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Protocol Title: Benefits of Microcor (μCor) in Ambulatory Decompensated Heart Failure

Short Title: BMAD HF

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BENEFITS OF MICROCOR (μCOR™) IN AMBULATORY DECOMPENSATED HEART FAILURE

Short Title: BMAD HF

ZOLL Study Lead: Matt Sundermann, PhD
121 Gamma Drive, Pittsburgh, PA 15238
+1-412-968-3333 ext 14413

Study Device: *μCor*

Protocol Number: *90D0182*

IDE Number: *NA*

Version Date: *May 15, 2018*

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

PRINTED NAME OF INVESTIGATOR	SITE NUMBER
INVESTIGATOR SIGNATURE	DATE

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Study Summary

Title	BENEFITS OF MICROCOR (μCor™) IN AMBULATORY DECOMPENSATED HEART FAILURE
Short Title	BMAD HF
ZOLL Protocol Number	90D0182
Study Design	Prospective and Observational Study
Study Duration	The study duration will last an estimated 2.5 years with 1 year estimated for enrollment
Study Center(s)	30 to 50 centers (Multinational)
Primary Objective(s)	To identify correlations between μCor measurements (thoracic fluid index, respiration rate, cardiac rhythm, physical activity, and posture) with occurrences of heart failure related clinical events within 90 days of hospital discharge for acute decompensated heart failure.
Study Population	Subjects hospitalized for acute decompensated heart failure or subjects presenting to an outpatient clinic within 10 days post-hospital discharge for heart failure. All subjects require an additional heart failure event within the previous 6 months.
Intervention	Subjects meeting the inclusion/exclusion criteria will wear the μCor for up to 90 days. During the study, clinic follow up will occur every 30 days. For all subjects, each scheduled clinic visit will include assessment of cardiac symptoms and any relevant clinically actionable events. The subject will be given a daily diary to track symptoms, unplanned hospital visits, medication changes, and all other heart failure related clinical events. Weekly phone calls to the subject will be given throughout the duration of the study to remind the patient to use the subject diary and to collect and record heart failure related clinical events. Subjects will be contacted six months and one year from initial enrollment to assess the vital status of the subject, any heart failure related clinical events since the end of μCor wear, and any health care utilization since the end of μCor wear.
Study Size	A total of 500 subjects
Reference therapy	NA

1 Introduction

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

1.1 Background

Annually, over 1 million patients are hospitalized with a primary diagnosis of heart failure (HF) [1]. Despite improvement in outcomes with medical therapy, readmissions for acute decompensated HF are common and place a significant burden on the healthcare system. Therefore, strategies for outpatient monitoring and fluid management are needed to reduce HF hospitalizations. Rather than low cardiac output, the main reasons for rehospitalization are symptoms associated with pulmonary and systemic venous congestion due to elevated ventricular filling (end-diastolic) pressures [2]. Remote monitoring of these pressure changes in addition to its surrogate measures, such as intrathoracic impedance, lung fluid levels, systolic time intervals, or the presence of abnormal heart sounds, may help to prevent hospitalization by detecting early evidence of HF decompensation [3, 4, 5]. In addition, remote monitoring may lead to better access to care and coordination of services.

Given the anticipated importance of remote HF monitoring and fluid management, ZOLL has developed a novel radiofrequency (RF) based heart failure and arrhythmia management system (µCor Heart Failure and Arrhythmia Management System). Using the RF data, µCor provides an estimate of the thoracic impedance. In addition, the system records the electrocardiogram (ECG) through adhesive electrodes and respiration rate, activity, and posture through a tri-axial accelerometer. The purpose of this study is to correlate µCor readings with clinically actionable heart failure events during the ninety days after hospital discharge. In addition, the rate of occurrence of VT/VF episodes and arrhythmic death in patients with an LVEF greater than 35% will be observed.

1.2 Preclinical Data

In animal testing, µCor's noninvasively determined RF thoracic fluid content was compared with invasive thermodilution extravascular lung water measurements (PiCCO - Pulsion Medical Systems, Munich, Germany). Pulmonary edema was induced in 15 sheep by intravenous volume and pressure overload. µCor was placed on the left lateral torso of the sheep. The emitted and reflected RF signals are used by µCor to assess thoracic fluid. These readings were compared with the readings from the PiCCO device. Results of the study showed that all 15 sheep developed increases in left ventricular end diastolic pressure, and the onset of pulmonary congestion and edema. A consistent linear correlation ($r = 0.97$) between measurements of invasive lung water fluid and noninvasive thoracic fluid content was observed. µCor RF signals were able to detect dynamic accumulation of lung water in the range of 50-60 ml increments. The change in lung water needed to produce congestion was between 250-500 ml. The results of this study support the use of ZOLL's external RF sensor for high resolution and precise fluid monitoring.

1.3 Clinical Data to Date

A validation study was conducted in human subjects to compare µCor noninvasively-determined RF thoracic fluid content with invasive thermodilution extravascular lung water

measurements (PiCCO - Pulsion Medical Systems, Munich, Germany). 36 patients in critical care unit with a clinical indication for thermodilution based extravascular lung water monitoring were studied. uCor was placed on the patients left chest. Noninvasive thoracic fluid assessment was compared to the invasive extravascular lung water measurement every 30 minutes. Cardiac output, systolic and diastolic blood pressure, and heart rate were also measured. Results showed that the pooled correlation between measurements of invasive lung water fluid and noninvasive thoracic fluid content was excellent (r = 0.86). Also, increases in lung water of 90 ml could be detected by the RF signal. Furthermore, lung water change did not correlate to systolic blood pressure, diastolic blood pressure, cardiac output, and cardiac index (correlation range, r = 0.12-0.54). This study demonstrated accuracy and usability of this RF technology to support its use for high resolution fluid monitoring in patients.

