

Protocol Number:

Title: Continuous Wearable Monitoring Analytics to Improve Outcomes in Heart Failure - LINK-HF2 multicenter  
implementation study

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Principal Investigator/Study Chair: Josef Stehlik, MD, MPH

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## Abstract

The study comprises of 1) the **main experimental procedures** to assess efficacy of early intervention based on alarms generated from data collected by the continuous wearable monitoring system on prevention of hospitalization due to heart failure exacerbation, with 240 participants and 2) the **non-experimental procedures for implementation research and qualitative research** based on **interviews and focus groups** consisting of 20 patients total and 10 clinicians/site.

For **experimental procedures**, we plan to recruit adult subjects with history of HF with reduced or preserved ejection fraction, New York Heart Association (NYHA) functional class II-IV hospitalized for HF will be eligible for study participation. Exclusion criteria include expected heart transplant or ventricular assist device implant within 90 days of enrolment, skin damage preventing use of study device, and visual or cognitive impairment that precludes ability to comply with study procedures. The study coordinators will screen prospective study subjects. The study will be discussed in detail with patients interested in participation, informed consent obtained, and subjects enrolled at hospital discharge.

Remote monitoring will start at the time of hospital discharge and continue for 90 days. The adhesive sensor patch will be attached to the subject's chest and paired with a smartphone. Continuous data will be uploaded automatically to a secure server for analytical platform processing. While all enrolled study subjects will receive the remote monitoring device, the subjects will be randomized in a 1:1 ratio to intervention vs. control arm. In the intervention arm, once physiological derangements correlated with impending HF exacerbation are identified by the analytical platform, a clinical alert will be generated and messaged to the electronic medical record (EMR). This alert will be visible to the local team providing heart failure care for the corresponding subject. If applicable, another convenient means of a backup notification to be defined in the implementation process may also be generated. Each site will have designated heart failure clinicians that will respond to the alerts. To reduce variation in response to clinical alerts, clinicians at the study sites will follow a standardized response algorithm. Based on the remote monitoring data, clinical symptoms and blood pressure the HF nurse will determine the suggested clinical action - medication up-titration, clinic visit or emergency room (ER) visit, and confirm with the physician that this action should be implemented. In the control arm, information from the sensor will be collected, but clinical alerts will not be generated or communicated to the providers.

For **non-experimental procedures**, a comprehensive **implementation program** will be developed and analyzed in the vanguard settings and then applied at all of the participating centers. Key stakeholders will be identified at each site and the proposed logic model will be reviewed with each group to revise it for local application. An initial training program will be conducted for clinician participants caring for patients. In addition, a subset of enrolled patients will be approached to participate in a semi-structured interview that will examine their experience with the study procedures as part of a **qualitative research** part of the study. Qualitative analysis will identify salient concepts and barriers and facilitators to successful implementation of remote monitoring in clinical practice. Authorization documents/cover letters will be read to the subjects before the interviews to confirm their willingness to participate in the interviews.

## List of Abbreviations

AE	adverse event
CFR	Code of Federal Regulations

CRF	case report form
DSMB	Data Safety Monitoring Board
EHR	VA electronic health record
GCP	good clinical practice
HF	heart failure
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
ISO	Information Security Officer
LSI	Local Site Investigator
PHI	protected health information
R&DC	Research and Development Committee
SAE	serious adverse event
SSN	Social Security number
VA	Department of Veterans Affairs
VHA	Veterans Health Administration

## Contents

Protocol Title:.....	1
1.0 Study Personnel .....	4
2.0 Introduction .....	5
3.0 Objectives .....	6
4.0 Resources and Personnel.....	7
5.0 Study Procedures .....	8
5.1 Study Design .....	12
5.2 Recruitment Methods.....	12
5.3 Informed Consent Procedures.....	14
5.4 Inclusion/Exclusion Criteria .....	16
5.5 Study Evaluations.....	17
5.6 Data Analysis.....	17
5.7 Withdrawal of Subjects.....	18
6.0 Reporting.....	18

7.0	Privacy and Confidentiality.....	21
8.0	Communication Plan.....	21
9.0	References.....	23

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## **1.0 Study Personnel**

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This is a multi-center study which will take place at 6 VAMC: Salt Lake City VAMC  
Gainesville VAMC, Richmond VAMC, Palo Alto VAMC, Houston VAMC, Portland VAMC

**Local Collaborators:** Charlene Wier, PhD, Jorie Butler, PhD, Susan Zickmund, PhD,  
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## 2.0 Introduction

HF is a major public health problem affecting more than 5 million Americans and more than 23 million patients worldwide. It is responsible for major health care expenditures in the U.S., with a projected annual direct cost increase of 210% - from \$21 billion currently to \$53 billion in 2030. In the U.S., hospitalizations for HF represent 80% of costs attributed to HF care. HF is the most common hospital discharge diagnosis for Veterans. Furthermore, hospitalization for HF is associated with adverse prognosis - the risk of mortality increases more than 4-fold in the first 3 months after discharge. Within the VA system, the importance of decreasing preventable HF hospitalizations has been recognized by The Chronic Heart Failure Quality Enhancement Research Initiative (CHF QUERI), and the 30-day readmission rate is one of the VA's Strategic Analytics for Improvement and Learning (SAIL) measures.

A number of approaches aimed at reducing the risk of HF readmission have been tested. Tracking of daily weight, as recommended by current HF guidelines, was tested as part of several remote monitoring strategies. However, this approach did not lead to reduction of the risk of HF hospitalization, most likely as the weight gain is a lagging indicator, rather than a leading event. It is therefore likely that physiological parameters other than weight may be needed to detect HF exacerbation in a timely manner. Within the VA system, Hospital to Home (H2H) initiative aimed to reduce 30-day readmission in patients with HF through addressing medication reconciliation and education; early follow-up after discharge; and patient recognition of symptoms indicating deterioration. However, this initiative did not lead to reduction of readmission.

Utility of several implantable devices to detect impending HF exacerbation was previously tested with mixed results. Until now, only the CardioMEMS system using an implantable pulmonary artery pressure monitor has shown reduction in hospitalization rates and has been approved by the Food and Drug Administration. However, implantation of a dedicated device poses additional risks in the fragile HF population.

