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

Short Title: BMAD Treatment

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

Study Device: *μCor*

Protocol Number: *90D0202*

IDE Number: *NA*

Version Date: Nov 1 *2019*

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 (BMAD Treatment
Short Title	BMAD Treatment
ZOLL Protocol Number	90D0202
Study Design	Prospective non-randomized study
Study Duration	The study duration will last an estimated 2.5 years with 2 year estimated for enrollment
Study Center(s)	Up to 80 centers (International)
Primary Objective(s)	To assess investigator engagement of μCor system data in the context of heart failure management
Study Population	Subjects hospitalized for acute decompensated heart failure and enrolled in the study within 10 days post-hospital discharge. All subjects require an additional heart failure event within the previous 180 days.
Intervention	Subjects meeting the inclusion/exclusion criteria will wear the μCor for up to 90 days. During the study, face to face follow up will occur every 30 days. For all subjects, each scheduled clinic visit will include assessment of cardiac signs, symptoms, and any relevant clinically actionable events. The subject will be given a daily diary to track symptoms, 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. The subject's health care provider team will receive the μCor data through reports delivered to the team by an independent clinical review team. The data updates will allow the health care provider team to take action when the data indicate worsening heart failure, within the context of standard of care medical practice and patient specific parameters. Weekly data reports will be delivered to the investigators. 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 300 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 fluid index (TFI). To calculate TFI, the thoracic fluid baseline is determined, and the normalized value is presented as TFI. In conjunction with standard clinical practice for patients with fluid balance issues, the direction of change of TFI over time may provide clinically useful information. In addition to TFI, 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 assess investigator engagement of μCor system data in the context of heart failure management.

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

NA

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.

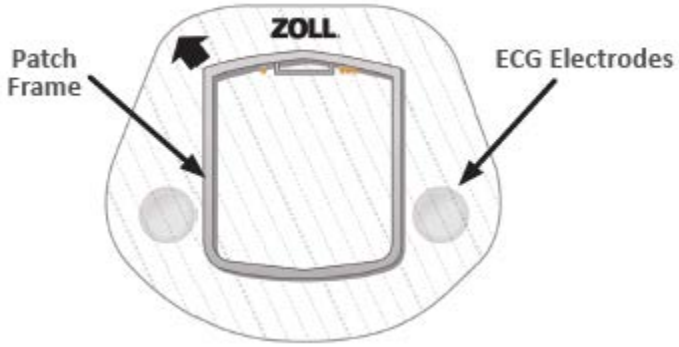

Figure 2: Patch

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.

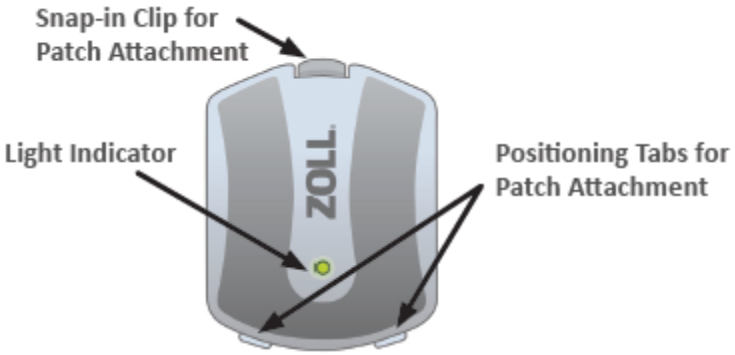

Figure 3: Sensor's front view

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.

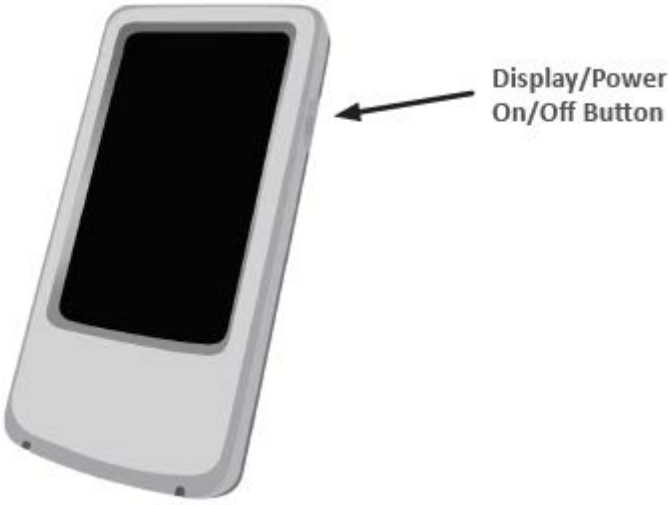

Figure 5: Gateway

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

The location of the patch is along the left anterior axillary line in line with the nipple.

