Innovative Care of Older Adults with Chronic Heart Failure (I-COACH): A Comparative Effectiveness Clinical Trial

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Study Title: Innovative Care of Older Adults with Chronic Heart Failure (I-COACH): A Comparative Effectiveness Clinical Trial

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Background and Rationale

An estimated 6.5 million adults in the U.S. have heart failure (HF) with an estimated cost of >$30 billion annually and projections show that the prevalence will increase 46% by 2030, because of population aging.[11] One- and five-year fatality rates after HF hospitalization are exceptionally high at 22% & 42%.[11] HF is characterized by poor quality of life due to a trajectory of worsening symptoms until death, but HF is amenable to management and prevention of symptoms. [12, 13] When symptoms occur, it is an indicator that hemodynamic measures are out of normal range, which requires intervention before symptoms accelerate into a patient crisis requiring emergent medical intervention.[13] The most common HF symptoms also serve as warnings for impending crisis: chest pain, dyspnea, edema, fatigue, orthopnea, and anxiety/fear.[13]

The amount of support available from providers to manage daily patient symptoms and complications is far beyond what is feasible during episodic primary care provider visits.[14] Self-care patient behaviors are well known to improve HF outcomes; however, self-care is underutilized and underappreciated while pharmacological interventions are seen as more important by patients, clinicians and healthcare systems.[15] Recommended self-care behaviors are: accurate and timely symptom perception, daily management and ongoing preventive maintenance to include behaviors such as smoking cessation, maintenance of normal weight, regular physical activity, reducing dietary sodium, decreasing alcohol use, maintaining a healthy diet and cholesterol, monitoring blood pressure (BP), and blood glucose.[15] Other prevention actions include annual dental exams, flu shots, health screenings and check-ups. The complex needs of these patients require a new vision and paradigm for delivery of health care services, such as an Mobile Health (mHealth) management model. mHealth technologies such as blue-tooth enabled BP, heart rate, weight, and pulse oximetry (POx) remote monitoring permit sharing of immediate real-time biometric data and video messages with providers & delivery of instantaneous feedback to patients before symptom crises.[16]

mHealth interventions have been studied worldwide in >30 low-and middle-income countries.[17] Recent meta-analyses and systematic reviews agree mHealth monitoring is generally effective in reducing HF hospitalization[18-23] and short term mortality.[17-21, 23, 24] Research is more limited and often equivocal but found somewhat effective in improving quality of life,[19, 20, 23-27] medication adherence,[17] cardiac lifestyle behaviors and disease management,[17, 19, 27] and sometimes patient satisfaction.[20] Most studies used hospitalizations and mortality as primary outcomes and *gaps in knowledge remain* with important patient-centered outcomes, such as self-care, symptom management, functional capacity, psychological distress, and caregiver burden.[16, 25, 28-30] Additionally,

most studies did not stratify outcomes according to demographic variables[23] or engage samples that were sufficiently racially/ethnically diverse.[23, 27]

mHealth technologies have established efficacy in the care of patients with HF, yet there is a decisional dilemma because HC systems, providers and payers do not know which care model should be used for a particular patient profile according to severity of HF, co-occurring multi-morbidities, or other patient characteristics or living situations, etc. Prevailing gaps in knowledge remain: Which patients will a mHealth model would work better than the traditional provider-directed model for management of HF? Considering patient-centered outcomes, which model improves outcomes important to patients, such as function, symptom control, distress, quality of life, and caregiver burden?

Specific Aims and Hypotheses

Aim 1.

The principle aim of our proposed clinical trial is whether an enhanced *mHealth care management model* with connected health technology used in partnership with the healthcare system team, an older person with heart failure (HF), and their caregiver are more effective than a *provider directed management model* using non-connected home equipment kits. Self-care of HF, quality of life and quality care are represented by multiple outcome measures that are important to patients, caregivers and healthcare (HC) systems. Specifically,

Aim 1a. Patient-centered outcome measures**:** We hypothesize that the mHealth model will increase measures from baseline to 3- and 6-month for the primary outcome of self-care management of HF[1] compared to the provider-directed model. Further, we hypothesize that the mHealth model will increase measures from baseline to 3- and 6-month for secondary outcomes of Self-efficacy to manage symptoms, medications, & treatments[2]; self-care confidence[2]; physical function, sleep, social roles, (Promis 43v2.1 Health profile[3]); heart failure knowledge;[4] satisfaction with care[5]; quality of life[6]; informational support[3] and equipment usability (3 and 6 months),[3, 7]while decreasing health distress,[8] anxiety, depression, fatigue, and pain[3] compared to the provider-directed model.