Noninvasive monitoring may be a more practical and cost-effective approach, especially if used during periods of increased risk of HF exacerbation. The Multisensor Monitoring in Congestive Heart Failure (MUSIC) was a proof of concept study to show predictive value of wearable monitoring based on several physiological signals. This investigation was limited by technical shortcomings of the monitoring device and data transmission capabilities at the time. Since then, technological advances including sensor miniaturization, improved battery life, Bluetooth technology and ubiquitous use of rapidly evolving handheld devices provided new opportunities. We evaluated the utility of this approach in the VA sponsored LINK-HF study, where we used a novel noninvasive remote patient monitoring platform called pinpointIQ (PhysIQ, Inc, Naperville, IL). This included a wearable sensor, a smartphone that securely uploaded the continuous data from the device to the cloud, and a machine learning analytics platform for the prediction of HF exacerbation. In our pilot study, we demonstrated that our platform based on a multi-sense wearable patch device can provide accurate early detection of impending rehospitalization with a predictive accuracy comparable to implanted devices. Therefore, the clinical efficacy and generalizability of this low-cost noninvasive approach to rehospitalization mitigation should be further tested.

The LINK-HF2 study is a randomized trial on the effectiveness of early interventions to prevent heart failure related hospital admissions based on data obtained from an ambulatory wearable multi-sensor system in patients with heart failure. The study follows the successful LINK-HF pilot study which demonstrated device safety, reliability, good patient compliance and high accuracy of a predictive AI-based algorithm to detect HF decompensation / impending HF hospitalization.

### 3.0 Objectives

**STUDY AIMS** Aim 1. Implement remote monitoring into the clinical workflow of HF care.

Aim 1a. Design implementation strategies for non-invasive remote monitoring and algorithmic response to clinical alerts generated by the predictive analytics platform. In HF programs at five VA medical centers, eligible patients will be invited to enroll at the time of hospital discharge for HF exacerbation and receive a wearable monitor and a smartphone with cellular service for a 90 day period. We plan to enroll and randomize 240 subjects. Data continuously uploaded to a secure server will be analyzed by the predictive analytics algorithm and a clinical alert will be generated when physiological derangements correlated with impending HF exacerbation are identified. A clinical response algorithm will provide instructions for management response to the alert, to include medication changes and/or urgent/non-urgent outpatient assessment. The intervention will include electronic health record integration. We will design implementation processes for this program using the integrated Promoting Action on Research Implementation in Health Services (i-PARIHS) framework, adapted for the VA QUERI. We will design 3 phases of implementation: 1) implementation intervention planning through workflow analysis, technology assessments, and recipient/stakeholder interviews; 2) formative evaluation of pilot implementation at two vanguard sites to test initial acceptability and equipment performance; and 3) implementation fidelity monitoring by assessing consistency and satisfaction.

Aim 1b. Evaluate implementation outcomes, including clinician and patient perceptions and adoption of the use of ambulatory remote monitoring data. We will use both quantitative and qualitative research methods to examine the eight core dimensions of implementation outcomes. Focus groups and semi-structured interviews will be done to assess clinician and patient perceptions of acceptability and feasibility. We plan to enroll up to 10 clinicians per site and 20 patients for this qualitative part of the study. Adoption behaviors will be tracked including alert response rates and appropriateness of decisions. Fidelity of implementation will be monitored by assessing compliance with all aspects of the study protocol. Penetration and sustainability will be evaluated by assessing variation in implementation outcomes across the five study sites as well as participant perceptions from the qualitative work at the end of the study.

Aim 2. Conduct a feasibility study of non-invasive remote monitoring in chronic HF.

Aim 2a. Define key characteristics that will inform design of a pivotal trial of non-invasive remote monitoring aimed at reducing rehospitalization and improving quality of life in HF. We will enroll a total of 240 patients between five VA centers hospitalized for HF exacerbation. At enrollment, subjects will undergo 1:1 randomization to intervention or control arm. While all study subjects will use the monitoring device for 90 days after discharge, in the intervention arm, clinicians will be notified of clinical alerts and will follow the response algorithm to modify HF treatment and/or recommend urgent clinic visit/emergency room visit. In the control arm, information from the sensor will be collected, but clinical alerts will not be generated or communicated to providers. The main study outcomes will include the proportion of randomized patients who meet the algorithm's criteria for at least one alert, the proportion of time the remote monitor is in use and functioning properly, HF hospitalization rate, length of hospital stay, and health-related quality of life. Implementation factors identified in Aim 1 will help clarify the results of this aim.

Aim 2b. Identify costs associated with implementation and clinical use of non-invasive remote monitoring in HF. Correct classification of costs associated with implementation of non-invasive remote monitoring will set the stage for cost-effectiveness analyses in a future pivotal trial.

Recent advances in technology and in machine learning provide an opportunity for processing of new sources of real-time patient-level data to generate clinically actionable information. An important knowledge gap is how to best implement this technology-based approach into clinical practice. Our study addresses this critical question of clinical implementation and will generate feasibility data for a design of a pivotal clinical trial of non-invasive remote monitoring with predictive analytics during the high-risk period after hospital discharge. This work has potential to result in changes to care of Veterans with HF and other chronic health conditions.

## **4.0 Resources and Personnel**

- PI/SC, Josef Stehlik, MD, MPH Veterans Affairs SLC Health Care System (VAMC), access to protected health information; involved in recruiting subjects; obtaining informed consent; administering survey/interview procedures; and performing data analysis.
- Project Mgr., Heather Hanson, CCRC Veterans Affairs SLC Health Care System (VAMC), access to protected health information; involved in recruiting subjects; obtaining informed consent.
- Co-I, Line Kemeyou, MD, Veterans Affairs SLC Health Care System (VAMC) will serve as local Co-I.

- Co-I, Thomas Hanff, MD, Veterans Affairs SLC Health Care System (VAMC). Dr Hanff will serve as local PI.
- Richard Nelson, PhD, Veterans Affairs SLC Health Care System (VAMC), Health Economist.
- Charlene Weir, PhD, Veterans Affairs SLC Health Care System (VAMC), administering survey/interview procedures and performing data analysis, Implementation Research Scientist.
- Jorie Butler, PhD, Veterans Affairs SLC Health Care System (VAMC), administering survey/interview procedures and performing data analysis, Implementation Research Scientist.
- Michael Yaoyao Yin, MD, Veterans Affairs SLC Health Care System (VAMC), Qualitative Research Scientist.
- Susan L. Zickmund, PhD, Veterans Affairs SLC Health Care System (VAMC), Qualitative Research Scientist.
- Matthew Samore, MD, Veterans Affairs SLC Health Care System (VAMC), Dr. Samore will provide methodological guidance throughout the study and contribute to the costeffectiveness analyses.