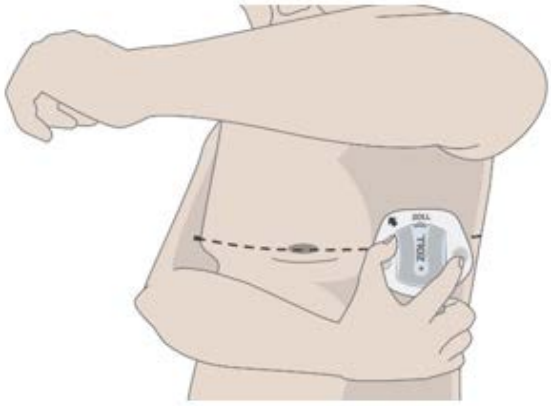

Figure 6: Device (Sensor + Patch) placement location.

2 Study Objectives

2.1 Primary Objective(s)

The following primary objectives will be evaluated during BMAD-Treatment:

2.1.1 To assess investigator engagement of μCor system data in the context of heart failure management

2.2 Secondary Objective(s)

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

2.2.1 To identify correlations between μCor measurements (physiologic variables including thoracic impedance, cardiac rhythm, respiration rate) and heart failure related clinical events. A heart failure related clinical event is defined in section 6.1.3.

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 readmission rate, physician visit rate, and outpatient clinic visit rate of subjects during the study period.

2.2.4 To identify the mortality rate, cause of death, quality of life (QoL), and health care utilization among patients six months and one year after enrollment into the study.

2.3 Safety Objective(s)

2.3.1 To document the number and severity of all adverse events that are causally related to the μCor system or study specific procedure.

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. 300 total patients will be enrolled. Subjects will be fitted with μCor during discharge of a heart failure related hospitalization 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. Any LVEF will qualify for the study. 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.

Phone calls will be based on weekly data reviews or data updates. A review of the data will be conducted by the site before the weekly phone call and the most recent (Transthoracic Fluid Index) TFI will be recorded. 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. The weekly phone calls will continue if the subject has stopped wearing the device. 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.

A review of the data will be conducted by the site before the office visit and the most recent TFI will be recorded. Study face to face 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.

Unplanned visits to the physician office or hospital will be captured and defined as visits that the subject did not plan beyond 48 hours. 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.

Data updates will be delivered to the site when the day averaged TFI exceeds a threshold greater than three standard deviations of the baseline TFI level for three consecutive days. Upon receiving a device data update, the investigator will receive detailed information into how the device measurements have tracked over the days leading up to the notification. When receiving a data update, the site will be required to review the most recent report within 24 hours, and explain their reasoning whether they choose to contact the subject or not to contact the subject. The data review must occur prior to every scheduled subject contact.

When acting upon the data update, the site may contact the subject to assess the subject's current symptoms and history, and make an informed decision within the context of both device measurements and standard medical care as to what actions to take with the subject. Potential actions the site could take will include, a prescription drug change or titration, a request for an office visit, a request for hospitalization, and request for lifestyle or diet modifications. The site will document any changes to subject care within the case report forms. Unscheduled contacts that the subject initiates will be recorded as well.

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.