Aim 1b. Caregiver outcome measures: We hypothesize that the mHealth model will reduce caregiver burden,[9] while increasing caregiver health[10] compared to the provider-directed model from baseline to 6-months.

Aim 1c. Health system outcome measures: We hypothesize that the mHealth model will reduce hospital admissions, 1-month readmissions, emergency department

visits, and 6-month mortality of HF participants while increasing satisfaction with care,[5] compared to the provider-directed model.

Aim 2.

We aim to explore associations of outcome measures with certain patient characteristics to determine which patients benefit the most from each care model, considering important patient-centered characteristics such as function, HF severity, rurality, and other demographic characteristics; and considering location of caregivers, and HC system outcomes such as emergency department visits and readmissions.

Aim 3.

We aim to explore whether changes in self-efficacy,[2] HF knowledge,[4] and/or skills[1] mediate the effect of self-care management.[1]

Study Design and Procedures

This will be a single-blinded comparative effectiveness randomized controlled trial conducted in a real-world setting. Subjects with HF and their caregivers (dyads) will be recruited and randomly assigned to one of two study arms:

- a provider-directed management model (with home monitoring equipment), a standard care-plus, OR
- an enhanced-mHealth care management model (with connected monitoring equipment).

Both groups will receive HF guideline-directed usual care, defined by the American Heart Association and College of Cardiology HF Guidelines[13] with widely demonstrated effectiveness[12] and have the same opportunity for education, nutrition counseling, nurse management, and HC provider access. This is usual care at UAMS.

Recruitment: Research participants will be recruited consecutively from the UAMS Medical Center. The project director will receive a daily list from UAMS bioinformatics core via UAMS secure/encrypted email of patients admitted to the hospital with a primary or secondary diagnosis of heart failure. Patients will be visited by the research team when they are stable and likely the day of discharge from the hospital (that way, likely the family/caregiver will be here as well). At that time, information will be given to the patient (and family/caregiver if present) about the study. If they would like to, we will obtain consent from both the patient and the caregiver if agreeable. Alternatively, they can think and talk about whether they want to participate and we will follow up after return home.

See section on participants and human subject protection for more details on

recruitment & consent.

The randomization will be generated using a computer algorithm using random permuted blocks (of differing size) to ensure balance over time in the numbers allocated to intervention groups and to avoid study staff anticipating the next treatment allocation. Randomization will be centrally generated by Co-I Ounpraseuth and study staff who allocate interventions will be blinded to both the sequence and size of the blocks.

Participants will be randomized then they will complete baseline measures (self-reported survey measures, see Table 1.). Because all participants & caregivers will participate in the same recruitment procedures, measure timelines, and will receive monitoring equipment, participants will be blinded to their assigned group and will not be informed of which is the active intervention group. Both groups will receive standard education provided by the hospital and clinic providers, in addition the study staff will emphasize portions of the standard education provided regarding *emergency situations that require immediate action from the patient and/or caregiver such as; hypertension crisis, stroke signs and symptoms, and signs and symptoms of heart attack.*

The provider-directed management model is the current standard of care in the treatment of patients with HF including guideline-based HF care and a fee-for-service payment model in which the number of services and procedures that are provided are billed. Patients are typically scheduled for provider visits at a periodic interval rather than on patient needs, preferences, or circumstances.[36] Care delivery is based on convenience of provider and sometimes on priority-based queues, that is If patients are having problems, they typically call the providers office or set up an appointment to visit the clinic weekdays and get priority scheduled. If problems occur at a different time, they frequently go to the emergency department (ED) at a local hospital[36] or UAMS.