#### Operational Partner / Contractor

PhysIQ, Inc, Chicago, IL

- Matthew Pipke, Chief Technology Officer; will provide technical support for remote monitoring
- Karen Larimer, PhD, Director of Clinical Development, WOC VA status, will provide training to VA personnel in use of the remote monitoring platform

PhysIQ staff will have access to PHI that will be submitted through eCRFs, and they will also be able to identify which deidentified remote monitoring data correspond to individual subjects. PhysIQ will support data coordinating center functions and will be participating in data analysis.

PhysIQ staff will not be involved in recruiting subjects; obtaining informed consent or administering survey/interview procedures; The following agreements are in place:

- **Principal Investigator initiated Investigational device clinical trial cooperative research and development agreement (CRADA).** Executed between US Department of Veterans affairs represented by SLC VAMC / Josef Stehlik, MD and collaborator PhysIQ inc. This agreement includes statement of work that outlines the activities to be performed by the VA investigators and by PhysIQ during this 4-year study

- **Contract agreement between VHA Innovations Ecosystem and PhysIQ Inc.**

This agreement includes a schedule of deliverables that outlines activities PhysIQ will perform under this contract, to include remote monitoring platform set-up, clinical and research staff training, and conduct of remote monitoring in patients enrolled in the study.

## 5.0 Study Procedures

### 1). Experimental Procedures

**Participant Identification:** We will identify patients for inclusion in the study during hospitalization at the VA hospital prior to discharge or during routine clinic visits at the Heart Failure/Cardiology Clinic. The principal investigator (Dr. Josef Stehlik) or the research coordinator (Heather Hanson) or the co-investigator will approach the patients in the hospital during their

stay or at the Heart Failure/Cardiology Clinic to discuss participation in this study. Charts will be screened at study locations for diagnosis of heart failure. Patients with such diagnosis will be approached in person by the aforementioned study team members and told about the study. If the patient is interested, further review will be completed with them all in a confidential manner.

**Participant Recruitment and Training:** All patients admitted to VA Medical Center in Salt Lake City with heart failure or seen in the Heart Failure Clinic or General Cardiology Clinic, who meet eligibility criteria, will be screened by a research coordinator, PI and Co-investigators. Patients meeting eligibility criteria will be approached regarding participation in this study. The PI and the other sub-investigators will be responsible for the care of these patients when they get admitted to the hospital or seen in the clinic. The PI, the Co-investigators and study coordinators will invite the potential participants into the study (if they meet inclusion/exclusion criteria) and explain to them the procedure in detail. If the patients agree to participate in the study, they will be asked to sign the consent form. We are not planning to post flyers or send recruitment letters. Follow-up phone calls will be made within one week to one month after enrollment.

After consenting, all subjects will be trained on placement of the device on the skin with supervision, guidance, and directions from the study team. The subject will have ample time to try the device themselves as the site will have extra adhesives and inactive devices for the purposes of demonstration. Subjects may be trained and fitted as hospital in-patients and re-trained in clinic when necessary. Written take-home instructions will also be provided.

The initial device that the subject wears will be placed, and data collection started at the end of the in-hospital training session. Subsequently, additional adhesive patches (and replacement devices as needed) will be provided to subjects via mail by PhysIQ (along with a supply of adhesive remover wipes), and subjects will be asked to replace the device adhesive at home on their own whenever sent. Subjects will be provided with a technical support phone number to call for assistance.

Subjects will also be provided at this time with a smartphone that is paired with the wearable device and serves to receive data from the device and upload it to the analytics server via cellular network or WiFi internet. Subjects will be asked to return the smartphones at the end of the study during a routine clinical visit or in a prepaid mailer provided to them. Patients who complete the 90-days of telemonitoring will be given an option to keep the smartphone for their personal use (once all study related data is erased). Subjects will be provided with a technical support phone number to call for assistance. Subjects will be asked to wear the device as much as possible, with an ideal aim of near continuous data collection throughout study participation. However, it is anticipated that the subject may have acceptable periods of time when the device is not worn and data is not collected due to any of the following:

- Removing the device due to failing adhesive or to swap out a device.
- Removal of a depleted device while awaiting a replacement.
- Removal of the device for an interval for any reason of necessity of the subject (e.g., travel, procedure, etc.)

**Participant Follow up:** Subjects will participate in the trial for up to 90 days. Subjects will be mailed replacement adhesives as needed. Subjects will replace the adhesive themselves, per written take-home instructions. Data from the device will be uploaded in real-time and reviewed

by PhysIQ; in the event that data from the device indicates a problem with device function, placement or use, the subject will be called to confirm placement and use instructions.