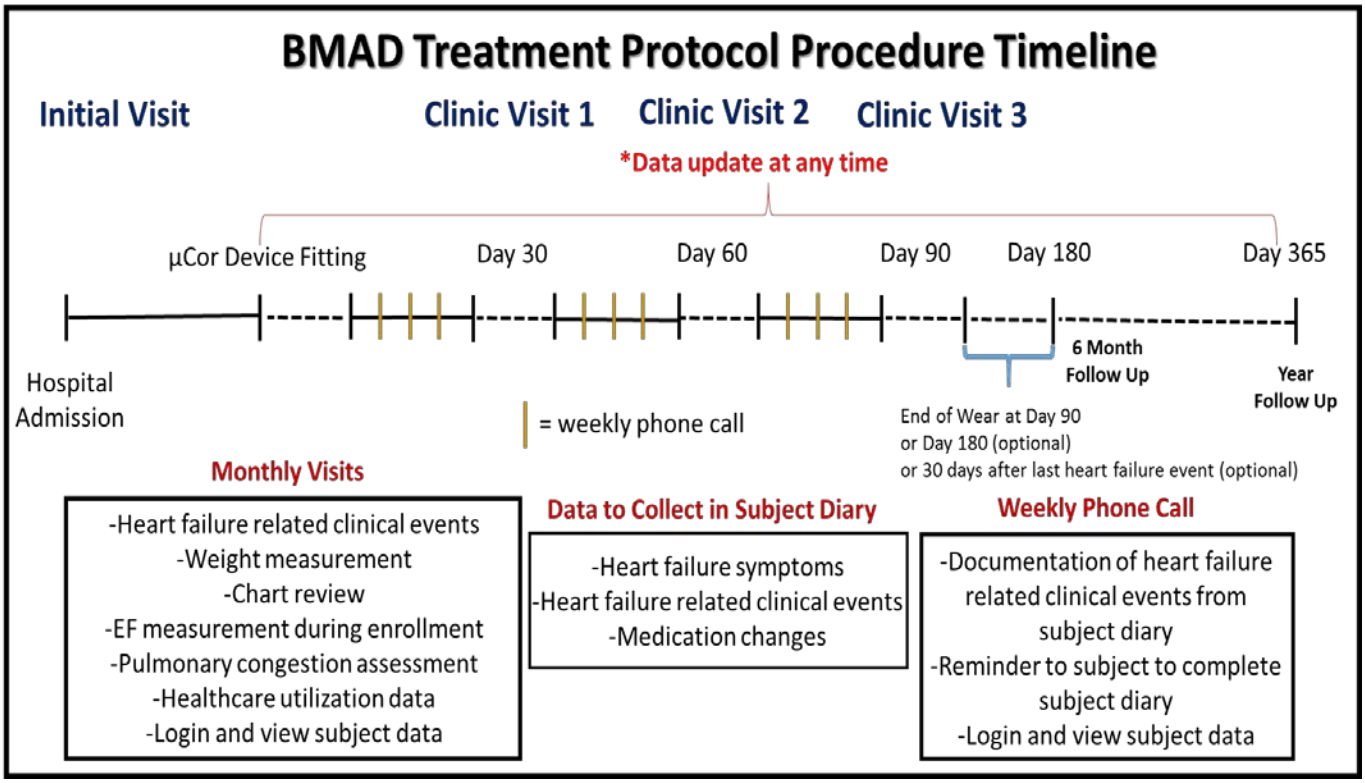

Figure 7: Procedure Flow of BMAD Treatment Study

3.1.2 Expected Duration of the Study
The anticipated enrollment period will be 2 years. The total anticipated study period will be 2.5 years.

3.2 Primary Study Endpoints

The primary endpoint that will be evaluated at the end of the study includes:

3.2.1 Investigator Engagement: Investigator engagement will be assessed at the study site level as well as across all study sites.

Investigator engagement will be assessed through the number of data updates delivered by the µCor subject management system, the time spent reviewing each data report, the number of medication changes based on µCor data, the number of lifestyle modifications that are recommended to the subject, the number of medication changes based on symptoms reported by subjects or from subject incidental findings, and the number of times high µCor measurements are reduced below threshold levels after medication was titrated or lifestyle modifications were recommended.

3.3 Secondary Study Endpoints

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

3.3.1 Correlation between µCor measurements and clinically related heart failure events.

3.3.2 Correlation between µCor measurements and subject reported symptoms.

3.3.3 Hospital readmission rate, physician visit rate, and outpatient clinic visit rate during the study period.

3.3.4 Mortality, heart failure related events, quality of life (QoL), and health care utilization data at 6 months and one year post enrollment.

3.4 Safety Endpoints

3.4.1 The number and severity of all adverse events that are causally related to the µCor system or study specific procedure.

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. The index hospitalization and six month prior event must have started two weeks apart from one another.

4.1.1 Subjects hospitalized for acute decompensated heart failure and enrolled in the study within 10 days post-hospital discharge.

4.1.2 Subjects who have had an acute heart failure event requiring medical management in the previous 180 days of index hospitalization admission. This acute heart failure event admission must be at least 2 weeks apart from the event admission in 4.1.1

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 research other than a non-interventional registry at the time of enrollment.

4.2.9 Subjects currently implanted with an LVAD.

4.2.10 Subjects with self-reported pregnancy.

4.2.11 Subjects currently being actively managed with any device based remote HF monitoring.

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 300 subjects.

5.3 Enrollment Period

The anticipated total enrollment period for this study is 2 year, with a total anticipated study period would be 2.5 years.

5.3.1 Data Usage, Informed Consent and Reflection Period

All subjects will 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 subject to a central scientific database. Sufficient time will be allowed for data usage information to be read and for questions to be asked during the informed consent process. The subjects will be informed that withdrawal of their consent in the clinical study is possible at any time and that a withdrawal is possible without stating a reason, is conducted without prejudice, and does not place the subject at any disadvantage in the study. The subject will receive detailed training on the use of the device by the site researcher. This will give the subject the opportunity to raise further questions about the device and data handling to the responsible physician.