1.4 Study Device

1.4.1 **System Components**

µCor consists of the following components:

A) Patch
B) Sensor
C) Charger
D) Data transmission device (Gateway)
E) Server

Once activated, the wearable Sensor automatically acquires ECG, RF readings, heart rate, respiration rate, activity, and posture measurements. Data are automatically transmitted from the Sensor to the Data transmission device, and from there to the Server for analysis (see Fig. 1).

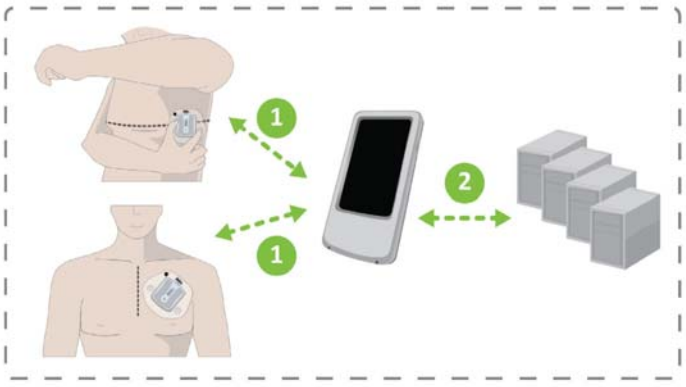

Figure 1: Data transmission of µCor

1.4.2 Patch

The Patch (Fig. 2) consists of a plastic frame intended for housing the Sensor, and two ECG electrodes on each side of the frame. The Patch is a single-use, disposable item.

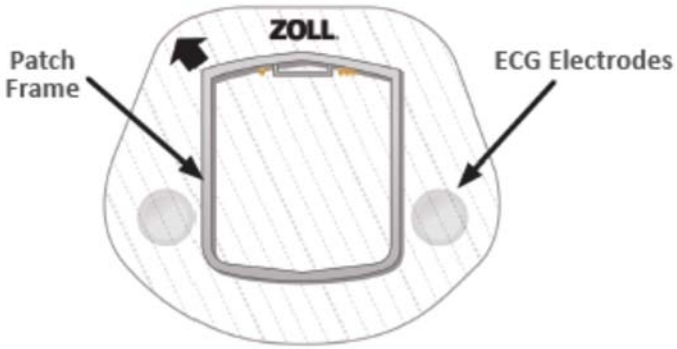

Figure 2: Patch

1.4.3 Sensor

The Sensor (Fig. 3) is a battery powered unit that acquires data. The Sensor connects to the Patch via the snap-in clip and positioning tabs. Through the adhesive backing on the Patch, the device becomes wearable. The Sensor is not disposable and needs to be returned to ZOLL upon the completion of the study. A light indicator is located close to the center and serves to communicate the Sensor's status at different points of use. Note that the light indicator is visible only when lit.

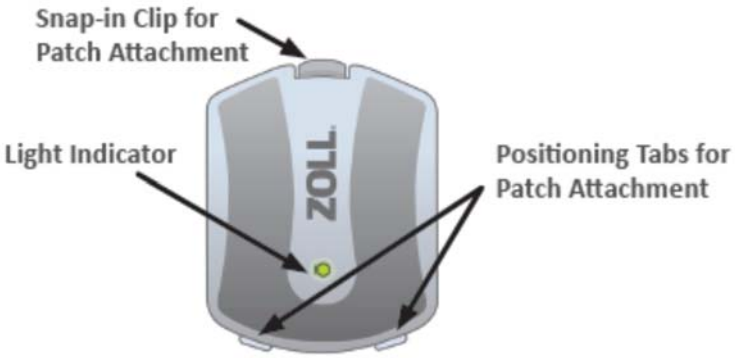

Figure 3: Sensor's front view

1.4.4 Charger

A dedicated Charger (Fig 4) is supplied with the µCor System for recharging the Sensor and the Data Transmission Device. A blue light appears when the Charger is connected to an AC outlet.

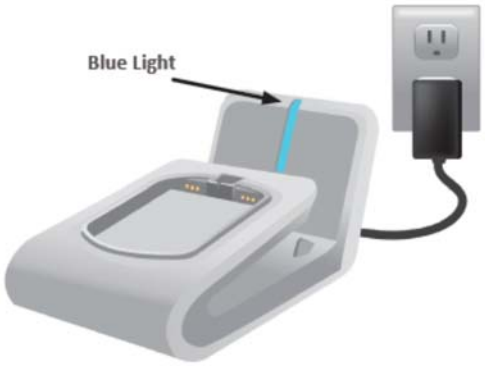

Figure 4: Charger

1.4.5 Data transmission device (Gateway)

A Data Transmission Device or Gateway is responsible for sending data from the Sensor to the Server for data analysis. When the screen display is on, the gateway battery status is visible on the screen. Once the battery status is under a certain level, a short beeping sound will be made every few minutes until the battery is depleted or the Gateway is placed in the Charger.