Caregiver burden is substantial in this model considering the patients' problem solving, care, and transportation needs.[16] Our previous research[35] confirmed both the traditional call/wait approach and ED alternative as usual means of provider communications. However, in this study, we are supplementing standard care by providing and training each patient in the use of an analog kit: (not internet connected) weight scale, blood pressure cuff, pulse oximeter, and a Log for recording their vital sign measures. Patients will be trained on the equipment and told to obtain a reading of weight, BP, and POx saturation every morning when they arise. Participants will make appointments, receive consultations, case-management, and resolve problems through in-person appointments or telephone communications as usually scheduled during the 6-month study follow-up.

Subjects will be instructed to record their daily readings on a paper log provided by the research team. These monitoring devices will not transmit readings to a centralized location and no one will be alerted to out-of-range readings or compliance with taking daily vital sign measures. At the front page of the log, normal ranges will be described with brief instructions about what participants/caregivers should do if their readings are out-of-range. These instructions will be developed with guidance from physicians/providers in the cardiology department. Per protocol, participants will be instructed to telephone the provider's office or the standard "on-call" line for further consultation and evaluation as needed. The number of provider visits will be collected using the electronic medical record and patient self-report). Patients will be encouraged to bring their vital sign measure logs to their provider appointments. Logs will be collected at the completion of their participation in the study. The log data will be recorded and saved for further data analysis.

The mHealth care management model. We will provide each patient randomized to this group with a weight scale, blood pressure cuff, & pulse oximeter (POx) kit connected to a Bluetooth-paired Android Health Tablet over the 6 months. This will allow real-time collection and monitoring of patient's vital sign measures, instantly accessible 24 hours a day, every day, by both patients and their clinicians, via a wireless gateway that transmits readings to a secure cloud-based clinician portal. The clinician portal will be monitored by the hospital's call center where registered nurses (RNs) will be specially trained to triage these patients according to physician/provider and study team-developed protocols.

Patients will be trained on the equipment and obtain a reading of weight, BP, and symptom survey every morning when they arise. A POx saturation reading will be obtained as needed. We used identical procedures in our pilot study and reported high patient daily adherence (85%) and call center accuracy (90%).[35] Patients have the option to receive patient-centered education, nutrition counseling, nurse & medication management, and problem-based medical visits through live audio and video connected technology in their home. Diagnostic testing and some problems, if needed, will necessitate a visit to a local laboratory, regional UAMS clinic or main campus as usual. Caregivers will be encouraged to attend sessions or telehealth appointments from any location virtually. We will work with the providers, case managers, and our hospital system to train for telehealth visits as well as coding and billing.

Vital sign readings will be sent to the secure cloud-based software. Patients will be encouraged to take their vital signs daily. If the readings are out-of-range, the Registered Nurse (RN) Call Center will be automatically alerted via an email message. Protocols were developed by the medical providers as to acceptable and unacceptable

vital sign ranges/readings and actions. (We did this with the pilot study, and the procedure worked well). If within normal range, no intervention would be needed, and readings will be saved for future data analysis. This is considered a “green light”, that is no alert is triggered and no intervention is needed.

If readings are missed or trending out of range, or out of range now, the call center RN will follow the provider/study team developed protocol or algorithm for “yellow light” “orange light” or “red light”, in order of severity. The call center will monitor patients Monday-Friday 7-4pm as per the provider developed protocol. Patients will be instructed on what to do outside of those hours.

A “yellow light” alert means that the readings may begin to trend close to abnormal (too high or too low), or that the participant forgot to take the readings for that day. These patients will be flagged for follow-up. Yellow light follow up: RN call center reviews the new readings and if the trend has not continued, then no action will be taken. If the participant remembered to take his readings and they are within ranges set, no action will be taken. Participants will be encouraged to take readings daily but will not receive a call until they have multiple missed readings per provider developed protocol.

If the additional readings are “out of range” per protocol, then this is an “orange light” the RN call center nurse will telephone the participant and follow protocol. 1) for a missed readings: “inquired as to why they have been missing readings and ask the patient to take a reading now” if ok, no action will be taken and this encounter will be recorded.