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, Subject Screening, and Definitions

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 Definitions

An acute heart failure event requiring medical management, and a heart failure related clinical event, 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 face to face visit along with face to face visits at day 30, 60, and 90. There will also be weekly phone calls to the patient. No monthly visits 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 subject wear, phone calls will be accompanied by the weekly data review. The data review will need be completed before the phone call. There will be a weekly report sent to the site.

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, study questionnaires, 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 Patients meeting the initial Inclusion/Exclusion criteria will be approached for consenting.

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

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

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, and height will be recorded.

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

6.2.1.7 All medications will be recorded.

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 (US Sites) Device training will be given to the subject.

6.2.1.11 (European Sites) Subjects will be fitted with μCor at hospital discharge or departure from clinic.

6.2.1.12 (European Sites) Device fitting will follow current Instructions for Use (IFU)

6.2.1.13 (European Sites) 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 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

6.2.2.6 Daily cardiac medications taken by the subject will be reviewed and compared to the last listed cardiac medications documented by the study. Any new cardiac medications or changes in medication will be recorded (i.e. dosage changes or new medications administered)

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 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.

6.2.2.6 Daily cardiac medications taken by the subject will be reviewed and compared to the last listed cardiac medications documented by the study. Any new cardiac medications or changes in medication will be recorded (i.e. dosage changes or new medications administered)

6.2.4 Visit 4: μCor Wear Day 90.

6.2.4.1 μCor use will be discontinued unless subject 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 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

6.2.2.6 Daily cardiac medications taken by the subject will be reviewed and compared to the last listed cardiac medications documented by the study. Any new cardiac medications or changes in medication will be recorded (i.e. dosage changes or new medications administered)

6.2.4.7 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

6.3.1 Clinic visits, ED visits, and hospitalizations that have resulted from a device data update will be defined as unscheduled events. Separately, all heart failure related contact with the subject either initiated by the subject or the site will be defined as an unscheduled visit. Heart failure contact includes, but is not limited to, contact with the subject concerning new or worsening heart failure symptoms such as dyspnea, pedal edema, and shortness of breath.

6.3.2 Upon receiving a data update, which will be initiated when the day averaged TFI readings have exceeded for three consecutive days a threshold defined by three standard deviations of baseline TFI, the site study team will reach out to the subject within 24 hours. The data update will be delivered to the site via either fax, email, or phone call.

6.3.3 The investigator will make a decision whether to contact the subject or take no further action based on the data update, and document the reason. There will be a structured interview between the investigator and subject. The investigator will have access to a report that displays the device data.

6.3.4 If the subject is called after device data update, the subject's symptoms and recent history will be documented, and a medical decision, within the context of standard of care,

will be given to the patient. The medical decision may include assessment with no action required, adjusting or starting new medication, requesting an office visit, requesting and ED visit, requesting a lifestyle/diet change, requesting a hospital admission, or no change at all. All decisions will be documented.

6.4 Long-term Clinical Outcome Assessment

The subject will receive a follow up phone call 6 months (180days) and 1 year (365 days) 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. These follow-up calls must occur within +/- 2 weeks of the scheduled call.

6.5 Study Procedures Table (For all scheduled visits)

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

Table 1: Visit Procedure List (*Only for sites outside the US. **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. The calls will be accompanied by a weekly data review of the subject's µCor data that will occur before the subject is contacted. If the study site determines that a change in medical care or lifestyle recommendation is warranted based on the data review, the site will document all such changes.

6.7 ECG Monitoring

ECG will be recorded by the device continuously during the study, but will not be included in any real-time reports or update reports to the physician.

7 Study Device Management

Sites Located Within the United States
The μCor device management will be managed by the sponsor.

Sites Located Outside the United States
Sites outside the United States 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 subject 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, the site, with the support of sponsor's technical support, will try to troubleshoot and alleviate the reasons for subject's non-compliance.

7.2 Managing μCor Therapy

NA. The μCor is a monitoring device

7.3 Dispensing, Storage and Return

7.3.1 **Dispensing of Study Device**

Sites Located Within the United States
The sponsor will be responsible for dispensing the study device. In order to initiate device dispensing in a timely matter, the site will inform the sponsor of subject enrollment on the same date as enrollment.

The sponsor will initiate a device shipment directly to the subject via courier within one business day of subject enrollment notification. The site will call the subject daily until receipt of the device is confirmed by the subject and instruct the subject to register the device by following the set-up instructions in the package and contacting ZOLL technical support for final instruction and initiation of the device.

