A randomized study of the effectiveness of an integrated tele-monitoring and patient-centric health coaching strategy (Tele-HC) in adult patients recently hospitalized with Acute Decompensated Heart Failure (ADHF) compared to standard care

NCT# NCT02391987

Date 4/3/2018

MAYO CLINIC

Cardiovascular Research Center

A randomized study of the effectiveness of an integrated tele-monitoring and patient-centric health coaching strategy (Tele-HC) in adult patients recently hospitalized with Acute Decompensated Heart Failure (ADHF) compared to standard care

Study Chair

Charles J. Bruce, M.D.
Mayo Clinic
200 First Street, SW
Rochester, MN 55905
[redacted]

Co-Principal Investigators

[redacted]

Study Statistician:

[redacted]

Funding Sponsor: National Institutes of Health (NIH)

Protocol Number: Tele-HC

Document History	**(Effective Date)**
Activation date	29 May 2015
Version 2.0	09 Jul 2015
Version 3.0	17 Feb 2016
Version 4.0	13 Apr 2016
Version 5.0	25 Jan 2017
Version 6.0	10 Nov 2017
Version 7.0	03 Apr 2018

Protocol Resources

Questions:	Contact Name:
Protocol document, consent form, Medidata Rave® access	Monica Olson Mayo Clinic Phone: (507) 255-2649 E-mail: Olson.Monica2@mayo.edu
Monitoring clinical sites, adverse event review and reporting	[redacted]
High-touch liaison	[redacted]

Table of Contents

LIST OF ABBREVIATIONS

ACC	American College of Cardiology
ADE	Adverse Device Effect
ADHF	Acute Decompensated Heart Failure
AE	Adverse Event/Adverse Experience
AF	Atrial Fibrillation
AHA	American Heart Association
APRN	Advanced Practice Registered Nurse
BEACH	Billing Encounter Archive for Clinic and Hospital
BG	BodyGuardian®
BP	Blood Pressure
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
CRF	Case Report Form
FDA	Food and Drug Administration
ECG	Electrocardiogram
ER	Emergency Room
EF	Ejection Fraction
GCP	Good Clinical Practice
HF	Heart Failure
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart Rate
IDE	Investigational Device Exemption
IRB	Institutional Review Board
MLHFQ	Minnesota Living with Heart Failure Questionnaire
NYHA	New York Heart Association
OCHEUD	Olmsted County Healthcare Utilization Database
PHI	Protected Health Information
PI	Principal Investigator
RR	Respiratory Rate
SAE	Serious Adverse Event/Serious Adverse Experience
SCHFI	Self-Care of Heart Failure Index
SOP	Standard Operating Procedure
TM	Tele-monitoring
UADE	Unanticipated Adverse Device Effect
UI	User Interface

Study Summary

Title	A randomized study of the effectiveness of an integrated tele-monitoring and patient-centric health coaching strategy (Tele-HC) in adult patients recently hospitalized with Acute Decompensated Heart Failure (ADHF) compared to standard care
Running Title	Tele-HC
Phase	III
Methodology	Randomized
Overall Study Duration	2 years
Subject Participation Duration	1.5 years
Objectives	To test an integrated tele-monitoring and patient-centric health coaching system to reduce hospital readmissions in HF patients.
Number of Subjects	304
Diagnosis and Main Inclusion Criteria	Diagnosis: Acute Decompensated Heart Failure (ADHF) Main inclusion criteria: Hospitalized for treatment of ADHF
Study Device	BodyGuardian® Remote Monitoring System
Duration of Exposure	60 days
Reference therapy	Standard clinical care
Statistical Methodology	The primary analysis will be a Cochran-Mantel-Haenszel Chi-square test to compare the 60-day readmission rates between the two interventions while controlling for enrolling hospital (site).

1.0 Background

1.1 Heart Failure Readmissions

Heart failure (HF) poses a significant public health burden as it affects approximately 6 million Americans, with 670,000 new cases/year and a projected annual cost of 56 billion Medicare dollars by 2020.[1,2,3,4] Chronic HF is characterized by suboptimal self-care behaviors, frequent hospitalizations, and a national 23% readmission rate at 30 days.[5,6,7,8]

The drivers of readmission are multifactorial and often attributed to fragmented transitions from the hospital to the home or skilled facility due to a lack of communication and care coordination.[10-12] Behavioral factors including poor self-care combined with scarcity of economic resources, insufficient social support, and lifestyle choices also contribute to rehospitalization.[10,13-15]

1.2 Tele-monitoring

Tele-monitoring (TM), the use of remote monitoring technology, has been an integral part of transitional care for adult patients with HF for the past 2 decades.[16,17] However, TM interventions to prevent readmissions in HF have shown inconsistent results in effectiveness for prevention of HF-related and all-cause re-hospitalization which likely reflects the complexity of managing patients with HF and the challenges in readmission prevention. [17]

1.3 Health Coaching

Health coaching, rooted in motivational interviewing and education, is an integrative process of partnering with patients to change behavior .[18] The goal of health coaching is to facilitate patient self-management strategies for the purposes of preventing disease exacerbation and hospitalization.[18] Although health coaching has been widely used in chronic disease management and cardiovascular risk reduction, little has been published regarding this strategy for the HF population.[19-22] The use of technology to monitor patient clinical status at home in concert with a health-coach has been demonstrated to be a viable model to engage patients in self-care behaviors, close the patient-provider communication gap, foster patient autonomy, and enhance the patient experience.[23]

1.4 Self-care

The Self-Care of Heart Failure Model provides a framework for examining self-care behaviors in the context of a continuum of self-care maintenance and management.[15] Self-care maintenance includes fundamental behaviors to maintain physiological stability such as symptom monitoring and treatment adherence.[15] Self-care management reflects

an engagement in deliberate decision-making processes in response to symptoms.[15] Self-care maintenance incorporates symptom recognition and evaluation followed by treatment implementation and appraisal of response.[15] Self-care confidence both mediates and moderates the relationship between self-care behaviors and outcomes, secures the individual's progression, and is strengthened as the individual moves through the stages.[24]

A comprehensive transitional care model is needed that links providers, patients with chronic diseases, and health coaches to help navigate the health care system following an acute hospitalization. Acquired data will be reviewed to support clinical decision making. A model has been developed that significantly reduces re-hospitalization and improves patient self-care behaviors in managing their chronic disease, thus positively affecting the "triple aim".

The purpose of this study is to evaluate the impact of an integrated tele-monitoring and patient-centric health coaching (Tele-HC) strategy in adult patients recently hospitalized with ADHF compared to standard care on clinical outcomes using a randomized control design. The study will evaluate clinical outcomes by looking at all-cause 60 day readmission rates for ADHF.

2.0 Investigational Devices

2.1 BodyGuardian®

The end-to-end remote monitoring system is a mobile, multi-tiered healthcare platform which links personal health sensors (front-end) to secure mobile communication devices to enable transmission of discrete and summarized physiologic and symptom information to providers (back-end). The front-end includes an adhesive body sensor (BodyGuardian®) which acquires/quantifies HR, ECG, RR, and activity and has been FDA-cleared (510k) and CE Marked for detection of non-lethal cardiac arrhythmias. The BodyGuardian® control unit (including sensor) is a patch-style device which can be worn either horizontally or vertically on the chest and is comprised of the rechargeable control unit and a disposable adhesive strip (SnapStrip™). The SnapStrip™ has four conductive pads covered by pre-applied hydroelectric gel which can be worn while showering. The system is able to wirelessly communicate with a commercially available BP monitor and cuff (see BP Monitor and Cuff Manual) and scale (see Weight Scale Manuals).

The BodyGuardian® control unit has a 32-bit ARM processor with 1 Gigabit of on-board memory. The device uses a Lithium-ION rechargeable battery. The BodyGuardian® control unit runs approximately 24 hours between recharges. The sensors collect and correlate three areas of on-body physiologic measures: 1) ECG, HR, RR variability, and HR reliability that can be used to assess skin contact quality of the electrodes; 2)

respiration derived from bio-impedance measurements; and 3) body-position along with a summarized measure of activity derived from a 3-axis accelerometer. The system also acquires off-body measures via Bluetooth connectivity including weight and BP.