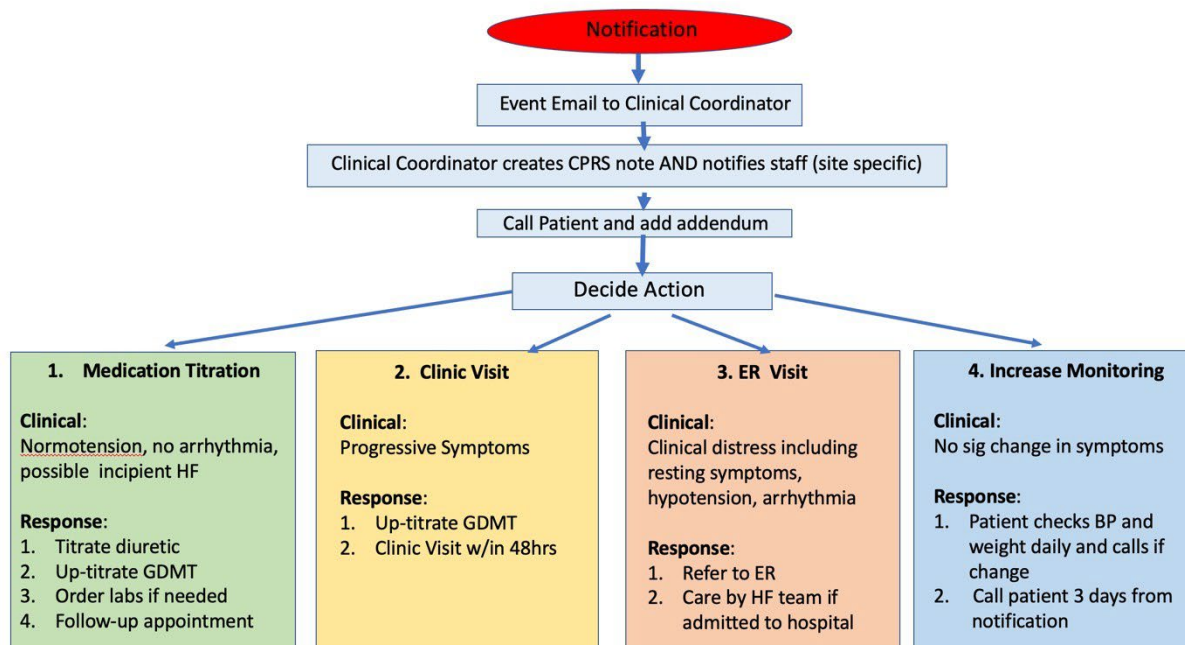
Should the subject damage, lose or have a malfunctioning study phone, a replacement will be provided to them at no expense. Such circumstances will not affect study participation nor incur any financial responsibility. However, if the subject has a pattern of losing the equipment generally it (phone /band aid) prevents acquisition of data and the study team may withdraw the subject.

After discharge from the hospital, the study staff will interact with the subject during follow-up visits scheduled for routine HF follow-up. Per clinical practice, the first clinic visit will be scheduled within 2 weeks of discharge. Subsequent study visits in the 90-day study period are expected to take place at day 30 and day 90 (+/- 7 days). If a face-to-face visit is not possible after a clinic visit the information will be obtained by calling the patient within the study visit window to address any study related questions, including device and phone functioning.

Additional encounters with providers will occur if alerts are generated based on remote monitoring data. The alert notification will be through the electronic health record (CPRS), and documentation of the response to the alert by the clinical team will also take place in CPRS. To reduce variation in response to clinical alerts, clinicians will follow a standardized response algorithm (**Figure 1**). Based on the remote monitoring data, clinical symptoms and blood pressure, the HF nurse will determine the suggested clinical action - medication up-titration, clinic visit, emergency room (ER) visit, or increase monitoring and confirm with the physician that this action should be implemented. In the control arm, information from the sensor will be collected, but clinical alerts will not be generated or communicated to the providers. Any treatment decisions will be made by the participant's clinical care team; the device only provides the alert and does not guide treatment. The research team will not be responding to the alarms. Of note, the remote monitoring data are not used for immediate decisions unrelated to the aims of the study. E.g., the device is not being used as an arrhythmia monitor and there is no real-time monitoring or clinician driven decision-making related to possible arrhythmias. In patients enrolled in the control arm, remote monitoring data are not being used for any clinical decisions. Patients are instructed to continue to seek care for their medical needs in the standard manner.

The subjects' medical record will also be reviewed to determine whether any medical events of interest took place within the VA medical system. Medical events of interest include all-cause hospitalizations, emergency room visits, unplanned outpatient visits with medical providers, and medication changes. Study relevant data will be entered in the electronic case reports system.

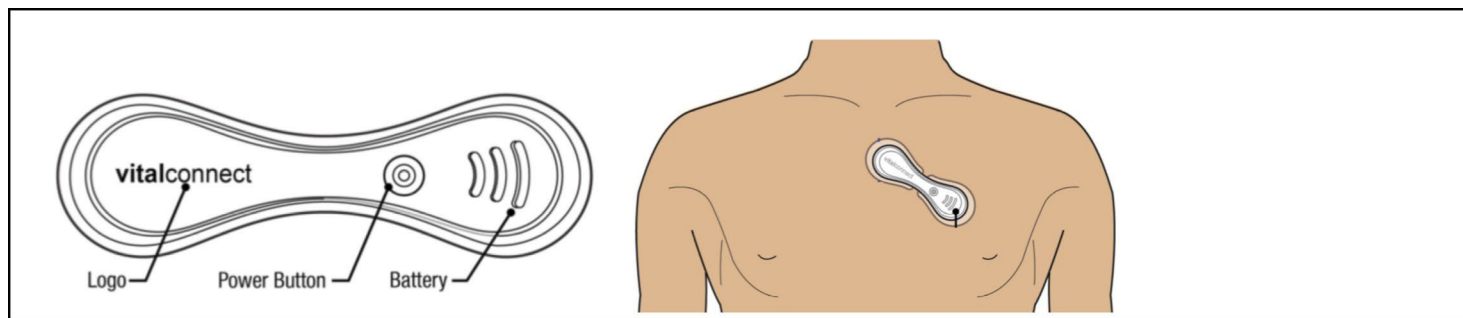
We will access VHA's national Electronic Health Record (EHR) by way of CAPRI and/or JLV to determine health care costs.



**Figure 1.** LINK-HF response algorithm to the clinical alert

**Study Device:** The device (VitalConnect wearable patch, Figure 2) is a wearable adhesive Band-Aid-like multi-sensor that will be used to collect continuous vital sign data including; ECG, triaxial accelerometer, skin temperature and Impedance indicative of skin contact from patients (PhysIQ, Inc, Naperville, IL).

The devices communicate wirelessly, and information is then transmitted to a provided smart phone given for patient to use while on the study. The smart phone securely uploads the information to remote computers which automatically analyze the data and make results available to study investigators.



**Figure 2.** The VitalConnect wearable patch

## **2) Non-Experimental Implementation and Qualitative research:**

A subset of up to twenty enrolled patients will be approached to participate in a semistructured interview that will examine their experience with the study procedures as part of a qualitative research part of the study.

As part of implementation research, up to ten clinicians of SLC VAMC and up to ten clinicians in each participating site will be approached to participate as clinician participants in cognitive task analysis before subject enrollment starts and in semistructured interviews after subject enrollment has initiated.

