protocol

Study Sponsor	ZOLL
Protocol Number	90D0153
Version	Rev A

Sponsor Representative:

I have reviewed and approve this protocol. My signature assures that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality.

Sponsor's Signature _____

Name _____

Date of Signature (DD MMM YYYY) _____

Principal Investigator:

I have read this protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined herein, including all statements regarding confidentiality. I will make a reasonable effort to complete the study within the time designated. I will provide copies of the protocol and access to all information furnished by the Sponsor to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the device and the study. I understand that the study may be terminated or enrollment suspended at any time by the Sponsor, with or without cause, or by me if it becomes necessary to protect the interests of the study subjects.

I agree to conduct this study in full accordance with all applicable regulations and Good Clinical Practices (GCP).

Investigator Signature _____

Name _____

Date of Signature (DD MMM YYYY) _____

PROTOCOL SUMMARY

Objectives

To conduct a prospective, validation study to evaluate the data accuracy of heart sounds recorded by the LifeVest® Wearable Cardioverter Defibrillator (WCD). To show equivalence, these data will be compared with the heart sounds data recorded by the FDA-cleared AUDICOR® AM device.

Study Size

The study will enroll a minimum of 27 and a maximum of 35 subjects.

Study Population

Participants will be adult patients (age ≥ 18 years) with at least seven patients over the age of 40 years. In addition, at least five patients with a history of heart failure will be included.

Intervention

First, participants will wear the AUDICOR® AM device for 15 minutes while sitting quietly. Then, the AUDICOR device will be removed and the participants will wear the WCD for 15 minutes while sitting quietly. Next, while wearing the WCD, participants will perform various activities of daily living, including at least 6 hours of overnight wear. Finally, the WCD will be removed and the participants will wear the AUDICOR® AM again for 15 minutes while sitting quietly.

Study Design

This is a single center, prospective, observational study. This is a non-significant risk device study as all biological study parameters will be measured noninvasively with the WCD defibrillation capability disabled. In addition, the study device will not be used as a replacement for regularly prescribed therapies or diagnostics.

1. INTRODUCTION

Heart sounds represent vibrations of the cardiohemic system (cardiac cavities, valves, and blood) due to acceleration and deceleration of blood, as result of pressure gradients [1]. These sounds are a direct expression of mechanical activity of the cardiovascular system and can be used to identify significant events in the cardiac cycle as well as detect irregular heart activity. For example, the presence of the third heart sound (S3) is recognized to be a clinical sign of left ventricle dysfunction and a predictor for adverse outcomes in patients with heart failure [2].

Acoustic cardiography is a diagnostic technique that consists of recording and algorithmically interpreting the heart sounds with concurrently recorded electrocardiogram (ECG) data [3]. This technique allows for identifying normal and abnormal heart sounds, and quantifying the timing of these heart sounds with respect to the cardiac electrical activity. These data can then be used to identify patients with cardiac dysfunction such as those with systolic heart failure [4].

The ZOLL LifeVest® Wearable Cardioverter Defibrillator (WCD) is an FDA-approved device that noninvasively monitors ECG signals during activities of daily living. If a life-threating ventricular tachyarrhythmia is detected, the device automatically provides external defibrillations in an attempt to restore a normal heart rhythm. Given the diagnostic utility of acoustic cardiography, ZOLL has modified its WCD system to incorporate a sensor to record heart sounds while simultaneously recording the ECG signals. To evaluate the data accuracy of the heart sounds recorded by the device, the WCD heart sounds data collected by a modified unit will be compared with the data recorded by the AUDICOR® AM system (Inovise Medical, Inc, Portland, OR), which is a FDA cleared, non-invasive, ambulatory, acoustic cardiography recorder.