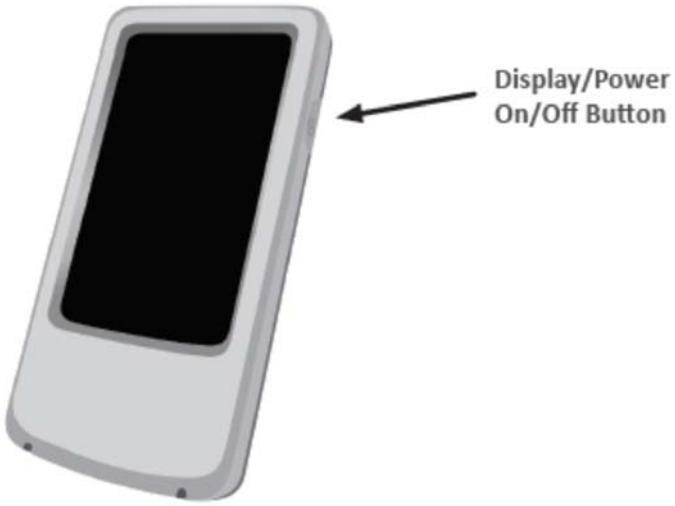

Figure 5: Gateway

1.4.6 Server

The Server refers to the hardware and the processing software and resides in a remote cyber-secure location. The software analyzes the data received from the Sensor via the Gateway and processes the data into clinical values.

1.4.7 Device (Sensor +Patch) Placement Location

There are two locations for device (Sensor + Patch) placement: (1) along the left anterior axillary line in line with the nipple (side location) and (2) along the left mid-clavicular line, above the nipple and below clavicle.

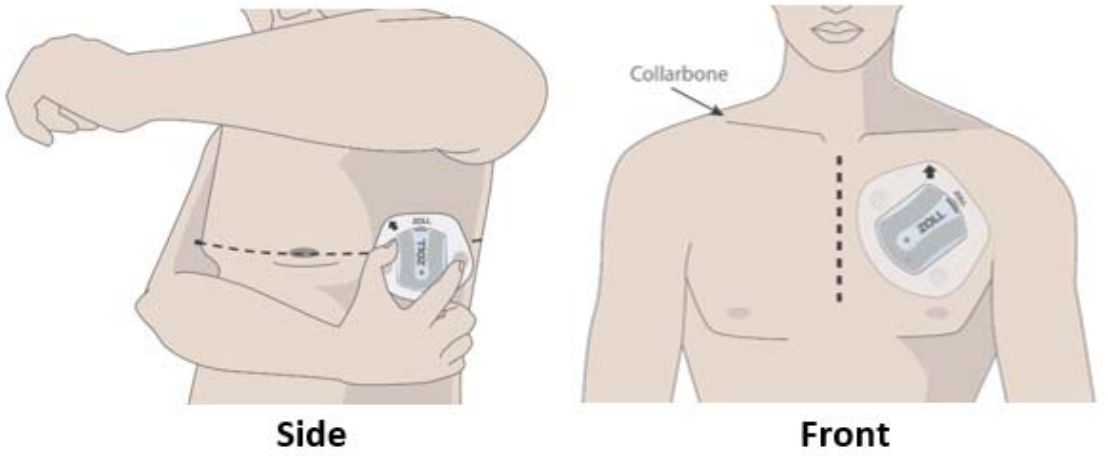

Figure 6: Device (Sensor + Patch) placement location. Side location is the left anterior axillary position. Front location is the left mid-clavicular position.

2 Study Objectives

2.1 Primary Objective(s)

The following primary objectives will be evaluated during the wear period of the μCor device:

2.1.1 To identify correlations between μCor measurements (thoracic fluid index, cardiac rhythm, respiration rate, physical activity, and posture) with occurrences of heart failure related clinical events occurring within 90 days of hospital discharge for acute decompensated heart failure.

2.2 Secondary Objective(s)

The specific secondary objectives that will be evaluated during the entire study include:

2.2.1 To identify the rate of occurrence of VT/VF and arrhythmic death in heart failure patients based on left ventricular ejection fractions (LVEF).

2.2.2 To identify correlations between μCor measurements (physiologic variables including thoracic impedance, cardiac rhythm, respiration rate,) and patient reported symptoms.

2.2.3 To identify the hospital admission rate of patients during the study period.

2.2.4 To identify the hospital admission rate of patients in the previous 90 days before enrollment into the study.

2.2.5 To define the mortality rate, cause of death, and health care utilization among patients six months and one year after enrollment into the study.

2.3 Safety Objective(s)

To document the number and severity of all adverse events that are causally related to the μCor system.

2.4 Additional Objective(s)

NA

3 Study Design

3.1 General Design

3.1.1 Study Description

Subjects meeting the inclusion/exclusion criteria will wear μCor for up to 90 days from the day of fitting. 500 total patients will be enrolled. There will be an interim analysis when the 200th subject has finished the study to assess for distribution of patients with reduced and preserved LVEF. The first 200 subjects enrolled in the US will exclusively wear the device in the side position. The subsequent subjects in the US will follow an alternating pattern of front position and side position placement.

Subjects will be fitted with μCor during discharge of a heart failure related hospitlatization or within a clinic visit that has occurred within 10 days of a heart failure related hospitalization. The μCor fitting will mark day 0 of the study. An LVEF measurement will be recorded during enrollment or within 30 days post enrollment if an LVEF measurement has not been recorded within 30 days prior to enrollment. An investigator assessment will be performed during all clinic visits. The assessment template is shown in Appendix A.

Subjects will be given a diary at enrollment that will ask them to rate their degree of specific symptoms of heart failure such as shortness of breath and fatigue as well as mark any heart failure related clinical events or medication changes that have occurred since the last entry. The subject diary is shown in Appendix A.