Physiologic information is securely transmitted to a remote data storage center (the Cloud) using mobile phone technology as the communication hub. The system can also function as an event recorder where the mobile phone automatically solicits symptoms (if directed by the physician) from the user-triggered events and by programs which analyze the acquired physiologic data. The secure central data center (the Cloud) stores information and a proprietary mid-tier logic layer supports development of automated alerts, messages, and other personalized health applications.

The *Preventice Care Platform* is the proprietary web and mobile software which enables the BodyGuardian® system access to data stored in the Cloud and includes server support, web-based user-interfaces (UIs), and access for mobile applications for clinicians. Server hardware physically resides in a secure SSAE-16 compliant data center. The server is built upon grid technologies that allow a dynamic increase or decrease in processing, storage, and network capacity based on workload. Personal health information and clinical measurements are stored separately.

The BodyGuardian® Connect mobile application runs on an Android smartphone which provides data transmission as well as user interfaces (UIs) for control and monitoring. Data are immediately sent to the *Preventice Care Platform* if network connectivity is available; otherwise data are stored on the handset until the network is available. The handset has the capacity to store several gigabytes of data locally when network connectivity is not available. Data are automatically forwarded to the Cloud where clinicians can review the information.

Remotely acquired data will be transmitted to the Mayo Heart Rhythm and Physiologic Monitoring Laboratory. This is a clinical area staffed 24/7 by Mayo Clinic monitoring technicians at [redacted] Hospital) who have been fully trained to use the BodyGuardian® system and are currently using this system clinically for remote monitoring of patients for non-lethal cardiac arrhythmia. Data will also be transmitted to a cloud-based management platform that is alert and protocol driven to assist the care team in patient management (see section below). Rhythm monitoring, classification and alerting will be the responsibility of the Mayo Clinic Remote Monitoring Center in [redacted] Alerts will be communicated via phone or the secure web-based portal during the hours of 7am-7pm EST, seven days a week; outside this time range alerts will be communicated via phone.

2.2 High Touch Service

The high touch service includes utilization of a cloud-based management platform built on an open source EMR architecture. Physiological data (ECG, HR, activity, respiration, posture, BP, and weight) will be uploaded directly to a cloud-based management platform. The cloud-based management platform patient data dashboard will identify, triage, and escalate actionable information for the study team to review via a secure web portal. Patient-generated biometric data will be continuously analyzed and displayed on an hourly basis. Patient-reported symptom information will also be captured. The dashboard uses color-coded (red, yellow, green) to quickly communicate exception data. Live data will be evaluated by the care team 7 days per week from 7am – 7 pm EST with additional monitoring and evaluation of the transmitted data on an as needed basis for calls generated outside of the 12-hour monitoring window.

An RN will be designated as the primary coach on the high touch team focused on disease management including symptom recognition, adherence to treatment strategies, care coordination, medication matters, and problem solving. Medication matters include initial medication reconciliation and the organization of resources to obtain medications for patients who have socioeconomic challenges. An RN will also be responsible for managing socio-economic challenges, and providing a nutrition and wellness assessment and goal setting.

The high touch team establishes a patient-centric relationship using techniques of motivational interviewing coupled with a transactional model of communication. Health literacy will be assessed using a validated tool to help personalize coaching interactions. Coaching topics will include the patient's understanding of their disease, establishing goals of health, treatment strategies, medication adherence, and therapy expectations. As the high touch team identifies knowledge deficits, they customize the education and employ the teach-back methodology to address the gaps.

2.3 Preliminary Data

Studies have been completed to evaluate the BodyGuardian® (BG) system in healthy elderly subjects and to test the usability from a subject's perspective and from a clinician's perspective.

In one study, twenty subjects were enrolled; 19 subjects completed the study and 1 withdrew because he could not manage to use the device. The 18 subjects were monitored for 22 days on average (in 21.7 days monitoring exceeded 80% of the day). Six subjects stopped wearing the BG monitor after less than 30 days due to: skin irritation (1); difficulty using/placing the monitor (4); or reluctance to use it due to aches and pains unrelated to the monitoring system (1). An evaluation was done on the ECG signal,

arrhythmia classification algorithm, respiration signal, accelerometer data, and the reliability of wireless connection with the BP cuff and scale. Heart rate data was obtained 99.2% of the time (91.4% reliable); respiration data was obtained 53.9% of the time. Weight and blood pressure were captured 75.7% and 74.0% of the time, respectively.

Since many HF patients have pacemakers and implantable cardiac defibrillators (ICDs), the system was evaluated for electromagnetic interference (EMI) with these devices. The BodyGuardian® module and adhesive electrode strip was applied to the skin directly over the implanted device in 100 subjects. In 208 successful acquisitions and transmissions of electrocardiograms, no EMI was detected (see Appendix 15.14 ICD Interference Letter and Abstract – Hayes).

The system has also been studied in 29 outpatients with atrial fibrillation (AF) who had undergone cardioversion or radiofrequency ablation to assess arrhythmia recurrence within thirty days. This study allowed for the testing of the usability of the body worn sensor, effectiveness of data transmission in a variety of ambulatory settings, and the ability to develop and refine the back-end monitoring infrastructure. The BG was worn for an average of 25 days and 58.6% of subjects had AF recurrence during monitoring; on average AF recurred 11 days and 9 hours after the procedure. We made the novel observation that physical activity is significantly increased in the 15 minutes prior to AF recurrence, suggesting that avoidance of vigorous exertion in the first month post rhythm intervention may be warranted. The BG system is now being routinely used clinically at Mayo Clinic for remote detection and monitoring of atrial fibrillation.

In-depth qualitative interviews have been completed, transcribed, and analyzed for 56 participants. These semi-structured individual interviews occurred at baseline, at end of study, and after any documented incident (R01 phase 2 trial only), totaling 111 completed interviews. The qualitative interview guide was revised in response to new findings and modifications of the BG system (e.g., technology updates) and instructions for use. Predominant themes (subject's opinions and concerns repeated by many) included skin discomfort from the adhesive strip, concern about not knowing if the unit was transmitting data properly, early confusion with the process of applying and using the system (learning curve which improves over time), misconceptions about the type and timing of feedback on monitoring data, and frustration with the process of charging two devices. Subsequent refinements, responsive to participant feedback (e.g., the education/instructional approach, phone display/feedback that data transmitted) positively impacted later interview data. Within the qualitative interviews, participants were asked to rate perceived burden of wearing the device, confidence to put it on properly each day, and confidence to wear it every day on a scale from 0 (not at all) to 10 (very much). End of study (n = 37) means (SD) were: burden = 3.14 (2.44); confidence to wear properly = 9.14 (1.93); confidence to wear every day = 9.30 (1.53). The majority of participants

would recommend the system to other patients. This data was evaluated to better understand acceptance of the monitoring system and usability so that refinement could be done before commencing with a randomized trial.

The BodyGuardian system incorporated into a high-touch model of care has also been recently studied. Findings from this descriptive, cross-sectional observational study of 30 older adult patients with demographics referenced in Table 1 who were hospitalized with HF between 06/01/2013 and 11/30/2013 show a 30-day all-cause readmission rate of 6% with no patients being re-hospitalized for HF. As seen in Table 2, patient self-care scores improved with all three categories reaching statistical significance ($p < .0001$).

A larger cohort experience of 142 patients from a single suburban hospital, including both HF and AMI patients treated with the tele-monitoring and patient-centric health coach (Tele-HC) intervention, show a 30-day all-cause readmission rate of 4.2% and a 30-day cardiac readmission rate of 2.8%.