The interviews will be transcribed and analyzed. Authorization documents/cover letters will be read to the participants before the interviews to confirm their willingness to participate in the interviews.

## 5.1 Study Design

Randomized, Placebo-Controlled Clinical Trial  
Vanguard site #1: Salt Lake City VAMC Vanguard  
site #2: Gainesville VAMC Additional sites:  
Houston VAMC  
Richmond VAMC  
Palo Alto VAMC  
Portland VAMC

## 5.2 Recruitment Methods

**Sample Size of experimental study:** 60-125 subjects from Salt Lake City VA Medical Center. 30-80 at each of the other five sites for a total of 240 enrolled subjects.

This is a multi-center study. Salt Lake City VAMC will be the first site to be activated. One more center will be activated later in year 1 of the study - Gainesville VAMC. Additional 3 centers (Richmond VAMC, Palo Alto VAMC, Houston VAMC) will be activated once implementation data from the two vanguard sites are evaluated. To optimize enrollment, one additional site will be activated – Portland VAMC (provision for an activation of an extra center was included and approved during the original HSR&D review process). All sites will follow the same process to submit the LSI local application for CIRB approval.

All patients admitted to the VA Medical Center in Salt Lake City with heart failure or seen in the Heart Failure Clinic or General Cardiology Clinic, who meet eligibility criteria, will be screened by a research coordinator Heather Hanson or a coinvestigator.

Patients meeting eligibility criteria will be approached regarding participation in this study. Dr. Stehlik, Heather Hanson or co-investigators will invite the potential participants into the study (if they meet inclusion/exclusion criteria) and explain to them the procedure in detail. If the patients agree to participate in the study, they will be asked to sign the consent form. Follow-up phone calls will be made within one week to one month after enrollment.

Since all patients eligible for participation will be cared for in the hospital, no flyers or recruitment letters will be identified.

There will be no monetary compensation to the participants. However, if patient participants complete the 90-day study, he or she will be given an option to keep the study phone after the data has been collected and removed, for personal use. Device will not include any paid cellular plans or WiFi internet service once given to subject.

*Identification of prospective participants:* A “recruitment waiver” of the Health Insurance Portability and Accountability Act (HIPAA) authorization from the VA Central Institutional Review Board (CIRB) allows study personnel to screen for prospective participants using approved electronic health information files (corporate data warehouse), rolls of patients attending specific clinics, or medical records, with the assistance of local clinical informatics (IT) personnel as required.

Site study staff may contact a treating healthcare provider to explain the LINK-HF2 study and discuss whether the treating provider believes an identified prospective participant is suitable for participation in the study.

To minimize the possibility of coercion or undue influence. We will explain to the patients and clinicians that they are not obligated to participate in the study. Additionally, we will explain to them that should they choose to become a study participant, they can withdraw any time after enrollment. Furthermore, we will explain to the patient participants that if they decline to participate in the study, their medical care will not be impacted, and they will receive the same medical care as planned before.

To allow adequate time to exchange information and questions between the investigator and participant. We will ensure that the participants clearly understand the study procedure. We will spend adequate time with the participants, to address all questions and concerns the participants may have. Subjects are then scheduled at a mutually convenient time and enrolled.

**Risks:** This is a non-invasive monitoring system in which adhesive surface of a sensor device is placed on the skin of the chest. The possible risks from the device are:

1. Skin irritation due to subjects who may have an allergy to rubber, latex or Band-Aid-type adhesives may experience irritation at the placement of device.
2. Skin damage due to adhesives: Subjects with delicate or thin skin may have skin abrasions or tears when removing the disposable adhesive, The risk of adhesive issues are minimized by advising the patient on methods for safe removal, such as soaking the adhesive patch with hot water, use of rubbing alcohol to dissolve the adhesive, as well as slow and careful removal.

If the reaction is determined to be more than mild by the study team member or by the study patient, the adhesive / device will be removed, and the subject withdrawn from the study.

The participants assigned to the active arm will have their treatment directed by an algorithmic response to clinical alerts generated by the remote monitoring predictive algorithm. While we anticipate this will result in improved outcomes, potential risks may include increased risk of adverse events normally seen with guideline directed therapy for heart failure (e.g hypotension, dehydration), or increased risk of hospitalization.

**Benefits:** Experimental Procedures

1. We believe data obtained from the wearable remote monitoring and the subsequent early interventions based on alarms generated the data will enable us reduce hospitalizations due to heart failure exacerbations.
2. Avoiding hospitalization due to heart failure exacerbation is also likely to improve patient quality of life.
3. On a healthcare system level, reducing the number of heart failure related hospitalizations reduces expenditures in the broad population of patients with heart failure.

**Confidentiality:** All study patient data will be stored both on paper and electronically on secured, password-protected computer systems in physically locked facilities at the VA and at PhysIQ offices. The only people who will have authorized access to any of this data are the investigative medical staff at the VA hospital, and authorized personnel of PhysIQ, all of whom have been certified under patient confidentiality training.

Data collection outlined in the protocol will be collected on electronic case report forms (eCRFs in OpenClinica. OpenClinica is a HIPPA compliant cloud-based data reporting system commonly used in multi-center clinical trials.

All research staff having access to study data have completed the VA Privacy and HIPAA training and the VA Privacy and Information Security Awareness and Rules of Behavior training within the past twelve months which will be locked at all times with access available only to the investigator team.

#### **Non-Experimental Implementation and Qualitative research:**

**Sample Size of qualitative part of the study:** As part of a qualitative research part of the study, a subset of up to twenty enrolled patients will be approached to participate in a semistructured interview that will examine their experience with the study procedures. In addition, up to ten clinicians of SLC VAMC and up to ten clinicians in each participating site will be approached to participate as clinician participants in semi-structured interviews that will be part of the implementation process and integration of remote monitoring into the clinical workflow at SLC VAMC.

Participants in the experimental part of the study will be approached during follow-up appointments to see if they are interested in participating in semi-structured interviews. The interviews will be explained to the patients. The interviews will be scheduled, and authorization documents/information sheets will be read to the subjects immediately before the interviews to confirm their willingness to participate in the interviews.

Up to 10 clinicians/site on the HF team will be approached to participate as clinician participants in cognitive task analysis interviews before subject enrollment starts and in semi-structured interviews after subject enrollment has initiated. Authorization documents/information sheets will be read to the participants immediately before the interviews to confirm their willingness to participate in the interviews.