2. SYSTEM DESCRIPTION

2.1 LifeVest® WCD system

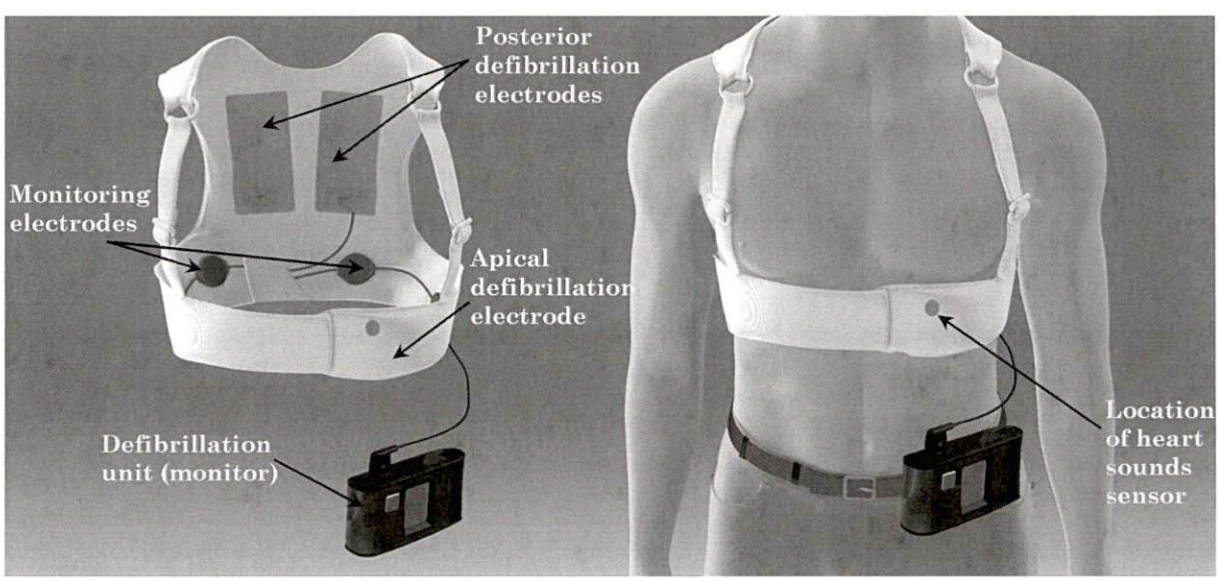

Figure 1: Components of the WCD system with the heart sounds sensor (see text for details).

The WCD is composed of four dry, non-adhesive monitoring electrodes and three defibrillation electrodes incorporated into a lightweight vest (garment), that are connected to a defibrillation unit (monitor) carried in a holster, which can be supported by over-the-shoulder strap or worn

on the hip (Fig. 1). The monitoring electrodes are positioned circumferentially around the chest to provide two surface ECG leads. One defibrillation electrode is placed in an apical position while the remaining two defibrillation electrodes are placed posteriorly. The apical defibrillation electrode is modified to incorporate a heart sounds sensor, such that the sensor sits left of the xiphoid process over the 5th intercostal space (Fig. 1). For the purposes of the study the defibrillation capability of the WCD will be disabled.

2.2 AUDICOR® AM system

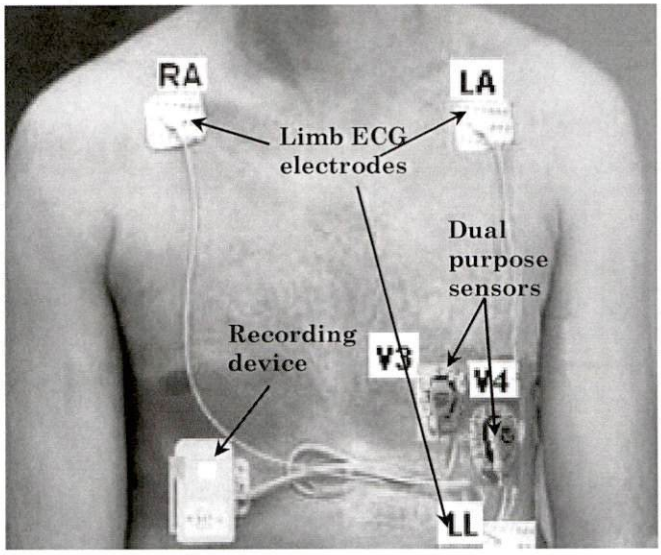

Figure 2: Components of the AUDICOR AM device (see text for details). RA-right arm; LA-left Arm; LL-left leg; V3 and V4 are precordial ECG positions.

The AUDICOR® AM device consists of three adhesive ECG electrodes arranged to form two bipolar limb leads, lead I (RA-LA) and lead II (RA-LL) (Fig. 2). In addition, there are two dual-purpose adhesive sensors in the V3 and V4 precordial positions that simultaneously acquire ECG and heart sounds data from each of these locations. The ECG and heart sound sensors are wired to a lightweight recording device that is placed on the right upper abdomen below the chest wall. The device performs automated acoustic measurements incorporating digital signal processing algorithms to detect and characterize the intensity and timing of heart sounds.