Table 1 Demographic Characteristics

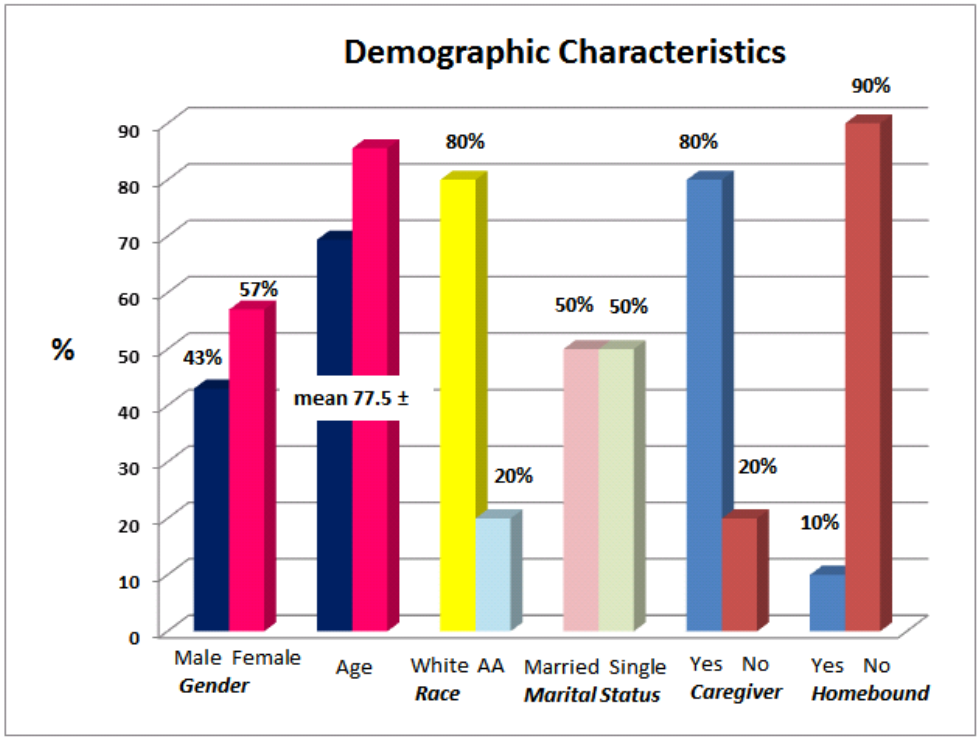
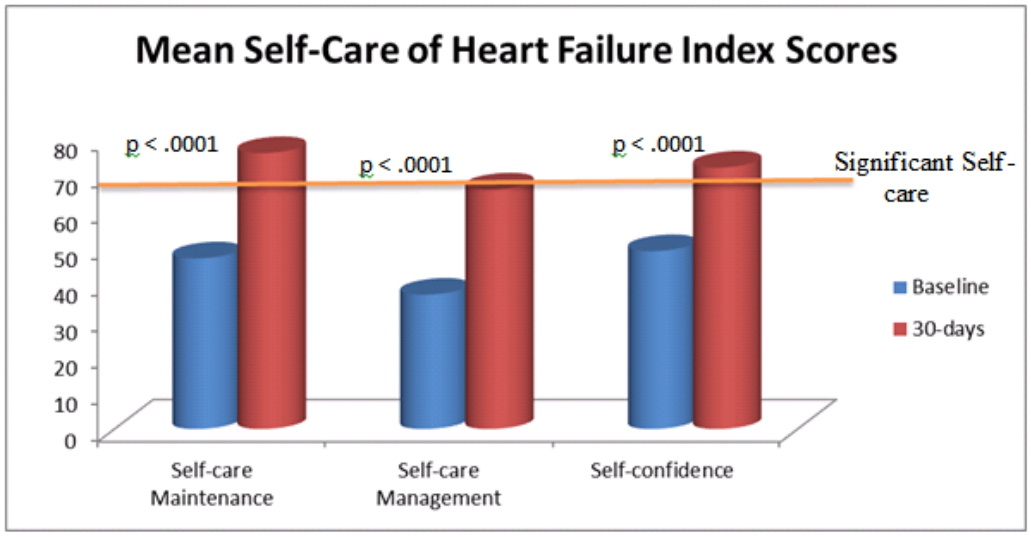


Table 2 Change in Mean Self-Care of Heart Failure Index Scores



Preliminary data from these studies demonstrate the feasibility and potential benefits of an integrated TM and health coach intervention for older patients hospitalized with HF. Interventions with personalized coaching on diet, lifestyle, pharmacotherapy, and other strategies engage patients as partners in their self-care, leverage technology, reduce hospital readmissions, and improve self-care outcomes.

2.4 Study Rationale and Risk/Benefits

2.4.1 Study Rationale

A comprehensive transitional care model is needed that links providers, patients with chronic diseases, and health coaches to help navigate the health care matrix following an acute hospitalization. The purpose of this study is to evaluate the impact of an integrated tele-monitoring and patient-centric health coaching (Tele-HC) strategy on hospital readmissions in adult patients recently hospitalized with acute decompensated heart failure (ADHF).

2.4.2 BodyGuardian® Risks

The BodyGuardian® is a Class II FDA cleared device for ambulatory monitoring of non-lethal arrhythmias. As a Class II ECG device, it has been classified as a Non-Significant Risk device that is not implantable, does not sustain human life, does not actively treat or cure disease, and does not pose a serious risk to the health and safety of the patient. In the context of this trial as described below, the BodyGuardian® Device and the Patient Care Platform will acquire physiologic data and provide individualized physician-prescribed automated alerts based on physician-prescribed thresholds. These alerts will then be reviewed by the appropriate medical staff as defined in the care protocols and within the scope of practice of the medical staff. This design uses the BodyGuardian® to acquire data and present to the medical staff data they have asked to review based on individual prescriptions for each patient. This design of a Class II device presenting relevant information to medical staff to review and confirm within their scope of practice is consistent with a Non-Significant Risk Device Study.

The BodyGuardian® is being used in this study consistent with its indications for use to remotely monitor ambulatory, non-lethal arrhythmias. The risk of direct harm to a subject using the BodyGuardian® as an external sensor is minimal. As part of the 510 K submission, the FDA reviewed a comprehensive hazard analysis and risk mitigation strategy. The most common potential adverse event is skin irritation or reaction to the adhesive on the SnapStrip™. This will be monitored for all subjects.

Skin irritation: Skin irritation may result from the SnapStrip™ adhesive. For ease in removal, subjects will be instructed to use a warm, damp cloth to soften the edges of the SnapStrip™ before slowly peeling back and rolling the adhesive away from the chest. Subjects should not rip or tear off the SnapStrip™ quickly and the SnapStrip™ should not be attached to broken, damaged, or irritated skin.

Delay in identifying or responding to an abnormal clinical finding. Subjects will be reminded that if they are having worrisome symptoms they should not rely on the BG platform, but rather contact their primary healthcare provider or if necessary, visit the emergency room (ER).

False reassurance: False reassurance that monitoring is occurring when data is not being transmitted due to poor connectivity is a possibility. Subjects will be educated that there may be periods where monitoring is not occurring, but that they will be informed by the technicians if no data is received after a 24 hour period.

User errors: User errors may result in missed events and/or data resulting in missed diagnosis.

Confidentiality: As with all research and any time information is transmitted over the internet, there is a chance that confidentiality could be compromised. However, precautions have been taken to minimize this risk.

2.4.3 Wireless Blood Pressure Machine Risks

Measurements may be distorted if the device is used close to televisions, microwave ovens, cellular telephones, X-ray, or other devices with strong electrical fields.

2.4.4 Expected Clinical Events

Expected clinic events include those related to heart failure. Examples include:

- ER visits
- Hospitalizations
- Death

2.4.5 Potential Benefits

Earlier detection of heart failure decompensation or clinically significant arrhythmias may lead to earlier intervention and potentially reduce re-hospitalization.

3.0 Study Objectives

3.1 Primary Objective

To demonstrate that Tele-HC in adult patients recently hospitalized with ADHF compared to standard care reduces all cause readmissions rates at 60 days.

3.2 Secondary objectives:

- Quantify the time to the first readmission or death
- Quantify the number of hospital readmissions or ER visits
- Quantify all-cause mortality

4.0 Study Design

4.1 General Design

This is a randomized controlled study evaluating consecutive adult patients hospitalized with primary or secondary diagnosis of ADHF. Patients will be randomized to receive either standard care or to the intervention group (Tele-HC model) to assess the impact of the intervention on 60 day all-cause readmission rates.

4.2 Randomization

Participants will be allocated to their respective treatment groups in a 4:1 ratio (intervention to standard of care), stratified by institution, sex, and NYHA functional classification. This unequal allocation ratio will lead to more patients receiving active intervention while maintaining a random component so that study staff and patients are unable to predict treatment assignment before randomization.

4.3 Study Procedures

Standard Care Arm

Standard care is defined as HF care based on current ACC/AHA HF guidelines implemented and orchestrated by a cardiologist and support staff at the participating institution.