Study follow up visits will occur at day 30, day 60, and day 90. There will be no follow up visit if the subject has stopped wearing the device. During follow up visits the subjects will be asked about any heart failure related clinical events or change in symptoms that have occurred since the last follow up. The subject will receive a study based weekly phone call asking the subject about any recent heart failure related clinical events or change in heart failure symptoms. During the weekly phone call the subject will be reminded to fill out the daily diary. No phone calls will be given on the week where there is a study follow up visit. There will be no follow up visit if the subject has stopped wearing the device. In case of adverse skin reaction to the μCor adhesive and/or electrodes, on the discretion of physician, subjects may discontinue wearing the device for

up to 48 hours. In the event the subject has stopped wearing the device completely, follow up phone calls will continue to be conducted per protocol in order to capture clinical information.

During the Day 90 visit, the subject will be given the option to continue wearing the µCor for an additional 90 days. Furthermore, if the subject experienced a heart failure related clinical event within the initial 90 days of wear, the subject will be given the option of wearing the µCor for 30 days following the heart failure event. If the subject chooses additional wear time, weekly phone calls and monthly visits will be structured identical to that of the main study period. The µCor will be returned at end of use.

There will be a follow up at six months and one year post enrollment to document mortality data, heart failure related clinical events, and health care utilization data. A timeline visualization of the study procedure is shown in Figure 7.

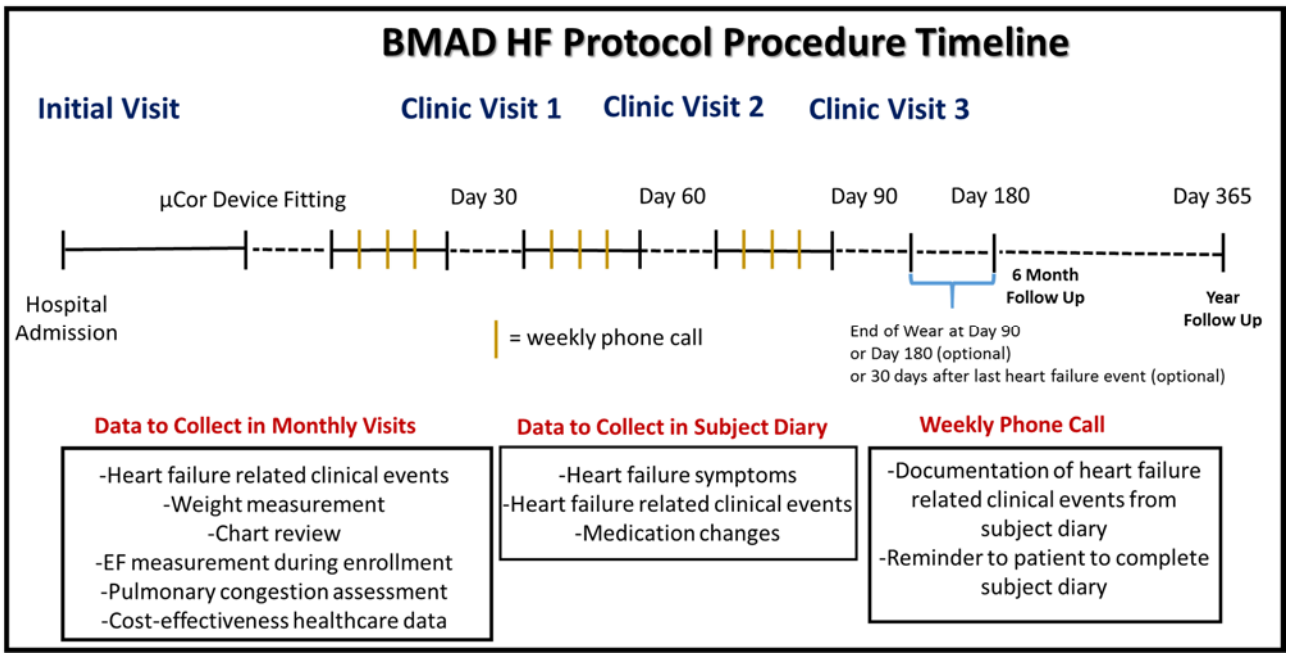

Figure 7: Procedure Flow of BMAD Study

3.1.2 Expected Duration of the Study

The anticipated enrollment period will be 1 year. The total anticipated study period will be 2.5 years.

3.2 Primary Study Endpoints

The primary endpoints that will be evaluated at the end of the study include:

3.2.1 Correlation of µCor readings (thoracic fluid index, cardiac rhythm, respiration rate, posture, and physical activity) to clinical events

3.3 Secondary Study Endpoints

The various secondary endpoints that will be evaluated during the entire study include:

3.3.1 Establishment of rate of occurrence of VT/VF episodes and arrhythmic death in patients.

3.3.2 Correlation between µCor measurements and patient reported symptoms

3.3.3 Frequency, timing, and severity of patient reported symptoms

3.3.4 Hospital readmission rate during the study period

3.3.5 Hospital readmission rate during previous 90 days prior to enrollment in study.

3.3.6 Cost-effectiveness data that supports a benefit in quality adjusted life years (QALY)

3.3.7 Mortality, heart failure related events, and health care utilization data at six months and one year post enrollment

3.4 Safety Endpoints

All adverse events related to the use of the µCor will be used to assess safety during the study.

4 Study Subject

4.1 Inclusion Criteria

The following criteria will be used to include subjects in the study: An acute heart failure event requiring medical management is defined in section 6.1.3.

4.1.1 Subjects being discharged from the hospital for acute decompensated heart failure either HFrEF (systolic) or HFpEF (diastolic) OR subjects who have been discharged from the hospital with either HFrEF (systolic) or HFpEF (diastolic) within the previous 10 days.