If vital sign readings are abnormal, they will first check (per orange-light protocol) that the patient took the readings properly and that they took their medications that morning as usual before readings were taken. The RN will direct the participant to retake the vital signs after sitting for 15-30 minutes (per national guidelines), inquire if they have taken blood pressure/diuretic medication yet that day, and how they are feeling. Per yellow and orange-light protocol, if the preceding has not been done and readings are retaken and are normal, no further action will be taken. The encounter will be recorded by the call center RN. The Call Center will also direct the patient to follow protocols prescribed to them by their cardiology provider, such as the diuretic protocol for fluid retention/weight gain.

If the readings continue to trend out of range, this is considered an “orange light” and the provider/clinic will be notified by the call center RN of the information collected and vital signs and information recorded in EPIC and will be handed off to the provider to follow up as needed for medical care, this will occur M-F 7 am to 4 pm. During triage of an “orange light,” the Call Center will also direct the patient to follow protocols that are prescribed to them by their cardiology provider, such as the diuretic protocol for fluid retention/weight gain.

At that time, the participant's treatment plan may be altered by the provider to include increased vital sign tele-monitoring for that day, a change in medications, a video telemedicine home or in person office visit, or instructions to report to the emergency department for immediate evaluation and treatment if needed. The study team will not interfere with medical treatment and will not determine medical treatment. They will instruct the participant to follow prescribed protocols from their provider.

A "red light" is considered severe symptoms and/or critically abnormal vital signs. These patients are instructed at enrollment in the study *about emergencies that require immediate action (call 911 or go to the local emergency department) without waiting for a call from the call center, such as hypertension crisis, stroke signs and symptoms, and signs and symptoms of a heart attack.*

The call center will follow up on red alerts to make sure the participant followed standard education previously provided regarding emergencies and reeducate them and their caregiver as needed. As with all triage calls, this will be documented in the medical record.
If a yellow, or orange light occurs, and the participant does not answer the phone, the caregiver will be called. The caregiver will be instructed to make contact with the participant to return a call to the call center for instructions. If participant and caregiver are not available, a message will be left about the readings with instructions to telephone the call center number as soon as possible. A second call to the home and caregiver will be done this day if a return call is not received and same protocol will be followed as above. If no answer and no return call, this procedure will be followed per call center triage protocol.

mHealth participants will be told they can contact the call center RN for problems or concerns using the tablet or telephone and these will be triaged by RN call-center per protocol. Daily vital sign measures, recommendations, and responses will be transmitted, provider visits counted, tabulated and saved for analyses.

Outcome Measures and Measurement Procedures

Measurement instruments are included in **Table 1** (next page) and grouped for the patient, caregiver, and system measures, specific aim addressed and type of outcome measure.

After screening to determine eligibility and fully informed consent process is followed and obtained, participants and caregivers will be randomized and asked to complete baseline assessments. Participants in both groups will be allowed to take assessment

questionnaires home to fill out within 1 week (+/- 1 week). The Research Assistant (RA) will travel to the participants' home, will be available by phone, or will arrange a convenient time before or after a closely timed provider appointment to complete the measures and train on use of the equipment. We will offer these convenience techniques at baseline, 3- and for the final 6-month follow-up measures.

Compensation

Participants and Caregivers will receive compensation for each measurement interval to thank them for their time and to encourage completion of the study. Participant incentives will be $25 each for baseline and 3-month measures, and $50 for the final 6-month measure (for a total of $100). Caregiver compensations are $25 each at baseline and at 6-months (total $50). Participants and Caregivers will also be reimbursed for gas mileage expense ($.58 per mile per PCORI standards).

Language

Instruments will be provided for English and Spanish-speaking patients, may be read to the participants if desired, and will be installed with large print and/or an easy-to-use format loaded on the tablet device. Outcome data/measures for the provider and hospital system will be obtained from the electronic medical record and hospital computer database within 30 days after the 6-month follow-up measures have been completed.