Intervention Arm

The Intervention arm (Tele-HC) will include standard care ***in addition to*** remote physiologic monitoring with a wearable monitor (BodyGuardian®, Preventice) coupled with tailored health coaching. Details of the remote monitoring platform and health-coaching infrastructure are described below.

ECG monitoring, HR, activity, and posture will be collected via on-body sensors while BP and weight data will be collected by off-body sensors linked to BodyGuardian®. Information will be obtained via Bluetooth enabled devices and transmitted to a cloud-based management platform that is alert and protocol driven to assist the care team in patient management. Rhythm monitoring, classification and alerting will be the responsibility of the Mayo Clinic monitoring center in Rochester, MN. Alerts will be communicated to the high touch care team via phone or the secure web-based portal during the hours of 7am-7pm EST, seven days a week. Outside of this time, alerts will be communicated via phone.

The remaining physiological data (HR, activity, posture, BP, and weight) will be uploaded directly to the cloud-based management platform. The cloud-based management platform patient data dashboard will identify, triage, and escalate actionable information for the study team to review via a secure web portal. Patient-generated biometric data will be continuously analyzed and displayed on an hourly basis. Patient-reported symptom information will also be captured. The dashboard uses color-coded (red, yellow, green) to quickly communicate exception data. Live data will be evaluated by the care team 7 days per week from 7am – 7 pm EST with additional monitoring and evaluation of the transmitted data on an as needed basis for calls generated outside of the 12-hour monitoring window.

An RN will be designated as the primary coach on the high touch study team focused on disease management including symptom recognition, adherence to treatment strategies, care coordination, medication matters, and problem solving. Medication matters include initial medication reconciliation and the organization of resources to obtain medications for patients who have socioeconomic challenges. A RN will also be responsible for managing socio-economic challenges, and providing a nutrition and wellness assessment and goal setting. The high touch study team establishes a patient-centric relationship using techniques of motivational interviewing coupled with a transactional model of communication.[24, 25] Health literacy will be assessed using a validated tool to help personalize coaching interactions. Coaching topics will include the patient's understanding of their disease, establishing goals of health, treatment strategies, medication adherence, and therapy expectations. As the high touch study team identifies knowledge deficits, they customize the education and employ the teach-back

methodology to address the gaps. The high touch study team will engage the patient in collaborative care planning and goal setting to ensure interventions are congruent with the patient's readiness for change, needs, values, culture, desires, and health goals. Patient engagement and self-care management will be measured with the Self-Care of Heart Failure Index in a pre-test/post-test fashion at the time of enrollment and at 60 days post-enrollment.

The research coordinator will screen patients hospitalized with ADHF. Those who meet all inclusion and exclusion criteria will be randomized with unequal allocation, 4:1 Tele-HC intervention to standard care and enrolled in the study. Demographic and clinical data will be collected.

All patients will be assessed at 30 days and 60 days for the occurrence of re-hospitalization and all-cause mortality. De-identified hospital records will be collected so that the study monitor can review to verify cause of re-hospitalization.

4.4 Intervention Protocol (Tele-HC)

Intake – high touch study liaison (pre hospital discharge)

- Program introduction
- Review medical history
- Introduce team members

On boarding- study team members or staff contracted by clinical site

- Patient visit prior to hospital discharge, medication reconciliation, sodium intake reconciliation, BodyGuardian® application

Stabilization phase – high touch study team member (day 1-14 post discharge)

- Baseline physiological data
- Daily review of patient generated data
- Medication adherence
- Low sodium adherence
- Reinforce self-care behaviors
- Daily touches at a minimum

Optimization phase – high touch study team member (day 15-60 post discharge)

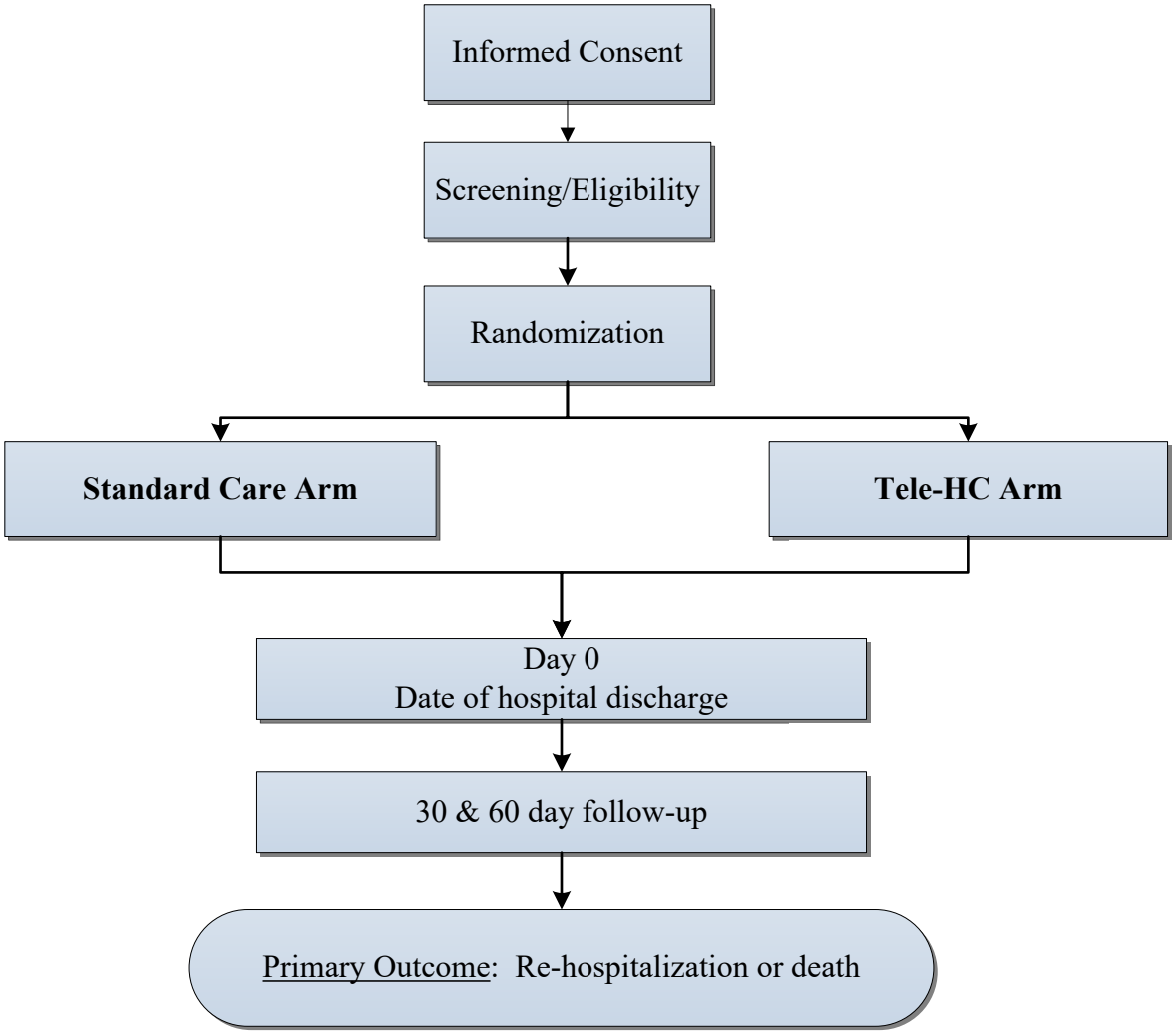
- Daily review of patient generated data
- Reinforce self-care behaviors
- Screen for depression and sleep apnea
- Optimize disease management (in collaboration with primary cardiologist)
- Targeted touches

Measured variables (to be obtained from both groups)

- 6 minute walk test (pre-discharge, 60 day)
- ECG (onboarding)
- SCHFI Self-care index and MLHFQ Heart Failure questionnaire (onboarding, 60 day)
- NYHA functional class (pre-discharge, 60 day)
- 60 day readmission
- Unscheduled clinic, hospital and/or ER visits
- Echocardiogram derived EF within 6 months prior to randomization
- Pre-discharge metabolic profile, creatinine, Hb, K, Na, GFR

Data collection obtained from clinically indicated investigations include the 6 minute walk, ECG, EF, chest x-ray, and blood test.