4.1.2 Subjects who have had an acute heart failure event requiring medical management in the previous 6 months.

4.1.3 Subjects 21 years of age or older on the day of screening.

4.2 Exclusion Criteria

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

4.2.1 Subjects who are wearing the wearable cardioverter defibrillator (WCD)

4.2.2 Subjects not expected to survive one year from enrollment from non-cardiac disease.

4.2.3 Subjects with skin allergy or sensitivity to medical adhesives.

4.2.4 Subjects anticipated to start dialysis within 90 days.

4.2.5 Subjects currently implanted with an S-ICD system.

4.2.6 Subjects who received a percutaneous coronary intervention (PCI) less than 24 hours after onset of heart failure related symptoms during index hospitalization.

4.2.7 Subjects who are unable to participate in all follow up visits.

4.2.8 Subjects participating in any other research at time of enrollment.

4.2.9 Subjects currently implanted with an LVAD.

4.2.10 Subjects with self-reported pregnancy.

5 Study Enrollment Plan

5.1 Enrollment Strategy

Patient enrollment strategies may be targeted at both the investigator and the patient as a way to engage all interested parties and provide information materials for the study. Strategies may include patient and/or investigator focus groups, educational lectures, web sites, flyers, or brochures to assist in the recruitment and screening process, if needed. Any patient facing materials will be submitted for approval to the IRB.

5.2 Study Size

A total of 500 subjects.

5.3 Enrollment Period

The anticipated total enrollment period for this study is 1 year, with a total anticipated study period would be 2.5 years.

5.4 Early Withdrawal of Subjects

5.4.1 **When and How to Withdraw Subjects**

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

5.4.2 **Data Collection and Follow-up for Withdrawn Subjects**

Reason for subject withdrawal from the study, if known, will be documented and all study data will be retained for data analysis. All possible attempts should be made to obtain follow up data at the end of study without contacting the subject. Only in the case of specific withdrawal of consent of use of data will the subject's data be deleted from the database (if possible).

6 Study Procedures

6.1 Subject Recruitment and Screening

6.1.1 Subject recruitment

Subjects will be identified from chart review. Subjects may be recruited in both inpatient and outpatient settings. The investigator will discuss the details of the clinical study including benefits and risks of participating in the study prior to enrollment.

6.1.2 Subject screening

Subject chart review will take place based on the inclusion/exclusion criteria.

6.1.3 **Screening definitions**

An acute heart failure event requiring medical management is defined as a hospitalization, emergency room visit, observation unit visit, or unplanned clinic visit where medical management or treatment for HF related pulmonary congestion is administered.

6.2 Scheduled Visits and Phone Calls

The scheduled visits are summarized in Table I and include the initial visit along with visits at day 30, 60, and 90. There will also be weekly phone calls to the patient. No monthly visits or weekly phone calls will occur if the subject has stopped wear. The phone calls will be conducted within no more than 2 days before or after the scheduled date. The scheduled visits will be conducted within no more than 5 days before or after the scheduled date. During the optional extended 90 day wear period, scheduled clinic visits and weekly phone calls will continue to take place following the procedures in Visits 2-4 with the exception of 6.2.4.6 (asking again for additional wear). Chart review and a follow up phone call will take place at 6 months and 1 year post enrollment.

6.2.1 Visit 1: Screening, enrollment and start (To occur during hospital discharge for decompensated heart failure or during a clinic visit in an out-patient setting no more than 10 days post hospital discharge).

6.2.1.1 All subjects will complete the Kansas City HF and study specific questionnaire.

6.2.1.2 A chart review will be used to evaluate patients for enrollment. A screening log will be maintained.

6.2.1.3 Patients meeting the initial Inclusion/Exclusion criteria will be approached for consenting.

6.2.1.4 The initial clinical and demographic data will be recorded in every subject. These may be done by chart review and will include:

6.2.1.5 Demographic characteristics, including gender, age, height and weight will be recorded.

6.2.1.6 Medical history will be recorded, including comorbidities, heart disease and physical disability.

6.2.1.7 Medical therapy for heart failure will be recorded for all subjects.

6.2.1.8 LVEF measurement within the past 30 days will be recorded if available. If a previous LVEF is not available, one will be obtained within 30 days of enrollment.

6.2.1.9 Subjects will be given a physical assessment.

6.2.1.10 Subjects will be assigned to wear the patch at either the front or side location (alternating 1:1)

6.2.1.11 Subjects will be fitted with μCor at hospital discharge or departure from clinic.

6.2.1.12 Device fitting will follow current Instructions for Use (IFU) procedures.

6.2.1.13 The date and time when μCor wear began will be recorded.

6.2.1.14 A clinic visit appointment will be scheduled to coincide with the end of the first 30 days of μCor wear.

6.2.1.15 The subject's weight will be obtained.

6.2.1.16 The subject's previous 90 day hospital admission rate will be determined through chart review.

6.2.2 Visit 2: μCor Wear Day 30.

6.2.2.1 All subjects will complete the Kansas City HF and study specific questionnaire.

6.2.2.2 An in-center appointment will be scheduled to coincide with the end of 60 days of μCor wear.

6.2.2.3 All subjects will be asked about the following events since their last visit:

- Any medication changes
- Any physician visits, both planned and unplanned
- Any hospitalization, including heart failure hospitalization
- Any emergency room visits
- Any symptoms, including syncope, dyspnea, palpitations and chest pain

6.2.2.4 A weight measurement will be obtained.

6.2.2.5 Subjects will be given a physical assessment

6.2.3 Visit 3: μCor Wear Day 60.

6.2.3.1 All subjects will complete the Kansas City HF and study specific questionnaire.

6.2.3.2 An in-center appointment will be scheduled to coincide with the end of 90 days of μCor wear.

6.2.3.3 All subjects will be asked about the following events since their last visit:
- Any medication changes
- Any physician visits, both planned and unplanned
- Any hospitalization, including heart failure hospitalization
- Any emergency room visits
- Any symptoms, including syncope, dyspnea, palpitations and chest pain

6.2.3.4 A weight measurement will be obtained.

6.2.3.5 Subjects will be given a physical assessment.

6.2.4 Visit 4: μCor Wear Day 90.

6.2.4.1 μCor use will be discontinued unless patient enters optional additional wear period.