3. OBJECTIVES

The objectives of the study are to:

3.1 Compare the heart sound measurements recorded by the AUDICOR® AM device versus those recorded by the WCD while subjects are sitting quietly.

3.2 Observe the variation of heart sound measurements recorded by the WCD across subjects with specific physical maneuvers, time, and repositioning (due to removal and reapplication) of the WCD.

3.3 Observe measurements of the sleep-disordered breathing index recorded by the WCD.

4. SUBJECT SELECTION CRITERIA

The following criteria will be used to include subjects in the study:

4.1 Healthy male and female volunteers who are able to fit in the WCD garment (26 to 56 inches measured circumferentially at the level of the xiphoid process).

4.2 Included in this group are at least five healthy subjects with a self-reported history of heart failure.

4.3 The subject must be 18 years of age or older on the day of screening, with at least 7 subjects 40 years of age or older on the day of screening.

The following criteria will be used to exclude subjects from the study:

4.4 Mental, visual, physical, literacy, and auditory limitations that prevent interaction with the WCD equipment.

4.5 Any acute medical conditions that prevent the following maneuvers: lying on back, lying on the right and left side, standing, sitting, and/ or leaning forward when sitting.

4.6 Any self-reported shortness of breath, fatigue, swelling of feet, ankles, or legs, and/or chest pain.

4.7 Currently has a pacemaker, an implanted cardioverter defibrillator (ICD), or a cardiac resynchronization therapy (CRT) device.

4.8 A previous history or current diagnosis of atrial fibrillation.

4.9 Employees or family members of Inovise and ZOLL.

4.10 Unable or unwilling to provide written informed consent.

5. PROCEDURE

At the beginning of the study a ZOLL representative will train the site study staff in AUDICOR AM and WCD device use. All testing will be performed on the site's premises. Before testing, ambient noise in the room should be minimized and if possible, the subject should be positioned away from sources of possible electrical interference.

5.1 Eligibility

Potential subjects will be screened to determine whether they meet the inclusion and exclusion criteria.

5.2 Consent

Informed consent will be obtained.

5.3 Enrollment

Once enrolled, each subject will be assigned a sequential identification number. Subject's clinical history will be assessed and will include measurement of blood pressure and heart rate.

5.4 AUDICOR® AM device setup and first use

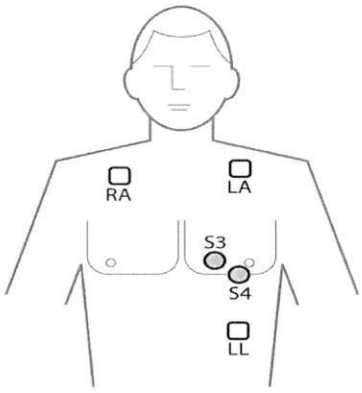

Figure 3: Placement position of the AUDICOR AM sensors. RA, LA, and LL represent the ECG sensors and S3 and S4 represent the dual heart sounds and ECG sensor (see text for details).

Setup of the AUDICOR device will follow the procedures described in AUDICOR® AM quick reference guide and will include:

- Inserting a blank 2 GB data storage card and a fully charged battery in each of the recording devices.
- Ensuring the skin is clean and dry where the electrodes are to be placed. Remove any debris, ointment, etc. with water and mild soap. Wipe of any excess moisture with a dry cloth.
- Shave excess hair before applying the electrodes.
- Applying the adhesive ECG electrodes: RA is applied below the right clavicle; LA is applied below the left clavicle; and LL is applied on the left upper abdomen below the chest wall (Fig. 3).
- Applying the dual heart sounds and ECG adhesive sensors: S3 is applied approximately in the V3 lead position, below the 4th intercostal space right of the left midclavicular line (Fig. 3). S4 is applied approximately in the V4 lead position, along the mid-clavicular line in the 5th intercostal space.
- Marking the sensor placements in the case report forms.
- Connecting the electrodes/sensors to the recording device via the patient cables, matching the labeling on the cable to the electrodes as shown in Figure 3.
- Placing the AUDICOR recording device in the holsters and applying the assembly vertically on the right upper abdomen below the chest wall.
- Securing the lead wires with tape to the chest with proper strain relief to prevent cable movement.
- Having the subjects sit in a chair comfortably, with their back straight. Instruct them to be relaxed, quiet and still as possible while sitting.
- Configuring the device to preview the data quality and then initiating the recording by:
    - Launching the Cardio-Pulmonary Holter (CiPH) program from the sponsor provided laptop
    - Launching the patient setup from the CiPH interface