Sites Located Outside the United States
For sites outside the United States, the investigator will be responsible for dispensing the study device and making necessary requests to the sponsor when inventory is low.

7.3.2 **Storage**

Sites Located Within the United States
Sites located in the United States will not store study devices.

Sites Located Outside the United States
Sites located outside the United States will store devices in an appropriate limited access room and 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 either during the final scheduled visit, or be couriered back to ZOLL once the indicated wear time has completed. ZOLL will facilitate return of devices from subjects in the US.

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 or malfunctions will be reported to the sponsor. In the case of device malfunction or defect in the US, subjects will call ZOLL technical support for all trouble shooting and support.

8 Statistical Plan

8.1 Sample Size

80 sites and 300 subjects will provide a reasonable estimate of site engagement with the device data. Three to five subjects per site will provide a reasonable estimate of site engagement per subject. We expect site variability in subject management. 80 study sites will be necessary to control for both site and regional differences in subject management.

8.2 Randomization Scheme

None

8.3 Endpoint Assessment

8.3.1 Primary endpoint

The primary endpoint will be assessed in an observational nature though the frequency and characterization of site engagement with uCor data. The assessment will be made study-wide in addition to geographic regions. Site engagement will be assessed through the following:

8.3.1.1 The number of data updates received by the µCor subject management system.

8.3.1.2 An assessment of the approximate time spent reviewing data reports assessed within sites and across sites. Investigators will be asked, for each report, whether they spent 0-5min, 5-10min, or greater than 10 minutes reviewing the data.

8.3.1.3 The number of medication changes based on µCor data and the number of lifestyle modifications were recommended to the subject.

8.3.1.4 The number of medication changes based on symptoms reported by subjects or from subject incidental findings.

8.3.1.5 The number of times high µCor measurements were reduced below threshold levels after medication was titrated or lifestyle modifications were recommended.

8.3.2 Secondary endpoints

8.3.2.1 Strength of association between µCor measurements and clinically related heart failure events.

8.3.2.2 Strength of association between µCor measurements and subject reported symptoms.

8.3.2.3 Descriptive statistics around hospital readmission rate, physician visit rate, and outpatient clinic visit rate during the study period.

8.3.2.4 Descriptive statistics around mortality, heart failure related events, quality of life (QoL), and health care utilization data at 6 months and on year post enrollment.

8.4 Statistical Methods

Concerning the primary endpoint, investigator engagement will be assessed through the number of data updates delivered by the µCor subject management system, frequency of medication changes based on µCor data, frequency of lifestyle modifications that are recommended to the subject, frequency of medication changes based on symptoms reported by subjects or from subject incidental findings, and frequency high µCor measurements that are reduced below threshold levels after medication was titrated or lifestyle modifications were recommended.

Concerning the secondary endpoints, associations between µCor measurements and clinically related heart failure events will be assessed through sensitivity/specificity analyses. µCor measurements at both baseline (first day of fitting) and the time of heart failure admission will be compared among subjects with or without heart failure related events using t-tests or other appropriate statistical methods.

For primary, secondary, and safety endpoints, descriptive statistics and qualitative analysis will be performed as appropriate. Descriptive statistics will include frequency of data updates delivered by the µCor data system, frequency of physician action to µCor data or µCor data updates, and physician action events as a percentage of all data updates received.

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.

8.7 Futility Analysis

NA

9 Health Economic Evaluation

The Kansas City Heart Failure Questionnaire and study specific questionnaire will be administered to subjects during monthly clinic visits. We will develop a model to examine the costs and benefits of using uCor. The model will use health care utilization data from weekly and monthly questionnaires, 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. Adverse events will also include any adverse events related to medication changes and medical procedures initiated by µCor data.

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

LVN data will be anonymized and imported directly into the research database.

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.

There are risks to medication changes and medical procedures associated with actions taken based on µCor data. These risks include but are not limited to radiation from chest radiography, adverse drug effects from medication changes, and adverse drug effects from medication titration.

Subjects in the study may benefit from outcomes associated with early detection of heart failure.

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 90D0202_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.

14.2.2 Subject Stipend

Study sites may decide to provide subject stipend for costs related to transportation to study procedures.

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
S-ICD – Subcutaneous Implantable Cardioverter Defibrillator
TFI – Thoracic Fluid Index
UADE – Unanticipated Adverse Device Effect
VF – Ventricular Fibrillation
VT – Ventricular Tachycardia

18 Bibliography

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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							
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27							
28							
29							
30							

Table 3: Sample month of subject diary for reported symptoms