4.5 Study Schema



4.6 Outcome Measures

4.6.1 Primary Study Endpoint

Occurrence of all-cause hospital readmissions or death within 60 days of randomization

4.6.2 Secondary Study Endpoints

- Time to readmission or death
- Number of hospital readmissions or ER visits (visits without admissions)

- All-cause mortality

4.6.3 Exploratory Outcomes

- Change in self-care score at baseline and at end of study in both groups
- NYHA functional class at baseline and at end of study in both groups
- 6 minute walk results at baseline and at end of study in both groups
- Quality of life scores (Minnesota Living with HF) at baseline and at end of study in both groups
- Correlation of data obtained from the BodyGuardian® remote monitoring platform with clinical outcomes

4.6.4 Primary Safety Endpoints

- All cases of skin irritation requiring prescription treatment and/or withdrawal from the study will be documented
- All Serious Adverse Device Events (SADE) and Unexpected Adverse Device Events (UADE) will be documented and reported according to IRB and federal guidelines.

4.7 Questionnaire Tools

4.7.1 Assessment of Depression and Adherence Tool

In order to assess adherence in future users, each subject will be asked to complete a baseline depression assessment survey (PHQ-9) and a demographic survey. If a PHQ-9 score indicates a more than minimal severity, standard of care treatment for depression will be followed.

4.7.2 Self-Care and Life Quality Evaluation

Each subject will be asked to complete two separate questionnaires at baseline prior to use of the remote monitoring system and again at completion of the study. The first questionnaire is the Self-Care of Heart Failure Index (SCHFI), and the second is the Minnesota Living with Heart Failure Questionnaire (MLHFQ), which are validated tools for quantifying self-care and quality of life.

The SCHFI is comprised of three subscales: self-care maintenance (choice of behaviors used to maintain physiologic stability), self-care management (response to symptoms when they occur) and self-care confidence. The maintenance, management, and confidence subscales are comprised of 5, 6, and 4 Likert questions, respectively. A higher score on the SCHFI indicates improved self-care.

The MLHFQ consists of 21 questions that use a 6-point Likert scale. The physical dimension score for the MLHFQ is the summation of 8 questions (e.g., Did your heart failure make you sit or lie down to rest during the day?), while the emotional dimension score is the summation of 5 other questions (e.g., Did your heart failure make you worry?). A lower score on the MLHFQ indicates higher quality of life.

4.7.3 Health Literacy Evaluation

One question regarding health literacy will be included in the questionnaire assessment. See Appendix 15.6.

5.0 Subject Selection, Enrollment and Withdrawal

This protocol will accrue 304 subjects hospitalized with a primary or secondary diagnosis of ADHF. These subjects will then be enrolled and randomized to receive either standard care or to the intervention group (Tele-HC model) to assess the impact of the intervention on 60 day all cause readmission rates.

Definition of ADHF: One or more of these symptoms: shortness of breath, orthopnea or edema AND may have one or more of these signs: rales, peripheral edema, ascites, or pulmonary vascular congestion on chest radiography

5.1 Inclusion Criteria

- Hospitalized with primary or secondary diagnosis of ADHF (one or more of these symptoms: shortness of breath, orthopnea or edema AND may have one or more of these signs: rales, peripheral edema, ascites, or pulmonary vascular congestion on chest radiography)
- Adult patients >18 years old

5.2 Exclusion Criteria

- Overall life expectancy < 2 months
- Known skin allergy to adhesives (hydrocolloid, silicone, acrylic)

- Active systemic infection
- End stage renal disease (ESRD) on dialysis
- Subject or caregiver is not visually and tactile capable of smartphone and home device usage
- Inadequate cell phone coverage (including international patients or international travel during study period)
- Subject or legal guardian is not willing and able to provide appropriate informed consent

5.3 Subject Recruitment, Enrollment, and Screening

Eligible subjects will be enrolled and randomized ~~prior to hospital discharge~~ to either remote monitoring or standard care. After randomization, participants will be remotely monitored for 60 days. Standard care will be per published guidelines (ACC/AHA HF guidelines). At these evaluations, routine and clinically-indicated investigations will include history and assessment of NYHA class, ECG, and blood work, as deemed appropriate by the clinician. Data from any clinical visits & assessments will be collected. Medication compliance will be assessed and adjustments in management made in accordance with individual subject needs as per the judgment of care providers. Rate of ER visits, hospital admissions, episodes of contact with health care providers, and mortality data will be collected by research assistants working with the clinical electronic medical record (EMR) and entered into Medidata Rave® for subsequent analysis. If the subject's primary provider requests information while the subject is on the study, identifiable information will be released to them for clinical care. Specifically, information regarding their ECG, weight, and overall health related to their heart failure.

Study Completion

A subject will be considered to have completed the study if he or she completed all assessments and procedures during the baseline and follow-up period of 60 days for primary endpoint events. All randomized patients will have a follow-up assessment at 30 and 60 days to determine survival status and hospitalization data. If the subject dies during this period, the study coordinator and/or PI should make every effort to obtain details of the subject's death from the relevant hospital or subject's physicians and/or relatives. If confirmation of death is not available through these mechanisms, the study coordinator and/or PI will attempt to confirm the subject's death through a death index search.

Study Withdrawal

If the subject dies after being randomized but prior to hospital dismissal, the subject will be withdrawn from the study.

If the subject is lost to follow up, every effort will be made to contact the subject and determine the reason that will then be documented, including the measures taken to follow-up. If subject withdraws or drops out of the study, the reason for withdrawal from the study is to be documented on the case report form (CRF) and in the source document. The study coordinator or investigator must attempt to document re-hospitalization data unless the subject expressly refuses to provide this information.

Treatment discontinuation

Subjects who terminate the use of the BodyGuardian® device will continue to be followed. Interruption of the BodyGuardian® device will not be considered treatment discontinuation.

6.0 Study Procedures

6.1 Study Schedule

Data Collection	**Screening through 2 working days post hospital dismissal**	**Follow-up Visits**	
		30 Days (-2/+7 days)	**60 Days (+/- 14 days)**
Informed Consent/Assessment of Eligibility	X		
Randomization	X		
Demographics/Medical History	X		
Medications	X	X	X
ECG (within 2 weeks)	X		
6 minute walk (to be taken from medical record if done)	X		X
Blood work (Creatinine, Hb, potassium, sodium, GFR)	X		
Ejection fraction (within 6 months)	X		
Home visit (BodyGuardian® implementation, medicine	X[1]		

reconciliation, nutrition review) [2]			
Self-Care of Heart Failure Index (SCHFI) [2]	X[2]		X[2]
Minnesota Living with Heart Failure Questionnaire (MLHFQ)	X[2]		X[2]
New York Heart Class	X		X
Health Literacy Measure	X		
Medical Outcomes General Adherence Measure (PHQ9)	X		
Subject training	X		
Follow-up outcomes/study endpoint events		X	X

[1] *Intervention Arm only*

[2] *The purpose of these measures is to summarize participant characteristics that may relate to later adherence behaviors (e.g., wearing the monitor and measuring body weight as instructed). The participant data will also be used to provide further context to qualitative interview data.*

6.2 Patient Confidentiality

The identity of the patients participating in this study will be protected by the use of a subject number on all study materials, including specimen requisitions, laboratory reports, case report forms, etc.

7.0 Statistical Plan

7.1 Sample Size Determination

The sample size for this study is estimated to be 152 participants / group (304 total) based on the primary outcome of 60-day all cause readmission. The calculation and assumptions made are detailed below:

Assumptions:

- Standard of care 60 readmission rate: 25%. This estimate is based on the Bon Secours Richmond Health System data for December 2013 - November 2014.
- A 50% reduction in the readmission rate would be a clinically relevant difference

- Type 1 error rate: alpha=0.05 (two-sided)
- No interim analysis
- No site effect so that the data across sites could be pooled for purposes of sample size determination

A chi-square test of proportions at the alpha=0.05 level of significance will have 80% to detect the 12.5 percentage point difference (i.e., 25% vs. 12.5%) in 60 day readmission rates provided 152 participants per group are enrolled. The sample size calculations are estimated using the bsamsize function from the Hmisc package using R version 3.1.1.