- Entering the appropriate sensor identification information in the patient setup
- Previewing the waveform from 3 ECG channels, labeled as I, II and V4RA, and 2 heart sounds sensor channels, labeled as SV3 and SV4
- Tapping near the heart sounds sensors, S3 and S4 and verifying that artifact from the tapping is observed on the preview
- If unable to see artifact, ensuring the cables are connected to the sensors and AUDICOR device, and if necessary, replacing the electrodes
- Entering patient number, and clicking start recording on the CiPH program to initiate the session.

Once the recording session is initiated, subjects will wear the AUDICOR device for 15 minutes while sitting quietly. During this time subjects are expected to be relaxed, quiet and as still as possible. After 15 minutes, the recording will be terminated by pressing the ON/Stdby buttons on the recording devices until the LED stops flashing. Then, the AUDICOR device will be disconnected and all electrodes/sensors will be removed from the subject's body. Finally, the battery of the recorder will be removed to access the data storage card. The data stored in the card will be transferred to a sponsor provided computer (for details, see AUDICOR® AM quick reference guide). Data from each subject will be stored under their previously assigned unique identification number.

5.5 WCD device setup and use

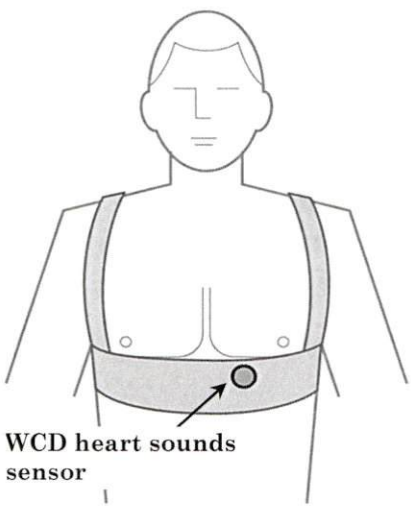

Figure 4: WCD vest placement on the subject with location of the WCD heart sounds sensor.

Application of the WCD will follow the procedures described in the LifeVest® Clinician Manual and will include:

- Programming the monitor and entering subject's identification number.
- Measuring the subject's chest size with the measuring tape centered at the xiphoid.
- Selecting the appropriate vest/garment size based on the chest size measurement.
- Assembling the garment with the monitoring and defibrillation electrodes, with the electrode belt disconnected from the monitor.

- Placing the assembled garment on the subject such that all clothing, including underwear, is worn over the device and not under it.
- Marking the location of the WCD heart sounds sensor in the case report form.
- Inserting a fully charged battery, connecting the electrode belt to the monitor, and starting the baseline process.
- Ensuring that the baseline process is successfully completed.
- Setting up the charger to allow for downloading of WCD monitoring data.

Following 5 minutes of inactivity for ECG stabilization, subjects will sit quietly for 15 minutes. The beginning of sitting will marked by tapping the WCD front therapy electrode twice and noting the time. During testing, subjects are expected to sit in a chair comfortably, with their back straight. Instruct them to be relaxed, quiet and still as possible while sitting. At the end of 15 minutes, the front therapy electrode will be tapped twice and the time noted.

Subjects will then perform the activities of daily living (ADL) maneuvers listed below for 10 minutes each.

5.5.1 Standing

5.5.2 Lying on the back

5.5.3 Lying on the left side

5.5.4 Lying on the right side

5.5.5 Sitting and leaning forward

After settling into the new position, the front therapy electrode will be tapped twice by the test administrator, the time after tapping will be noted as the start time, a manual recording will be performed by holding the response buttons for 3-seconds, and at the end of 10 minutes the front therapy electrode will be tapped and the time will be noted as the stop time. After all ADL maneuvers are complete, the study coordinator will remove the WCD device by disconnecting the electrode belt, unplugging the battery from the monitor, and removing the garment off the subject. After five minutes, the garment will be reapplied and then electrode belt and battery will be reconnected to the monitor. The subject will wear the device for 10 minutes while sitting quietly. The removal and reapplication times will be noted.