6.2.4.2 All subjects will complete the Kansas City HF and study specific questionnaire.

6.2.4.3 All subjects will be asked about the following clinically actionable events:
- Any medication changes
- Any physician visits, both planned and unplanned
- Any hospitalization, including heart failure hospitalization
- Any emergency room visits
- Any symptoms, including syncope, dyspnea, palpitations and chest pain

6.2.4.4 A weight measurement will be obtained.

6.2.4.5 Subjects will be given a physical assessment

6.2.4.6 Subjects will be asked if they would like to continue wear for an additional 90 days. If the subject had experienced a heart failure related clinical event within the previous 90 days, the subject will also be given the option to continue wear for 30 days following the most recent heart failure event.

6.3 Unscheduled Visits

NA

6.4 Long-term Clinical Outcome Assessment

The subject will receive a follow up phone call 6 months and 1 year from the enrollment date to assess for mortality status, heart failure related clinical events that have occurred since the end of µCor wear, and any health care utilization that has occurred since the end of µCor wear. A chart review will be performed during both of these calls as well. Subjects will answer mailed heart failure questionnaires and mail the questionnaires back to the site.

6.5 Study Procedures Flowchart (or Table)

Summary of the activities and procedures to be followed at each visit is as described below (Table 1).

	Visit 1	Visit 2	Visit 3	Visit 4	6 Months	1 Year
Eligibility Screening	X					
Consent	X					
Enrollment	X					
Physical Assessment	X	X	X	X		
µCor Setup	X					
EF Documentation*	X					
HF Event Documentation	X	X	X	X	X	X
Weight Documentation	X	X	X	X	X	X
HF Questionnaires	X	X	X	X	X	X

Table 1: Visit Procedure List (*All EF measurements will be documented if clinically indicated)

6.6 Weekly Phone Calls

There will be weekly phone calls to the subject to monitor changes in the health status of the subject. These calls will be performed by the site. The calls will reiterate the importance of completing the daily subject diary and document any health care usage by the subject. The calls will also document any heart failure related clinical events reported by the subject. No phone calls will occur if the subject has s topped wear.

6.7 Blinding and Unblinding of Study

During the study, physicians and subjects will be blinded to all µCor data. If the sponsor observes a potentially life threatening arrhythmia, the site will be notified.

7 Study Device Management

The µCor device log will be managed by the sponsor. The sites will keep a device log of all available µCor devices and make necessary requests to the sponsor when inventory is low. The study site will collect the device when the patient has ended wear. All used and unused devices will be returned to the sponsor when the study is completed. The investigator will be responsible for subject device accountability.

7.1 Subject Compliance Monitoring

µCor wear time will assessed throughout the study period. Wear time will be monitored by the sponsor based on the daily data transmissions from the µCor device. It is anticipated that the wear time with µCor system will be over 70% through the study period. For subjects who show early signs of non-compliance, the sponsor will inform the site, who will then make phone-calls to encourage subjects to continue wear the µCor system. In addition, site with the support of sponsor's technical support will try to trouble shoot and alleviate the reasons for subject's non-compliance.

7.2 Managing µCor Therapy

NA

7.3 Dispensing, Storage and Return

7.3.1 **Dispensing of Study Device**

The investigator will be responsible for dispensing the study device.

7.3.2 **Storage**

Devices will be stored in an appropriate limited access room. Storage conditions will adhere to the guidelines outlined in the Clinical Manual.

7.3.3 **Return of Study Device**

Return of the device will occur during the final scheduled visit.

7.4 Device Malfunction or Defect

In case of device malfunction or defect, subjects will call the site for initial troubleshooting. If the site cannot resolve the issue, the sponsor will be contacted for further troubleshooting. In case the defect or malfunction cannot be resolved, the sponsor will provide new equipment. All device defects of malfunctions related to device defect or malfunction will be reported to the sponsor on the appropriate CRF.

8 Statistical Plan

8.1 Sample Size and Power Calculation

The sample size was chosen to answer the primary and secondary objectives. We expect a 50/50 distribution between patients enrolled with an LVEF less than 35% and an LVEF greater than 35%. After the 200th patient is enrolled, we will conduct an interim analysis to confirm the LVEF distribution.

The first 200 patients will generate a convenience sample of heart failure related clinical events Assuming a 20% event rate within the first 30 days in patients with reduced LVEF, we estimate that we will observe at least 25-30 heart failure related events among patients with reduced EF through the length of the 90 day study period (accounting for not all patients reaching completion).

We believe that 25-30 heart failure related events will be enough events to draw meaningful correlations among μCor device measurements and heart failure related episodes.

Following the interim analysis, the additional 300 subjects will further generate heart failure related clinical events to answer the primary objective and be monitored for VT/VF arrhythmic events to answer the secondary objectives.

8.2 Randomization Scheme

The first 200 subjects in the US will exclusively wear the patch in the side position. In the following 300 subjects, the position of the patch location will be alternated by subject to either front or side location in a 1:1 scheme, stratified by site. Outside the US, all subjects will follow an alternating pattern of patch location wear.