7.2 Statistical Methods

7.2.1 Descriptive Statistics

Univariate descriptive statistics and frequency distributions will be calculated, as appropriate for all variables. Baseline values for demographic, clinical, and outcome variables (primary and secondary) will be tabulated for the treatment groups. These analyses will help identify potential confounding variables to be used as covariates in sensitivity analyses. Distributions across subgroups used in randomization will be compared to assess whether the randomization was successful in equalizing distributions of these prognostic variables across treatment groups. Putative prognostic variables that will be investigated through these descriptive analyses include variables such as age, subject inclusion group (inclusion criteria group), and proximity to the treatment provider.

Handling of Missing Data

Analyses will be conducted under intention to treat principles. All randomized subjects will be analyzed. The primary outcome (all-cause readmission within 60 days of randomization) is expected to be available for all participants through continuity of care documentation, patient/family contacts and medical record searches. Death prior to 60 days will be counted as an event (See Section 7.2.3 below). If there is loss to follow-up in the groups, the cumulative probability of readmission will be estimated using the Kaplan-Meier method as a sensitivity analysis to the primary analysis.

For the remaining outcome variables, all-available-data (for longitudinal measurements) and worst-case imputation will be considered alongside of multiple imputation to test the robustness of study findings to missing data.

7.2.2 Multiplicity

To avoid spurious results due to Type I error inflation, the primary endpoint of interest has been defined a priori. Secondary outcomes will not be adjusted for multiple comparisons. There are no planned interim analyses.

7.2.3 Primary Outcomes

Hypothesis: The 60-day readmission rate will be decreased with the addition of remote monitoring.

To test this hypothesis, a Cochran-Mantel-Haenszel chi-square test of proportions will be used. The stratification factor in this test will be the enrolling clinical site. The primary outcome is all cause readmission, so no adjudication is required for the primary objective. If a participant dies within 60 days of initial hospital discharge prior to any readmission, the participant will be considered as readmitted for the purpose of the primary outcome.

Intention to treat analysis will be used for the primary analysis. If there is loss to follow-up in the groups, the cumulative probability of readmission will be estimated using the Kaplan-Meier method as a sensitivity analysis to the primary analysis. Differences in the hazard rates will be tested using the stratified log-rank test. An additional sensitivity analysis will be conducted using the "per protocol" analysis set (see below), which consists of all subjects that completed the study and were adherent to monitoring.

7.2.4 Secondary and Exploratory Outcomes

General considerations: The secondary and exploratory endpoints require a variety of standard analytical methods along with sophisticated analytical strategies.

For the secondary endpoint of HF-related readmission, the same analytical approach described for the primary outcome measure will be used. The time to (first) hospital readmission will be modeled using a Kaplan-Meier survival and tested using a stratified log-rank test.

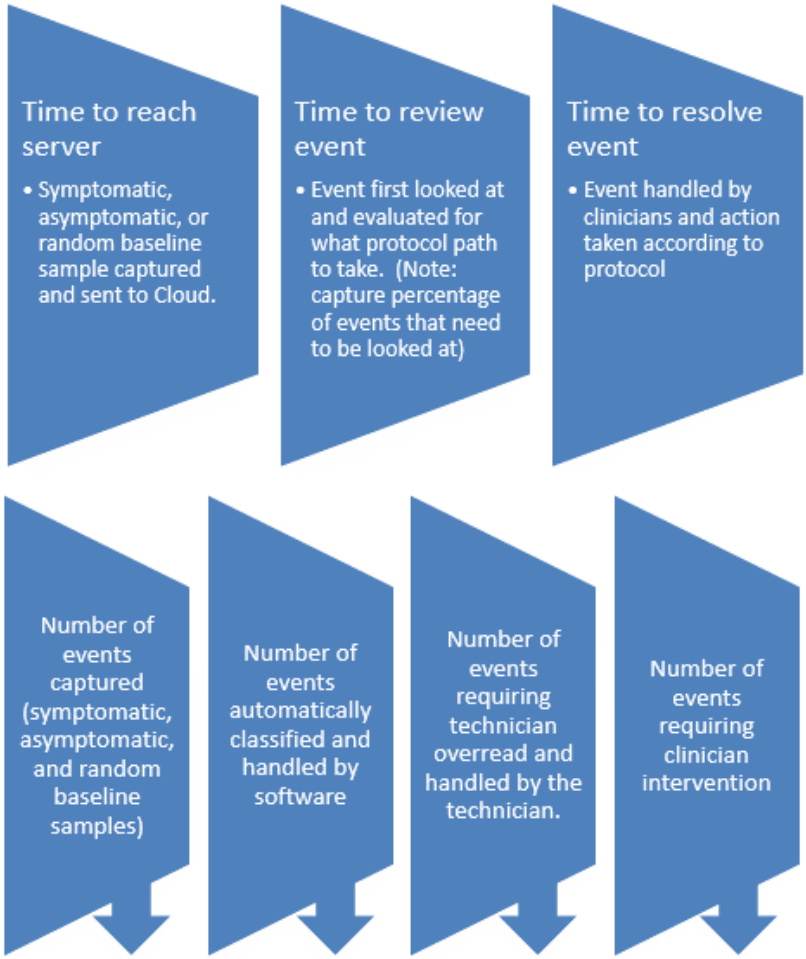
For all-cause mortality, the difference in the hazard for death will be tested using a stratified a log-rank test on the intention-to-treat sample.

For the exploratory outcomes involving serial measurements originating from the device, longitudinal summary statistics will also be used to condense the longitudinal data stream into meaningful summary measures (e.g., daily mean BP, incremental AUCs) prior to analysis. Longitudinal changes in weight and other continuous measures such as HR and

blood pressures will be modeled using mixed effects models that incorporate random slope and intercept effects.

When the patient is actively monitoring with a BodyGuardian® Control Unit, an activity measure is gathered every 60 seconds. This measure is gathered regardless of the signal quality of the ECG signal or bioimpedance signal quality. When monitoring for 24 hours, a subject should have 1440 samples per day. Adherence for a specific day is measured as the number of activity samples gathered divided by 1440 (expressed as a percentage). Adherence for a given monitoring period will be the number of days where the daily adherence is greater than 80% divided by the total number of days (expressed as a percentage of days monitored).

Figure 6 Secondary & Exploratory Outcomes Illustration



7.2.5 Interim Analysis

There is no planned interim analysis for efficacy.

7.2.6 Subject Population(s) for Analysis

Intention-to-Treat Analysis Set

The primary analysis will be conducted according to modified "Intention-to-Treat" (ITT) principles; that is, each subject will be analyzed according to the randomized treatment arm, whether or not that treatment was actually received and provided they are discharged from the hospital. The ITT method includes analysis of all subjects according to the treatment arm to which they were originally randomized irrespective of protocol violations, crossover, and events arising post randomization. Because randomization carries the expectation of creating treatment arms balanced with respect to known and unknown prognostic factors, removing randomized subjects from the analysis, even for the best of intentions, runs the risk of introducing differential selection biases into the treatment comparisons. Participants not discharged alive or which are transferred to another care facility that prohibits the randomized assignment from being implemented, will be excluded from the ITT analysis set.

Per-protocol Analysis Set

The per-protocol analysis set will be of participants followed according to the schedule outlined. For the primary analysis, which is based on 60 days, the per-protocol adherence is only during the first 60 days. The results of this potentially non-representative subset(s) will be compared to the results obtained using the ITT Analysis Set as a sensitivity analysis. Should the results disagree qualitatively, the ITT results will be considered the less-biased results; however, a careful examination of putative causes for the differences will be fully investigated to inform the design of subsequent research studies.

8.0 Participant Safety, Adverse Events, and Clinical Endpoints

All study-related adverse events occurring during the study, including those not meeting the criteria of an Unanticipated Adverse Device Effect (UADE) will be recorded on the appropriate case report form. Records of these events will be maintained and reports submitted to the FDA and IRB according to the regulatory requirements. Expected clinical adverse events and non-significant (not serious) clinical adverse events will not be reported. Expected clinical adverse events and anticipated adverse device effects are those listed in Section 2.4.

8.1 Institutional Review Boards

Before initiating this study, the protocol, informed consent forms, recruitment materials, and other relevant information will be reviewed and approved by each participating site's

institutional review boards (IRB). Any amendments to the protocol must be approved by each institution's IRB before they are implemented.