Following the removal and reapplication section, the subject will continue to wear the WCD until the total use of the device is 12 to 16 hours, with at least 6 hours of overnight wear. During the overnight wear the subject will be expected to sleep at the testing site. In addition, subjects will fill a diary (see Appendix A) to note their non-testing WCD activities before and after sleeping; any non-testing activity that causes the device to alarm; and any activity while sleeping that causes the WCD to alarm.

After the overnight wear, removal and reapplication of the WCD device will be repeated, following the procedure as described previously, and the subject will wear the device for 10 minutes while sitting quietly. At the end of the testing, recording from the WCD device will be terminated by removing the battery and the garment will be removed from the subject. Data from the WCD device will be downloaded to the ZOLL servers. In addition, at the end

of testing each subject, the WCD monitor will be cleaned, packed appropriately, and returned to ZOLL.

5.6 AUDICOR® AM device setup and second use

Following the overnight wear, removal and reapplication testing, and final removal of the WCD device, subjects will wear the AUDICOR device again for 15 minutes while sitting quietly (for details see section 5.4).

6. DATA COLLECTION

ECG and heart sounds data recorded by the AUDICOR® AM devices during the testing will be transferred from the data storage cards to the sponsor provided computer. Study coordinators will perform a manual download to transfer each subject's baseline and all automatically recorded ECG data by the WCD to the ZOLL servers. The WCD device will also collect and store complete recordings of ECG data, heart sounds data, device performance data, and subject-device interaction data. These data will be stored in the WCD monitor's removable storage and will be extracted upon return of the device to ZOLL. Case report forms will be used to collect general demographic and medical history information from subjects enrolled in the study. In addition, the study coordinator will record the start and end times of each activity of daily living maneuver and the removal and reapplication times of the WCD device.

7. DATA ANALYSIS

Data from all subjects in the study will be considered and/or analyzed. At a minimum, the full sample set as well as the subsample set (measurements made every five minutes and sleep scores) of the following variables will be analyzed:

- Electromechanical activation time (EMAT): Time from onset of QRS in the ECG signal to the first heart sound, S1.
- Percentage EMAT (EMATc): EMAT normalized by heart rate.
- Left ventricle systolic time (LVST): Time interval from S1 to the second heart sound, S2.
- Percentage LVST (%LVST): LVST normalized by heart rate.
- Presence of the third and fourth heart sounds, S3 and S4, respectively.
- Systolic dysfunction index (SDI): A multiplicative combination of ECG and heart sound parameters derived from QRS duration, QR interval, EMAT, and S3 strength.
- Sleep disordered breathing index (SDBI): A score to detect sleep disordered breathing events.

Equivalence of the modified WCD device to the AUDICOR device will be established by comparing the full sample EMAT data during quiet sitting (see section 8 for details). Additional descriptive statistics and qualitative analysis will be used to compare the heart sounds measures for each subject and as a group between the AUDICOR device and WCD device; across various activities of daily living maneuvers; before the removal and after the reapplication of the WCD; and across time for all the devices. These analysis are for observational purposes only and there are no endpoints associated with them.

8. EVALUATION OF RESULTS

Equivalence of the modified WCD device to the AUDICOR device will be established by comparing the full sample EMAT data during quiet sitting. EMAT was chosen to establish equivalence because previous studies have shown the utility of EMAT in predicting or identifying patients with left ventricular dysfunction [4,5,6]. The two one-sided test (TOST) [7] will be used to test equivalence. Because measurements from the two devices (WCD and AUDICOR) are made on the same subject, a paired T-test will be used. The equivalence margin will be set at 12-ms, which is 10% of the 120-ms EMAT threshold previously used to identify patients with left ventricular dysfunction (K051450 and K070136). Using TOST, equivalence will be established at $\alpha = 0.05$ significance level if a $(1 - 2\alpha) * 100\%$ confidence interval for the average difference in EMAT (WCD-AUDICOR) is contained within the interval [-12, 12].

9. STUDY SIZE

The study will enroll a minimum of 27 and a maximum of 35 subjects (see section 9.1 for details). At least 5 subjects will have a self-reported history of heart failure.