Table 1. Specific Aim Addressed, Measure, Outcome Type, Purpose of Measure, Administration Interval & Estimated Participant Completion Time

SP. AIM	Measure	Outcomes	Purpose of Measure	Base line	3 mth	6 mth	Completion Time
		PATIENT CENTERED OUTCOME MEASURES					
1a	*Self-Care of HF Index v7.2*	***Primary Outcome**:*	*Assess self-care management, symptom perception & maintenance skills*	X	X	X	*8 min.*
3	*Self-Care Confidence [44]*	***Hypothesized Mediator:***	*Assess confidence in ability to care for self*	X	X	X	*3-5 min.*
3	*Promis® Self-Efficacy to Manage Symptoms [3]*	***Hypothesized Mediator:***	*Assess ability to manage symptoms for chronic conditions*	X	X	X	*15-20 min.*
3	*Promis® Self-Efficacy to Manage Medications & Treatments[3]*	***Hypothesized Mediator:***	*Assess ability to manage medication & treatments for chronic conditions*	X	X	X	*20 min.*
3	*Dutch HF Knowledge Scale[4]*	***Hypothesized Mediator***	*Assess Knowledge of HF*	X	X	X	*5 min*
1a & 2	*Promis® 43v2.1 Health profile [3, 49]*	***Secondary Outcome Patient Characteristics***	*Assess physical function, anxiety, depression, fatigue, sleep, social roles, and pain*	X	X	X	*10-20 min.*
1a	*Health Distress [8]*	***Secondary Outcome Patient Characteristics***	*Assess psychological impact/health distress*	X	X	X	*1-3 min*
1a	*Promis® Informational Support v 2.0 6a [3]*	***Secondary Outcome***	*Assess perceived availability of helpful information or advice*	X	X	X	*2-4 min.*
1a	*System Usability Scale [7]*	***Secondary Outcome***	*Ease of using the technology*		X	X	*3-5 min.*
2	*St. Louis University Mental Status (SLUMS) Examination[41]*	***Secondary Outcome: Patient Characteristic***	*Cognitive assessment (OBJECTIVE MEASURE)*	X			*10 min.*
2	*Patient Demographics (self-report & medical record review)*	***Secondary Outcome: Patient Characteristics:***	*Education, income, rurality, HF severity, years diagnosed, caregiver location, etc*	X			*5 min.*
1a	*Minnesota Living with HF (MLHFQ)[6, 51]*	***Secondary & Long-Term Outcome***	*Assesses Quality of Life*	X		X	*5-10 min.*
2	*Newest Vital Sign[60]*	***Secondary Outcome: Patient Characteristics***	*Screens for Health Literacy*	X			*5 min.*
		CAREGIVER CENTERED OUTCOME MEASURES					
1b	*Caregiver Burden [9]*	***Secondary Outcome***	*Assess caregiver perception of burden*	X		X	*30 min.*
1b	*Optum ®SF-36® v2 Health Survey[52]*	***Secondary Outcome***	*Health domains- Functional Psych. Health & Well-being*	X		X	*5-10 min*
		PROVIDER & HEALTH SYSTEM MEASURES					
1c	*Satisfaction with Care[5]*	***Secondary Outcome***	*Patient assesses satisfaction with care*	X	X	X	*1-3 min*
1c & 2	*Hospital, Emergency Visits, Provider Visits, Mortality*	***Secondary Outcome***	*Counts from Medical Record*	X	X	X	*N/A*

Study Population

A sample of 400 patients with HF and their caregivers (dyads, a total of 800 subjects) will be recruited using consecutive recruitment from the UAMS hospital and clinics. We will employ a rolling recruitment strategy until target sample is reached and will consistently monitor progress in recruitment.

Inclusion Criteria HF Participants

- Adults aged > 55 years with HF (documented in medical record).
- Has capacity to understand informed consent.
- Able to stand (briefly) without assistance.
- Has a designated caregiver.
- Agrees to be followed (treated) by UAMS physician/provider for 6 months after discharge.
- Community dwelling

Exclusion Criteria HF Participants

- Speaks a language other than English or Spanish.
- Active psychosis or other severe cognitive disorder that interferes with capacity to understand and comply with study procedures.
- A history of drug or alcohol abuse impacting their health with an emphasis on drugs that cause hemodynamic fluctuations in the past 90 days (documented in medical record by their provider).
- Currently residing or being discharged to an in-patient rehabilitation facility, Long Term Care facility or Assisted Living, and/or Hospice care.
- Current COVID + infection, or on other contact isolation.

Inclusion Criteria Caregivers

- Self-identifies as a caregiver to the HF participant
- Adult 18 years of age or over

Exclusion Criteria Caregivers

- Speaks a language other than English or Spanish.