**Risks:** The risks are mostly limited to the possible loss of confidentiality since the interviews will be recorded. All appropriate precautions are being made to preserve confidentiality.

**Benefits:** There will be no immediate direct benefit to participants. On a system level, this research will help implementation of the studied approach to clinical workflow.

**Confidentiality:** All study patient data will be stored both on paper and electronically on secured, password-protected computer systems in physically locked facilities at the VA and at PhysIQ offices. The only people who will have authorized access to any of this data are the investigative medical staff at the VA hospital, and authorized personnel of PhysIQ, all of whom have been certified under patient confidentiality training.

The information collected for this study will be kept confidential. There will be no photographs or videos of the interview. Transcription services will be provided by VA Centralized Transcription Service Program (CTSP). All identifying information will be removed during the transcription process. All care provider data and interview recordings and transcripts will be stored both on paper and electronically on secured, password-protected computer systems in physically locked facilities at the VA offices. The only people who will have authorized access to any of this data are the investigative medical staff at the VA hospital and the study operational partner PhysIQ.

All research staff having access to study data have completed the VA Privacy and HIPAA training and the VA Privacy and Information Security Awareness and Rules of Behavior training within the past twelve months which will be locked at all times with access available only to the investigator team.

## 5.3 Informed Consent Procedures

### CONSENT PROCESS

The potential participants who meet inclusion/exclusion criteria will be approached a few days before discharge from the hospital or at the time of their routine follow-up clinic visit at the Heart Failure Clinic. After the participants consent to join the study, the non-invasive monitoring device will be fitted to the patients. Once the patients give their verbal consent, we will obtain their written consent immediately afterwards as well. Therefore, there will be no waiting period between the consent process and the procurement of written consent. The patients will be free to ask about any details pertinent to the study. They will also be allowed several hours, if needed, to discuss with family and significant others before making the decision to participate.

We will explain to the patients that they are not obligated to participate in the study. Additionally, we will explain to them that should they choose to become a study participant, they can withdraw any time after enrollment. Furthermore, we will explain to the patients that if they refuse to participate in the study, their medical care will not be impacted, and they will receive the same medical care as planned before.

We will ensure that the patients clearly understand the study procedure. We will spend adequate time with the participants, to address all questions and concerns the patients may have. Subjects are scheduled at mutually convenient time and enrolled. Their time is not a limitation. In the event we are

unable to continue using a hospital room for research purposes we will take the individual(s) over to the outpatient area prior to leaving the facility.

For the subset of enrolled patients and for clinicians participating in semi-structured interviews as part of implementation and qualitative research, authorization documents/cover letters will be read before the interviews to confirm their willingness to participate in the interviews.

## **SPECIAL INSTRUCTIONS AND DEFINITIONS OF EVALUATIONS**

### **Informed Consent**

Informed consent must be documented per local regulation. Documentation of consent must be noted in the subject's medical record and/or the original signed consent must be available for review. Consent will be additionally confirmed in an eCRF. Reconfirmation of consent should be verbally checked at every subsequent interaction. Withdrawal of consent shall be documented in the subject's record and in compliance with local regulations.

### **HIPAA Release Form**

HIPAA release document will be part of the informed consent document.

## **5.4 Inclusion/Exclusion Criteria**

### **Inclusion Criteria:**

- Subject must be 18 years old or older
- NYHA (New York Heart Association Functional Classification) Class II-IV, documented in site's medical record system.
- Subject able and willing to sign Informed Consent Document.
- Subject willing and able to perform all study related procedures.

### **Exclusion Criteria:**

- Expected LVAD (Left Ventricular Assist Device) implantation or heart transplantation in the next 30 days.
- Skin damage or significant arthritis, preventing wearing of device.
- Uncontrolled seizures or other neurological disorders leading to excessive abnormal movements or tremors in the upper body.
- Pregnant women or those who are currently nursing.
- Visual/cognitive impairment that as judged by the investigator does not allow the subject to independently follow rules and procedures of the protocol.

Subjects must meet all inclusion/exclusion criteria of the protocol; each study site will complete the eCRF in the electronic case report system within 72 hours of enrollment. Any deviation must be reported to the CIRB as per guidelines.

## 5.5 Study Evaluations

Experimental procedures:

After enrollment, the patients will be followed-up per clinical protocol. The study coordinator will collect clinical information regarding patient's medical therapy and the outcomes of interest and submit via eCRFs. The information will be collected through CPRS, and the coordinator may ask clarifying information from the subjects during their clinical visits. If care for the patient is provided at a non-VA hospital while enrolled in the study, the subject will be asked to sign a release of information form and relevant data collected from the corresponding medical records.

The patients will be asked to complete a short version of the Kansas City Cardiomyopathy Questionnaire (KCCQ-12) and a visual analogue scale (VAS) at the time of enrollment, at 30 days and at 90 days after enrollment or study exit if different than 90 days  $\pm$  7 days.

Qualitative research:

Up to 20 subjects enrolled in the randomized study will participate in a semi-structured interview that will examine their experience with the study procedures as part of a qualitative research part of the study. The interview will last 30 to 60 minutes.

As part of implementation research, up to ten clinicians of SLC VAMC and up to ten clinicians in each participating site will be approached to participate as clinician participants in cognitive task analysis before subject enrollment starts and in semistructured interviews after subject enrollment has initiated. The interview will last 30 to 60 minutes.

Authorization documents/cover letters will be read to the participants before the interviews to confirm their willingness to participate in the interviews. The interviews will be audio-recorded, transcribed, and analyzed.

## 5.6 Data Analysis

HF hospitalizations will serve as the primary outcome in a pivotal trial of the effect of the remote monitoring intervention. A key parameter for determining the statistical power in a pivotal trial of the effectiveness of the intervention for this outcome and other secondary outcomes is the proportion of subjects who meet the algorithm's criteria for an alert, and thus may potentially be affected by the intervention. The statistical power of the pivotal trial will also depend heavily on the proper functioning of the remote monitoring. Accordingly, data analyses of our study will estimate the following quantities:

- 1) The proportion of randomized patients who meet the algorithm's criteria for at least one alert;

- 2) The ratio of the number of days the remote monitor is functioning properly (patient wearing device and data quality sufficient to make the daily decision) to the total number of days in the study;
- 3) The rate of HF hospitalization, all-cause hospitalization and LOS for those hospitalized;
- 4) Standard deviations and serial correlations for PRO outcomes (KCCQ, VAS);
- 5) The proportions of patients for whom the KCCQ and VAS fall within subgroups defined by the clinical cutoffs 0-≤25, 25-≤50, 50-≤75, 75-≤100;
- 6) The proportion of randomized patients who are lost to follow-up prior to day 90.