8.2 Definitions

8.2.1 Unanticipated Adverse Device Effect (UADE)

A UADE is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

8.2.2 Study-Related Adverse Effect (Event)

Any untoward medical occurrence in a subject involved in a clinical study of an investigational device that has a causal relationship with the device or, if applicable, other study related treatment(s).

8.2.3 General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of a study-related adverse event must also be recorded and documented as an adverse event.

8.2.4 Hospitalization, Prolonged Hospitalization, or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as an unanticipated adverse device effect unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for a study-related adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.

- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the site PI.

8.2.5 Post-study Adverse Event

All unresolved study-related adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the local investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The local investigator should notify the study regulatory sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the local investigator should become aware of the development of problems, cancer, or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

8.2.6 Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period and the adverse event is considered to be study related.

8.2.7 Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)

Any unanticipated problem or adverse event that meets all of the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**

- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, **AND**

- Related: A problem or event is "related" if it is possibly related to the research procedures.

8.3 Clinical Endpoints/Adverse Event Reporting Period

For this study, the study treatment follow-up period is defined as 60 days following the administration of study treatment. The study period during which clinical endpoints and adverse events must be reported is defined as the period from the initiation of any study procedures to the end of the study treatment follow-up.

8.4 Recording of Clinical Endpoints

Information on all clinical endpoints will be recorded in the source documentation and in the applicable CRF.

When a hospital readmission occurs, the site coordinator will record the information in the source documentation and in the applicable CRF and will forward all relevant de-identified medical information to the Project Coordinator for review.

8.5 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on study-related adverse events by specific questioning and, as appropriate, by examination. Study subjects will be routinely questioned about study-related adverse effects at study visits. Information on all study-related adverse events should be recorded immediately in the source document, and also in the appropriate adverse event section of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic, laboratory, or procedure results should recorded in the source document.

All study-related adverse events occurring during the study period must be recorded. All observed or volunteered adverse effects (serious or non-serious) and abnormal test findings, regardless of the treatment group if applicable or suspected causal relationship to the investigational device or if applicable other study treatment or diagnostic product(s) will be recorded in the subjects' case history. For all adverse effects sufficient information will be pursued and or obtained as to permit: an adequate determination of the outcome; an assessment of the casual relationship between the adverse effect and the

investigational device; or if applicable other study treatment or diagnostic product. The clinical course of each study-related event should be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be at least possibly related to the study treatment or study participation should be recorded and reported immediately.

The Adverse Event CRF shall include the following information:

- Subject Study Number/Identifier
- Device information (BG kit and serial number)
- Date of event onset
- Date investigator became aware of event
- Description of the event
- Description of treatment the subject received as a result of the event
- Indication if study treatment was discontinued or if investigational device was removed
- Subject's current status or if the event was resolved
- Date of resolution
- Investigator assessment of the event and justification for determination
- Investigator assessment of causality and relationship to device and study treatment

8.6 Preventice Reporting of Unanticipated Adverse Device Effects and Unanticipated Problems

When a study-related adverse event has been identified, the study team will take appropriate action necessary to protect the study participant and then complete the Study Adverse Event CRF. Preventice will evaluate the event and determine the necessary follow-up and reporting required as it relates to device related events. Those that mayo necessitate reporting but are not device related will be addressed by Mayo Clinic.

Preventice will promptly review documented Unanticipated Adverse Device Effects and as necessary shall report the results of such evaluation to the FDA within 10 working days of initial notice of the effect. Thereafter, Preventice will submit such additional reports concerning the effect as requested.

8.7 Preventice Reporting, Notifying the FDA

Preventice will report to the FDA all unanticipated adverse device effects according to the required reporting timelines, formats and regulations.

Preventice will submit a completed FDA Form 3500A to the FDA's Center for Devices and Radiological Health for any observed or reported adverse effect that is determined to be an unanticipated adverse device effect. A copy of this completed form will be provided to the DSMB and all participating sub-investigators.

The completed FDA Form 3500A will be submitted to the FDA as soon as possible and, in no event, later than 10 working days after Preventice first receives notice of the adverse effect.

If the results of Preventice's follow-up evaluation shows that an adverse effect that was initially determined to not constitute an unanticipated adverse device effect does, in fact, meet the requirements for reporting; Preventice will submit a completed FDA Form 3500A as soon as possible, but in no event later than 10 working days, after the determination was made.

For each submitted FDA Form 3500A, Preventice will identify all previously submitted reports that that addressed a similar adverse effect experience and will provide an analysis of the significance of newly reported adverse effect in light of any previous, similar report(s).

Subsequent to the initial submission of a completed FDA Form 3500A, Preventice will submit additional information concerning the reported adverse effect as requested by the FDA.

8.8 Reporting Process

Unanticipated Adverse Device Effect reports will be submitted on FDA Form 3500A. The contact information for submitting reports is:

Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center - WO66-G609

10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

8.9 Deviations from the investigational plan

Mayo Clinic shall notify each participating sites' IRB (see 21 CFR 56.108(a) (3) and (4)) of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by Mayo Clinic is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB notification in accordance with 21 CFR 812.35(a) also is required.

8.10 Medical Monitoring

It is the responsibility of Mayo Clinic to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see Section 10, Study Monitoring, Auditing, and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

9.0 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI,

attempts should be made to obtain permission to collect at least vital status (long-term survival status that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

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

Any data where an electronic system will be used as the sole instrument for the recording and analysis of clinical and laboratory data related to the safety and/or efficacy of the investigational device will be compliant with FDA 21 CRF Part 11 and Guidance for Industry Electronic Source Data in Clinical Investigations, September 2013.

9.3 Case Report Forms

Electronic case report forms (eCRFs) will be created within Medidata Rave® to structure data entry for the study for each of the proposed outcomes and subject characteristics assessed in the study.

9.4 Data Management

The Medidata Rave® system supported institutionally by the Mayo Clinic [redacted] will be used for data processing. This online system has built-in training, security, and audit features that allow for 21 CFR Part 11 compliance. Data consistency checks will be programmed into the system to minimize the number of data entry errors. Furthermore, any changes to the data, once saved, is audited for both person and time of the change. The system includes an integrated randomization module, Balance, which will be used to determine the model of care for each participant.

Additional data as it pertains to latency and interactions with the BodyGuardian® device will be obtained by electronic retrieval through Preventice.

9.5 Data Security and Confidentiality

Database and web servers will be secured by a firewall and through controlled physical access. The Medidata Rave system has security features to ensure that study personnel accessing the database have the proper authority to perform the functions he or she requests of the system. Unix group-access control will provide access security for the secondary SAS data sets used by the Mayo statistician. Workstation login is secured by extensive user-password facilities under Unix and Windows.

9.6 Data Quality Assurance

Quality control will be ensured through oversight by Preventice, who will review the electronic data for participants on a regular basis for completeness and consistency. Quality and completeness of data entry will be reviewed as soon as possible after data entry, within 5 business days of data entry for the first 5 participants randomized at each site, and within 15 days of data entry thereafter. Preventice will generate data quality reports monthly for review by the study team. Data queries generated by identification of incomplete or inconsistent data will be raised directly within the electronic eCRF and should be resolved by the study coordinator or PI in a timely manner. Corrections or changes in the data management system are tracked with the retention of the original data and the corrected data with the date of data entry and submitting personnel. Sites with persistent delays or difficulties in data capture will be provided additional study-based training.

9.7 Records Retention

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The sponsor-investigator will retain the specified records and reports for:

- An investigator or sponsor shall maintain the records required by this subpart during the investigation and for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol. CFR 812.140

10.0 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The investigator will allocate adequate time for monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

This clinical study will be monitored for appropriate study conduct and data integrity including review of CRFs and parity checks with the source documentation including operator worksheets retained with CRF documentation and hospital charts. Periodic site visits shall be conducted. CRFs will be monitored by the study monitor(s) prior to submission to Mayo Clinic. Monitoring will include comparison of CRFs to source documentation for accuracy and appropriateness, study device accountability, review for/of adverse events, prompt evaluation of unanticipated adverse device effects, and site compliance.

Should discrepancies be identified between the comparison of source documentation and the data contained within the CRF, the most accurate information shall be recorded on a Data Clarification Form (DCF)/or query. Following conclusion of the study, site specific Study Closure Visits will be conducted. Site Study Closure Visits will occur no more than 3 months following study conclusion.