8.3 Endpoint Assessment

8.3.1 Primary endpoint

The first primary endpoint will be assessed by the strength of the correlation between μCor device readings and heart failure related clinical events.

8.3.2 Secondary endpoints

The secondary endpoints will also be assessed on their strength of correlation as well as the magnitude of rate of occurrence of VF/VT and arrhythmic death in the subjects with an LVEF greater than 35%.

8.4 Statistical Methods

For primary, secondary, and safety endpoints, descriptive statistics and qualitative analysis will be performed as appropriate.

8.5 Additional Statistical Analysis

NA

8.6 Handling Missing Data

As with any clinical study, missing data are to be expected during this study.

8.6.1 Sources of Missing Data

8.6.1.1 Medical records not available

8.6.1.2 Subjects who are lost to follow up

8.6.1.3 Device error

8.6.1.4 Missed phone calls

8.6.1.5 Missed visits

8.6.2 Preventing Missing Data

8.6.2.1 All attempts to maintain contact with the subject should be made by study personnel to assure that lost to follow up subjects are kept to a minimum. This may involve telephone calls. Multiple phone numbers/contacts for each subjects should be collected. Multiple reminders of upcoming visits should be made.

8.6.2.2 Reasonable windows of time (within 2 days for phone calls and 5 days for clinic visits) have been employed.

8.6.2.3 Routine site monitoring with data verification will occur throughout the study.

8.6.3 Handling missing data

8.6.3.1 Missing data will not be replaced by any algorithm.

8.6.3.2 If a subject is missing more than 50% of data, the subject's data will not be included in the analysis.

8.7 Futility Analysis

The study will be considered ineffective if the interim analysis determine the study will be unsuccessful enrolling the required number of subjects (≥1 subject per center-month), or if occurrence of the primary endpoint is deemed insufficient to successfully complete the study with the planned number of subjects.

Both an interim and futility analysis will be performed once the 200th subject has completed wear time. Primary and secondary endpoints will be assessed. With 200 patients completing wear time, it is expected that there would be about 25 -30 heart failure related clinical events. If during the interim and futility assessments, there are less than 5 heart failure events, a protocol change will be considered.

9 Health Economic Evaluation

The Kansas City Heart Failure Questionnaire will be given to the subjects at all monthly clinic visits. We will develop a model to examine the costs and benefits of using uCor. The model will use data from our review of monthly collected questionnaire, heart failure event, as well as data from recognized sources (e.g. national published data, finance department of hospital), and experts' advice

10 Safety and Adverse Device Effects

10.1 Definitions

All device related adverse effects will be recorded during the study. All adverse device effects (ADEs) will be classified by the investigator as anticipated or unanticipated.

10.1.1 **Foreseeable Adverse Device Effects with Study Device**

The most common foreseeable adverse event is skin rash. This is expected to occur in a small minority of patients.

10.1.2 **Unanticipated Adverse Device Effect (UADE)**

An unanticipated adverse device effect (UADE) is any adverse device effect not identified by nature, severity or frequency prior to the investigation. When the frequency of an ADE exceeds the previously reported frequency or pre-specified accepted level, and if such ADE is critical in evaluating one or more of the study endpoints (such as safety endpoint), then an ADE can become an UADE and it must be properly reported and evaluated.

10.2 Recording and Reporting of Adverse Device Effects

10.2.1 **Investigator Recording and Reporting**

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

The Investigator must next assess the seriousness of the adverse device effect. The Investigator should also assess whether the adverse device effect is anticipated or unanticipated. At each contact with the subject, the investigator must collect information on adverse device effects.

All adverse device effects occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse device effects that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse device effects that occur within 30 days after the study period should be recorded and reported promptly. The report will be sent to the medical monitor.

10.3 Protocol Deviations

Deviations from the protocol must receive both Sponsor and the investigator's IRB approval before they are initiated unless subject safety is at risk. Any protocol deviations initiated without Sponsor and the investigator's IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be reported to the Sponsor and to the investigator's IRB as soon as a possible, but no later than 30 working days (or less if specified by the investigator's IRB).

11 Administrative Responsibilities

11.1 Sponsor

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

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

11.2 Investigators

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

11.3 Data Coordination Center (DCC)

The Sponsor will act as the Data Coordination Center (DCC) and has responsibility for clinical data coordination. The DCC will provide management of data for the overall project. All case report forms will be collected directly by the DCC.

11.4 Steering Committee

There is no steering committee for this study.

11.5 Data Safety Monitoring Board (DSMB)

The study will be monitored by the Sponsor, who will periodically review all aspects of the trial to ensure the safety of the participants.

12 Data Collection and Management Plan

12.1 Data Collection

Anonymized subject data will be collected from original source documents and transcribed into the eCRFs. An electronic data capture (EDC) system with single entry capture will be used. Queries generated manually or by algorithm will be managed within the EDC system. LVN data will be anonymized and imported directly into the research database.

12.2 Data Handling and Record Keeping

12.2.1 **Source Documents**

Source data is all information, original records of clinical findings, observations, or other activities and are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete,

microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. Both ZOLL and Investigators will maintain and retain applicable source data as per the regulations

12.2.2 **Case Report Forms (CRFs)**

Data will be collected at the investigational sites using the electronic data capture (EDC) system Clindex*LIVE* (Fortress Medical Systems, LLC, Hopkins, MN). Electronic Case Report Forms (eCRFs) will be implemented within Clindex*LIVE* by ZOLL's Clinical Data Manager. Data will be entered at the investigational sites by trained staff. Entered data will be reviewed by the site investigator, who will affirm its accuracy and completeness by electronic sign-off. All data queries, whether automatically or manually generated, will be communicated to and cleared by investigational site staff via Clindex*LIVE*. A final comprehensive review of all of the data will occur at the conclusion of the trial. All queries will be resolved and all eCRFs will be electronically signed by appropriate site investigators prior to database lock.