The proportions in items 1, 5 and 6 will be computed in the full randomized cohort with exact binomial 95% confidence intervals (CI). We will also use estimates based on Kaplan-Meier curves (see below) to provide the proportions of subjects with at least one HF hospitalization in the 90 days after enrollment, the 90 days after end of monitoring and the first 180 days by randomized group, with 95% CI for these proportions within each intervention group and for the risk ratio between the intervention and control groups. The ratio of actual vs. intended intervention time the monitor is on and functioning properly will be expressed as the proportion of days the remote monitor is functioning properly, and will be displayed for the full cohort, by randomized group, and by clinical site using box plots and histograms. Summary statistics will be provided to summarize the ratio of actual vs. intended intervention time over the full intervention period. Standard deviations and serial correlations for the patient reported outcomes will be estimated.

A total of 240 randomized subjects (60-125 will be recruited at the Salt Lake City VA) will be sufficient to estimate the proportion of subjects who experience at least one alert to within a margin of error (defined as the half-width of the 95% CI) of no more than  $\pm 0.063$  for an analysis of the full cohort. Assuming  $\leq 25\%$  loss to follow-up,  $\geq 180$  randomized subjects with complete follow-up will be sufficient to estimate the proportion of subjects who experience at least one alert to within a margin of error of no more than  $\pm 0.073$ .

The 240 randomized patients will also be sufficient to estimate the ratio of actual vs. intended time the device is on and functioning properly to within a margin of error of  $\pm 0.042$  assuming complete data on at least 75% of patients and conservatively assuming the standard deviation of this ratio does not exceed 0.289.

## 5.7 Withdrawal of Subjects

We will explain to the patients that they are not obligated to participate in the study. Additionally, we will explain to them that should they choose to become a study participant, they can withdraw any time after enrollment. Furthermore, we will explain to the patients that if they decline to participate in the study, their medical care will not be impacted, and they will receive the same medical care as planned before.

Should the enrolled subject damage, lose or have a malfunctioning study phone, a replacement will be provided to them at no expense. Such circumstances will not affect study participation nor incur any financial responsibility. However, if the subject has a pattern of losing the equipment generally it (phone /sensor) prevents acquisition of data and the study team may withdraw the subject.

## 6.0 Reporting

## Medical/Treatment History

Medical and treatment history data will be captured in the electronic case report system, to ensure that the subject meets all of the inclusion/exclusion criteria, specifically inclusion criterion number.

## Medications

Subject's current medications will be captured in the electronic case report system. Start dates if available will be noted. During the course of the study if a medication is stopped, stop dates will also be noted.

## Status and Event Questionnaire

The questionnaire will be read to the subject by a member of the study team during the clinic visit or telephone call, and answers will be recorded in the electronic case report system. The questionnaire identifies medical events that the subject can recall and report for the interval since the last inquiry, including events that occur at health care facilities outside the clinical setting of the investigator's site and which may otherwise be unknown to the site clinical staff. Events may include acute care utilization or adverse events, in which case AE/SAE evaluations are triggered.

## Adverse Event and Serious Adverse Event

Interim analyses. Two interim analyses will be performed, once 50 subjects and 100 subjects complete the study. The main goal of the interim analyses will be monitoring of patient safety. The anticipated possible adverse events fall into two categories: adverse events related to the study sensor and adverse events related to heart failure therapy.

Interim analysis of adverse events related to the study sensor. We will report to the DSMB the rate of AEs related to the study sensor. We anticipate these may include local allergic reaction to the adhesive, skin rash or skin abrasion. While not reported previously, systemic allergic reaction to the adhesive could also occur.

Interim analysis of adverse events related to heart failure therapy. The study intervention is expected to improve clinical outcomes in subjects with heart failure. However, since the algorithmic response triggered by a study alert calls for changes in heart failure therapy or changes in follow-up, there could be adverse events related to these changes triggered by study procedures.

The following events will be recorded, adjudicated and reported to the data coordinating center: - Over diuresis

- Hypotension induced by heart failure medications
- Other adverse events attributed to HF therapy
- Hospitalization

Reporting of interim analyses. The data coordinating center will tabulate the rates of adverse events at the time of the interim analyses.

Adverse events related to the study sensor will be presented for all study subjects, since all study subjects will wear the sensor regardless of randomization assignment. Adverse events related to

heart failure therapy will be tabulated by randomization assignment. This information will be generated by the data coordinating center and provided to the DSMB. The detailed data by randomization group will not be shared with study investigators unless a protocol modification is deemed necessary by the DSMB.

An Adverse Event is any undesirable experience (as judged by the principal investigator) associated with the use of a medical product in a subject that is not judged to be serious. The event will be deemed a Serious Adverse Event and should be reported to the IRB as such when the subject outcome is: Death, Life-threatening, Hospitalization (initial or prolonged), Disability or Permanent Damage, Required Intervention to Prevent Permanent Impairment, or other serious events as judged by the principal investigator. (See for reference FDA definition at:

<http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm>)

All events shall be reported as per institutional guidelines.

Medical record request to non-VA hospital or emergency department or clinic

In the event that an acute care episode (a primary event) occurs at a non-VA facility, medical records will likely be provided to the clinical team. In the unlikely situation that this does not take place, the subject will be asked to sign a medical record release form, and the study team will obtain the records in question. Relevant data will be entered into the electronic case report system. A subject may also sign the medical record release at the time of consent to cover any possible outside admissions during enrollment.

Determination of Exacerbation timing/Cause

In the event that an acute care episode (a primary event) occurs and is determined to be an exacerbation of a subject's chronic conditions, the site PI will make a determination of the timing and cause of the exacerbation.