9.1 Study size justification

EMAT will be used to establish equivalence between the modified WCD and the AUDICOR device (see section 8 for details). Using the TOST, the sample size calculation is based on testing the following two-sided hypotheses:

Null hypotheses: $\mathbf{H_0}$: $|EMAT_{WCD} - EMAT_{AC}| \geq \delta$

Alternative hypotheses: $\mathbf{H_A}$: $|EMAT_{WCD} - EMAT_{AC}| < \delta$

where, $|EMAT_{WCD} - EMAT_{AC}|$ is the absolute value of the mean of the differences in EMAT measured by the WCD and AUDICOR devices and δ is the equivalence margin. The sample size for tests of equivalence of means of paired variables (paired T-test) is given by [8]:

$$n = \left[\sigma \frac{Z_{1-\alpha} + Z_{1-\beta/2}}{\delta - |EMAT_{WCD} - EMAT_{AC}|}\right]^2 \quad (1)$$

where, n is the sample size, σ is the standard deviation of the differences, α is the significance level, and β is the probability of type II error (1- β is the power).

Internal testing on seven subjects provided the following summary statistics:

$\lvert EMAT_{WCD} - EMAT_{AC} \rvert$	7.26
σ	8.36
90% CI-lower limit	-13.4
90% CI-upper limit	-1.13

Using an equivalence margin (δ) of 12-ms, $\alpha = 0.05$, and 1- $\beta = 0.8$ the sample size using Eqn. 1 is 27. Although all enrolled subjects are expected to complete the study, the maximum enrollment is specified as 35 subjects to ensure a sample of 27 subjects who complete the study.

10. RISKS AND BENEFITS

Some subjects may experience minor discomfort and skin irritation due the adhesive electrodes of the AUDICOR system and the vest assembly of the WCD system. Alarms from the WCD device due to poor contact of its electrodes may startle the subjects during testing. There will be no risk of shock to the subject because the defibrillation capability of the WCD system will be disabled.

There are no direct benefits for the subjects participating in the study.

11. ADVERSE EVENTS

Adverse events will be recorded on the Case Report Form only if the Investigator feels the event may be causally related to the AUDICOR or the WCD systems. The Investigator must assess the severity as indicated on the Case Report Form.

Serious adverse events include any event that is fatal or life threatening, requires or prolongs hospitalization, or is permanently disabling. The Investigator will assess whether the adverse event is anticipated or unexpected. An unexpected adverse event is any adverse event not identified by nature, severity or frequency prior to the investigation. Anticipated events include, but are not limited to:

- Skin rash or irritation is commonly associated with the use of adhesive electrodes and the garment assembly.
- WCD alarms may startle subjects due to poor electrode contact.

An unanticipated adverse device effect (UADE) is defined as "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects" (21 CFR 812.3(s)). UADEs must be reported by the clinical investigator to ZOLL and the reviewing IRB, as described below:

- For device studies, the investigator is required to submit a report of a UADE to the sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event (§ 812.150(a)(1)).
- ZOLL must immediately conduct an evaluation of a UADE and must report the results of the evaluation to the reviewing IRBs and investigator within 10 working days after first receiving notice of the effect (§§ 812.46(b), 812.150(b)(1)).

12. SUBJECT CONSENT AND CONFIDENTIALITY

Each subject will be informed of the potential risks and benefits, the purpose of the investigation, and the investigational nature of the study prior to their enrollment. The subject must freely sign the IRB approved Informed Consent Form prior to the start of the study.

Each subject will receive a unique subject identification number. Although the patient's name and identity will be known to the investigators and to ZOLL, no HIPAA sensitive data will be stored except on consent forms. Authorized personnel from the IRB will have access to subject records as required.

Subject data will only be accessible by a unique subject identifier. The database will not contain subject names nor will the LifeVest network (a password protected and encrypted website).

13. ADMINISTRATIVE RESPONSIBILITIES

The protocol, informed consent document, and relevant supporting information must be submitted to the IRB for review and must be approved before the study is initiated. In addition, any subject recruitment materials must be approved by the IRB prior to being used. This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and applicable regulatory requirements. The study must be conducted in accordance with the regulations of FDA as described in 21 CFR 50 and 56, applicable laws and the IRB requirements.

ZOLL, as sponsor of the investigation, has responsibility for the overall study administration, including providing necessary materials for conducting the study. The investigator will be responsible to assure IRB approval of the protocol.

The sponsor must submit any protocol change to the IRB for review and approval before implementation. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately provided the reviewing IRB is notified within 5 working days.

The investigator is responsible for following the study protocol and maintaining records of all protocol deviations, protocol amendments, and significant correspondence related to the study. The investigator is responsible for obtaining and maintaining the original Informed Consents and Case Report Forms. All Report Forms must be signed by the investigator or by investigator's designee.