12.2.3 **Electronic Data Capture (EDC) System**

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

12.3 Data Transmission from Sponsor

NA

12.4 Study Monitoring Plan

Monitoring activities will be conducted according to the Sponsor's standard operating procedure.

13 Risks and Benefits

µCor is a noninvasive medical monitoring device. Common risks associated with devices using medical adhesives include but are not limited to discomfort, skin irritation, itching, rash, contact dermatitis, or breaching of skin if the patch adhesive is the removed too quickly.

No study specific benefits to participation are anticipated.

14 Ethical Considerations

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

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

14.1 Subject Consent and Confidentiality

All subjects for this study will be provided an information and consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Document 90D0182_ICD for a template of the Subject Informed Consent Form. This informed consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the EC/IRB-approved informed consent form, must be obtained before that subject undergoes any study specific procedure.

Each subject will receive a unique anonymous subject identification number. The subject's name and identity will be known to the local principal investigator. The relevant IRB and regulatory authorities may have access to original subject records.

At the end of the data collection period, a fully de-identified, Health Insurance Portability and Accountability Act of 1996 (HIPAA) compliant dataset will be created using all variables available from the Case Report Forms and device data. This dataset will be used for analysis and publication purposes.

14.2 Subject Financial Responsibility and Stipends

14.2.1 Subject Financial Responsibility

The cost of a subject's ongoing medical care that is not study specific and would have occurred in the absence of the study will remain the responsibility of the subject. Sufficient study devices will be provided to the Investigator at no cost to the subjects. At end of use the subjects will return the devices to the Investigator.

15 Publication Plan

15.1 Authorship

The **publication committee** will consist of the following members:

1) The sponsor's Vice President of Medical and Clinical Affairs and/ or their representatives, up to three individuals in total.
2) Investigator members will be chosen by the sponsor using the following criteria:
   A. Contribution to study design
   B. Contribution to patient enrollment
   C. Willingness to contribute to data analysis

D. Willingness to contribute to manuscript preparation

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

15.2 Data ownership

The database(s) resulting from this study are the property of the sponsor. Investigators will maintain and retain study records as per the regulations. The sponsor shall have access to all such records during this period with adequate prior notice and during normal business hours.

16 Intellectual Property and Patents

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

17 List of Abbreviations

ADE – Adverse Device Effect
CRF – Case Report Form
CRT – Cardiac Resynchronization Therapy
DCC – Data Coordination Center
DNR – Do Not Resuscitate
DSMB – Data Safety Monitoring Board
EC – Ethics Committee
ECG – Electrocardiogram
GDMT – Guideline Directed Medical Therapy
HIPAA – Health Insurance Portability and Accountability Act
ICD – Implantable Cardioverter Defibrillator
IRB – Institutional Review Board
LVEF – Left Ventricle Ejection Fraction
LVN – LifeVest Network
NYHA – New York Health Association
PHI – Protected Health Information
SCA – Sudden Cardiac Arrest
SCD – Sudden Cardiac Death
UADE – Unanticipated Adverse Device Effect
VF – Ventricular Fibrillation
VT – Ventricular Tachycardia

18 Bibliography

1. Gheorghiade M, Vaduganathan M, Fonarow GC, Bonow RO. Rehospitalization for heart failure: Problems and perspectives. *J Am Coll Cardiol*. 2013;61(4):391-403.

2. Zile MR, Bennett TD, St. John Sutton M, et al. Transition from chronic compensated to acute d compensated heart failure: Pathophysiological insights obtained from continuous monitoring of intracardiac pressures. *Circulation*. 2008;118(14):1433-1441.

3. Bhimaraj A. Remote monitoring of heart failure patients. *Methodist Debakey Cardiovasc J*. 2013;9(1):26-31.

4. Abraham WT, Stough WG, Pina IL, et al. Trials of implantable monitoring devices in heart failure: which design is optimal? *Nat Rev Cardiol*. 2014;11(10):576-585.

5. Sung S-H, Yu W-C, Cheng H-M, Chang Y-P, Chen C-H. Use of Acoustic Cardiography To Guide Outpatient Therapy of Patients With Acute Heart Failure Syndrome. *J Am Coll Cardiol*. 2014;63(12):A541

Appendix A

Signs/symptoms	0	1	2	3
Dyspnea	None	Seldom	Frequent	Continuous
Orthopnea	None	Seldom	Frequent	Continuous
Fatigue	None	Seldom	Frequent	Continuous
Jugular Venous Distension (cm)	≤6	6–9	10–15	≥15
Rales	None	At bases	At bases to 50% way up the posterior lung field	At bases to > 50% way up the posterior lung field
Pedal edema	Absent/trace	Slight	Moderate	Marked

Table 2: Investigator Assessed Congestion Survey

Month 1							
Subject Diary							
Please rate your symptom (0 = Good 10 = Bad)						Yes or No?	
		Symptom				Event	
Day	Date	Shortness of Breath	Fatigue	Cough	Swelling	Hospitalized?	Medication Change?
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
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18							
19							
20							
21							
22							
23							
24							
25							
26							
27							
28							
29							
30							

Table 3: Sample month of subject diary for reported symptoms