### **Inventory of Procedures/ Tests on Readmission**

In the event that a primary event occurs, the PI will have made an inventory of acute care interventions and diagnostic tests carried out on the subjects, as well as length of stay,

### **Study Discontinuation**

Insufficient or poor-quality data

If subjects opt not to wear the device, or if the telemonitoring data are of poor quality, the study team may decide to discontinue the subject from the study.

### **Definition of Medical Events**

Primary Events

1. The proportion of randomized patients who meet the algorithm's criteria for at least one alert;
2. The ratio of the number of days the remote monitor is functioning properly (patient wearing device and data quality sufficient to make the daily decision) to the total number of days in the study;
3. The rate of HF hospitalization, all-cause hospitalization and LOS for those hospitalized;

#### Additional Event Characterizations

For each of the above primary and secondary events, additional details will be captured to relate them to disease and to identify the window for precursor detection and the impact of the event:

1. HF-related or not
2. Exacerbation or not
3. Date of intervention
4. Onset date of first symptoms (if reported)
5. Date and nature of trigger/cause for event, as assessed by PI (if possible)
6. Intervention performed
7. Diagnostic tests performed
8. Outcome of intervention
9. Length of hospital stay

### **DATA MONITORING**

All study patient data will be stored both on paper and electronically on secured, password-protected computer systems in physically locked facilities at the VA and at PhysiQ offices. The only people who will have authorized access to any of this data are the investigative medical staff at the VA hospital, and authorized personnel of PhysiQ, all of whom have been certified under patient confidentiality training.

All centers will use eCRF's-OpenClinica. All research staff having access to study data have completed the VA Privacy and HIPAA training and the VA Privacy and Information Security Awareness and Rules of Behavior training within the past twelve months which will be locked at all times with access available only to the investigator team. Data regarding adverse events will be sent to PhysiQ. All other data will be completed via eCRF. Queries will be issued by PhysiQ for non-conformant/incomplete data. The VA Health Services Research and Development Office will provide oversight in the form of an Data Safety and Monitoring Board (DSMB).

The Data Safety and Monitoring Board (DSMB) is convened by the HSR&D VA office in Washington, DC. and will provide data monitoring oversight to the study approximately every 6 months.

The investigators will provide the requested data and summary reports to the DSMB. Then the DSMB will summarize their findings in letters provided back to the site.

## 7.0 Privacy and Confidentiality

### HIPAA Release Form

All study patient data will be stored both on paper and electronically on secured, password-protected computer systems in physically locked facilities at the VA and at PhysIQ offices. The only people who will have authorized access to any of this data are the investigative medical staff at the VA hospital, and authorized personnel of PhysIQ, all of whom have been certified under patient confidentiality training.

Data collection outlined in the protocol will be collected on electronic case report forms (eCRFs in OpenClinica. OpenClinica is a HIPAA compliant cloud-based data reporting system commonly used in multi-center clinical trials).

All research staff having access to study data have completed the VA Privacy and HIPAA training and the VA Privacy and Information Security Awareness and Rules of Behavior training within the past twelve months which will be locked at all times with access available only to the investigator team.

The implementation and qualitative research study procedures and recorded interviews will be in safeguarded on password protected computers.

## 8.0 Communication Plan

- Dr. Josef Stehlik at the Salt Lake City VA Medical Center will be responsible for the oversight, coordination, and project management of this study. Josef Stehlik will serve as the contact PI and will assume fiscal and administrative management including maintaining communication among investigators, consultants, PhysIQ partner and other key personnel. Additionally, Josef Stehlik will oversee decisions on possible necessary changes in research direction and have the authority to reallocate funds and resources between PIs based on patient enrollment and other considerations.
- Dr. Thomas Hanff, Dr. Biykem Bozkurt, Dr. Karim Sallam, Dr. Carsten Schmalfuss and Dr. Neil Lewis, will be responsible for project administration including regulatory compliance, study team training and study procedure compliance at their respective sites. The investigators will define strategies for patient recruitment and regularly evaluate whether enrollment rate matches the expected progress. Dr Charlene Weir, an implementation scientist, will guide implementation efforts at all the study sites, starting with the vanguard implementation sites in Salt Lake City, UT and Gainesville, FL. She will work closely with Dr Stehlik and keep him informed of any issues requiring his attention. Dr Weir is located in Salt Lake City which will further facilitate communication with the study PI. Susan L. Zickmund, PhD, a qualitative scientist, will work with the study sites to set up provider focus groups and patient interviews. Dr Stehlik will facilitate communication between Dr Zickmund and the local PIs and will assist in identifying providers and patients who will participate in the qualitative research. Dr Stehlik and Dr Zickmund have an established track record

of collaboration. Dr Richard Nelson will identify costs associated with implementation and clinical use of non-invasive remote monitoring in HF and will work closely with Dr Stehlik and other coinvestigators to secure the necessary source data for his analyses. Dr Stehlik will also work closely with Dr Matthew Samore. Dr Samore, a coinvestigator on this project, is the Director of the

Informatics, Decision Enhancement, and Analytic Sciences (IDEAS) HSR&D Center of Innovation (COIN) at the Salt Lake City VA and as such has extensive experience with VA multi-center collaboration, decision-making, and implementation. Dr Samore will be an important resource to the study conduct and also specifically to Dr Stehlik in his leadership role of this multi-center investigation.

- Dr Stehlik will maintain seamless communication with PhysIQ, the industry partner providing remote monitoring hardware and software, participating in site startup, clinical personnel training and serving as data coordinating center. Dr Stehlik will assure that all the study procedures outlined in the study plan proceed as expected and according to the established timeline. PhysIQ was an industry partner in the pilot LINK-HF study funded by the VA Center for Innovation - this collaboration was successful, and no issues of concern were identified.
- The study team will participate in conference calls and investigator meetings. The Principal Investigators will communicate with the study team at least quarterly through conference calls to discuss study progress, any difficulties in following study procedures and any adverse events. Additionally, we plan one in-person investigator meeting. Any decisions involving possible need for changes in study procedures or any other modifications to the research approach will be discussed during investigator calls and input from all the PIs will be sought.
- Heather Hanson, project manager at the SLC VAMC will ensure that regulatory approval at all the 6 participating sites is maintained and communicate closely with local study coordinators. Heather Hanson will monitor progress of approvals of any amendments to the protocol.

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