It is the responsibility of the investigator to provide each subject with full and adequate verbal and written information using IRB approved informed consent document, including the objective and procedures of the study and possible risks involved before inclusion in the study. Informed consent must be obtained prior to performing any study-related procedures. A copy of the signed informed consent must be given to the study subject.

All written materials, data, and reports will be kept confidential; however, the results may be submitted to the FDA or other regulatory bodies as part of the evaluation of the device.

14. REFERENCES

1. Rushmer RF. *Cardiovascular dynamics.* 4th Edition, WB Saunders, Philadelphia, 1976.
2. Drazner MH, Rame JE, Stevenson LW, Dries DL. *Prognostic importance of elevated jugular venous pressure and a third heart sound in patients with heart failure.* N Engl J Med. 2001; 345:574-81.
3. Erne P. *Beyond auscultation- acoustic cardiography in the diagnosis and assessment of cardiac disease.* Swiss Med Wkly. 2008; 138:439-52.
4. Wang S, Lam YY, Liu M, Fang F, Wang J, Shang Q, Sun JP, Sanderson JE, Yu CM. *Acoustic cardiography helps to identify heart failure and its phenotypes.* Int J Cardiol. 2013; 167:681-86.

5. Dillier R, Kobza R, Erne S, Zuber, Arand P, Erne P. *Noninvasive detection of left-ventricular systolic dysfunction by acoustic cardiography in atrial fibrillation.* Cardiol Res and Pract. 2010; 2011:173102.

6. Chao TF, Sung SH, Cheng HM, Yu WC, Wang KL, Huang CM, Chen CH. *Electromechanical activation time in the prediction of discharge outcomes in patients hospitalized with acute heart failure.* Intern Med. 2010; 49:2031-2037.

7. Schuirmann DJ. *A comparison of the two one-sided tests procedure and the power approach for assessing equivalence of average bioavailability.* J Pharmacokin Biopharm. 1987; 15:657-680.

8. Chow S, Shao J, Wang H. 2008. *Sample Size Calculations in Clinical Research*. 2nd Ed. Chapman & Hall/CRC Biostatistics Series. Page 54.

Appendix A
Subject Diary

Subject Number: _________ Subject Initials: __________

Activity and Alarm Log

Date/Time	Primary Activity	WCD alarm
Date (mm/dd/yyyy): ___/___/_____ Time (hh:mm): _____:______	☐ Sitting ☐ Standing ☐ Walking ☐ Reclining ☐ Sleeping ☐ Other:________________ ____________________	☐ Siren alarm Activity during alarm:__________ ☐ Gong alarm Activity during alarm:__________
Date (mm/dd/yyyy): ___/___/_____ Time (hh:mm): _____:______	☐ Sitting ☐ Standing ☐ Walking ☐ Reclining ☐ Sleeping ☐ Other:________________ ____________________	☐ Siren alarm Activity during alarm:__________ ☐ Gong alarm Activity during alarm:__________
Date (mm/dd/yyyy): ___/___/_____ Time (hh:mm): _____:______	☐ Sitting ☐ Standing ☐ Walking ☐ Reclining ☐ Sleeping ☐ Other:________________ ____________________	☐ Siren alarm Activity during alarm:__________ ☐ Gong alarm Activity during alarm:__________
Date (mm/dd/yyyy): ___/___/_____ Time (hh:mm): _____:______	☐ Sitting ☐ Standing ☐ Walking ☐ Reclining ☐ Sleeping ☐ Other:________________ ____________________	☐ Siren alarm Activity during alarm:__________ ☐ Gong alarm Activity during alarm:__________
Date (mm/dd/yyyy): ___/___/_____ Time (hh:mm): _____:______	☐ Sitting ☐ Standing ☐ Walking ☐ Reclining ☐ Sleeping ☐ Other:________________ ____________________	☐ Siren alarm Activity during alarm:__________ ☐ Gong alarm Activity during alarm:__________
Date (mm/dd/yyyy): ___/___/_____ Time (hh:mm): _____:______	☐ Sitting ☐ Standing ☐ Walking ☐ Reclining ☐ Sleeping ☐ Other:________________ ____________________	☐ Siren alarm Activity during alarm:__________ ☐ Gong alarm Activity during alarm:__________