The clinical site will be monitored routinely for fulfillment of Investigator duties and responsibilities, the clinical study as it is conducted in accordance to GCP, EN ISO 14155 and timeliness/completeness of CRF submission to Sponsor. Any evident pattern of non-compliance (i.e. non-reporting of AE or protocol deviations, device accountability inconsistencies, etc.) may initiate remedial actions. If corrective actions are not subsequently undertaken, the clinical site may be withdrawn.

10.2 Auditing and Inspecting

The sponsor-investigator will permit study-related monitoring, audits, and inspections by the IRB, the monitor, and government regulatory agencies of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The sponsor-investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

Participation as a sponsor-investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

11.0 Ethical Considerations

This study is to be conducted according to United States government regulations and institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This 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 Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed and dated by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

12.0 Study Finances

12.1 Funding Source

This study is financed through a grant from the National Institute of Health (NIH).

12.2 Conflict of Interest

Any study team member who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor-investigator prior to participation in this study. The investigational device manufacturer shall also require a Financial Disclosure form to be completed by the Principal Investigator and all co-investigators.

13.0 Publication Plan

The Principal Investigator may publish the results of work performed under this research protocol. However, copies of any abstracts, papers, or manuscripts shall be provided to the investigational device manufacturer for review at least thirty (30) days prior to submittal for publication or presentation. When reasonably requested by the investigational device manufacturer, the Investigator and Institution will delay

publication up to sixty (60) days to allow manufacturer to protect its rights in patentable or copyrightable material.

This study shall be registered in ClinicalTrials.gov (https://register.clinicaltrials.gov/) prior to subject recruitment and enrollment, as well as posting of results to ClinicalTrials.gov within 12 months of final data collection for the primary outcome.

14.0 References

1. Jessup M, Abraham WT, Casey DE, et al. ACCF/AHA guidelines for the diagnosis and management of heart failure in adults: A report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines developed in collaboration with the International Society for Heart and Lung Transplantation. *J Am Coll Cardiol*.2009; 53(15):1343–1382.

2. Lloyd-Jones D, Brown TM, Carnethon M, et al. Heart disease and stroke statistics—2010 Update.*Circ*. 2010; 121(7):e46 –e215.doi:10.1161/circulation aha.109.192667.

3. Roger VL, Lloyd-Jones DM, and Adams R J, et al. Executive summary: Heart disease and stroke statistics--2011 update: A report from the American Heart Association.*Circ.* 2011; 123:459–463. doi:10.1161/cir.0b013e31820c7a50.

4. Heidenreich PA, Trogdon JG, Khavjou OA, et al. Forecasting the future of cardiovascular disease in the United States. *Circ.* 2011; 123(8):933–944. doi:10.1161/CIR.0b013e31820a55f5.

5. Brandon AF, Schuessler JB, Ellison KJ. The effects of an advanced practice nurse led telephone intervention on outcomes of patients with heart failure. *Appl Nurs Res.* 2009; 22(4):e1–e7. doi:10.1016/j.apnr.2009.02.003.

6. Rogers JG, Bostic RR, Tong KB. Cost-effectiveness analysis of continuous flow left ventricular assist devices as destination therapy. *Circ. Heart Fail.*2012;5(1):10-16. doi:10.1161/circheartfailure.111.962951.

7. Rose EA, Moskowitz AJ, Packer M, Sollano J, et al. The REMATCH Trial: Rationale, design, and endpoints. *Ann Thorac Surg.* 1999; 67(3):723–30.

8. Gheorghiade M, Vaduganathan M, Fonarow G. Rehospitalization for heart failure: Problems and perspectives. *J Am Coll Cardiol*.2013; 61(4):391–403.

9. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart Disease and Stroke Statistics—2012 Update A Report From the American Heart Association. *Circulation*. 2012;125(1):e2-e220. doi:10.1161/CIR.0b013e31823ac046.

10. Bennett S, Huster G, Baker S, et al. Characterization of the precipitants of hospitalization for heart failure decompensation. *J Crit Care.*1998; 7(3):168–74.

11. Forster AJ, Murff HJ, Peterson JF, et al. The incidence and severity of adverse events affecting patients after discharge from the hospital. *Ann Intern Med.* 2003; 138(3):161-167.

12. Naylor MD, Brooten D, Jones R, et al. (1994). Comprehensive discharge planning for the hospitalized elderly. *Ann Intern Med.* 1994; 120(12):999 –1006. doi: 10.1059/0003-4819-120-12-199406150-00005.

13. Jessup M, Abraham WT, Casey DE, et al. ACCF/AHA guidelines for the diagnosis and management of heart failure in adults: A report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines developed in collaboration with the International Society for Heart and Lung Transplantation. *J Am Coll Cardiol.* 2009; 53(15):1343–1382.

14. Krumholz H, Parent E, Tu N, et al. Readmission after hospitalization for congestive heart failure among Medicare beneficiaries. *Arch Intern Med.* 1997; 157(1):99–104.

15. Riegel B, Carlson B, Moser D, et al. Psychometric testing of the self-care of heart failure index. *J Card Fail.* 2004; 10(4): 350–60.

16. Kulshreshtha A, Kvedar JC, Goyal A, et al. Use of remote monitoring to improve outcomes in patients with heart failure: A pilot trial. *Int J Telemed App.* 2010; 2010(3). doi:10.1155/2010/870959.

17. Roger V L. The changing landscape of heart failure hospitalizations. *J Am Col Cardiol.* 2013; 61(12):1268–1270.

18. Huffman M. Health coaching: a new and exciting technique to enhance patient self-management and improve outcomes. *Home Healthc Nurse*, 2007; 25(4): 271–4.

19. Edelman D, Oddone E, Lieboitz R, et al. A multidimensional integrative medicine intervention to improve cardiovascular risk. *J Gen Int Med.* 2006; 21(7):728-734. doi:10.1111/j.152-1497.2006.00495x.

20. Ivey S, Tseng W, Kurtovicj E, et al. Evaluating a culturally and linguistically competent health coach intervention for Chinese-American patients with diabetes. *Diab Spect,* 2012;25(2):93-102. doi:10.2337/diabspect.25.2.93.

21. Vale M, Jetliner M, Best J, et al. Coaching patients with coronary heart disease to achieve their target cholesterol: A method to bridge the gap between evidence-

based medicine and the "real world-" randomized controlled trial. *J Clinic Epidem,* 2002; 55(3): 245-252. doi.10.1016/S0895-4356 (01)00460-7.

22. Vale M, Jelinke M, Best J, et al. Coaching patients on achieving cardiovascular health (COACH): A multicenter randomized trials in patients with coronary heart disease. *Arch Int Med,* (2003); 163(22): 2775-2783. doi:10.1001/archinte.163.22.2775.

23. Gellis ZD, Kenaley B, McGinty J, et al. Outcomes of a telehealth intervention for homebound older adults with heart or chronic respiratory failure: A randomized controlled trial. Gerontologist. 2012;52(4):541–552. doi:10.1093/geront/gnr134.

24. Riegel B, Lee C, Dickson V, Carlson B. An update on the self-care of heart failure index. *J Cardiovasc Nurs.*2009; 24(6):485–97. doi:http://dx.doi.org/10.1097/JCN.0b013e3181b4baa0.

25. Van Walraven C, Dhalla IA, Bell C, et al. Derivation and validation of an index to predict early death or unplanned readmission after discharge from hospital to the community. *Canadian Med Assoc.* 2010;182(6):551–557. doi:10.1503/cmaj.091117.

15.0 APPENDIX

15.1 Blood Pressure Monitor and Cuff Manual

15.2 BodyGuardian® Manual

15.3 Case Report Forms

15.4 Data and Safety Monitoring Plan

15.5 Drug Dictionary

15.6 Health Literacy Measure

15.7 Medical Outcomes General Adherence Measure (PHQ9)

15.8 Minnesota Living with Heart Failure Questionnaire (MLHFQ)

15.9 New York Heart Association (NYHA) Functional Classification

15.10 Self-Care of Heart Failure Index (SCHFI)

15.11 Skin Irritation Treatment

15.12 Follow-up Script

15.13 Weight Scales Manual

15.14 ICD Interference Letter and Abstract – Hayes