Risks and Benefits

A risk to study participants is the potential for loss of confidentiality of study data. Measures to protect the confidentiality of study data will be implemented as described in the Data Handling and Recordkeeping section below. Other risks to participants in this study are minimal. We will minimize risks to the participants by using procedures already being performed with the subjects for diagnostic or treatment purposes, and we will only monitor the number of provider and hospital visits via the medical record. The medical management of the HF patients will not be changed or dictated in any way by this proposed research; only the mode of delivery, and only when applicable. If the participant needs diagnostic testing or an in-person appointment as determined by the provider, we will not dissuade or intervene in any way.

All participants will receive standard education provided by the hospital and clinic providers, in addition the study staff will emphasize portions of the standard education provided regarding emergency situations that require immediate action from the patient and/or caregiver such as; hypertensive crisis, stroke signs and symptoms, and signs and symptoms of heart attack. Participants and caregivers will be instructed to take *immediate action by calling 911 or going to the local emergency department without waiting for a call from the call center.*

We have a 24-hour RN call center that mHealth participants may contact if questions or problems, or they can contact their providers as they have in the past, using standardly developed procedures, such as calling the provider's office number or the "on-call" number if after hours. The call-center has been in existence for >10 years and has highly skilled RNs that are accustomed to handling issues/problems. Participants in the provider-based model will continue with standard access to their providers.

There will be no direct benefits to the study participants; however, knowledge gained from the study could potentially benefit patients in the future.

COVID -19 Research Guidelines

The Study Team will follow the UAMS Requirements on Human Subjects Research Studies during the COVID-19 Outbreak (https://tri.uams.edu/wp-content/uploads/2020/09/REVISED-Interim-UAMS-Requirements-for-Human-Subjects-Related-Research-Studies-during-COVID-19-Outbreak-051820.pdf_). All Team members recruiting patients will be screened daily and have documented PPE training located in the Training Manual for the iCOACH study. Appropriate PPE, handwashing, and distancing will be maintained to protect our potential participants and research team

per protocol. Accordingly, research visits with participants will be conducted remotely when feasible.

Data Handling and Recordkeeping

The Principal Investigator will carefully monitor study procedures to protect the safety of research subjects, the quality of the data and the integrity of the study.

A study Data Management Plan (DMP) will be developed. The Team will be trained on organizing, handling and storing data per the DMP. HIPAA Privacy Rules, confidentiality and protection of human subjects will be followed according to national standards (see Human Subjects section).

Each subject is assigned a unique study code that will be used to track and manage all study data. A separate document containing the association between this unique study code and the subject's identity will be created and stored separately from the analyses dataset in a locked cabinet in the Principal Investigator's office and/or on a UAMS password-protected served accessible only by the Principal Investigator and study staff. The resulting de-identified dataset will be reviewed, descriptively analyzed, and statistically analyzed (where appropriate). Once the necessary data quality control/assurance measures have been addressed and the data analyzed, we plan to prepare the study for publication.

At the conclusion of the study, the data and data key will be stored for at least 7 years and will share data using PCORI standards by storing the de-identified final analyzable data set appropriately, and by making the full data package available to other researchers after the research is completed. We will also share de-identified results with our local UAMS supports such as the UAMS Institute for Digital Health and Healthcare Innovation and the UAMS Translational Research Institute to inform their efforts for this and other projects.

Data Analysis

Data will be examined for completeness, outliers, and normality. Frequencies and percentages will be generated for screen failure reasons, for randomized participants, reasons for dropout and missing data. Descriptive statistics will be generated by intervention assignment and overall at 3 and 6 months. Baseline patient, caregiver, and system level characteristics will be compared according to intervention assignment to assess the success of the randomization; if there are imbalances, then consideration will be given to including the specific characteristic as a covariate to adjust intervention group comparisons. Continuous baseline variables will be compared using two-sample t-tests or nonparametric Wilcoxon rank sum & categorical variables will be compared using chi-square or Fisher's exact test.

For the Primary Outcome (Self-Care of Heart Failure Index, management subscale, Aim 1), we plan to compare arms in terms of change from baseline using a repeated measures mixed model analysis of covariance (ANCOVA) with an interaction between time and adjusting for baseline subscale score and other covariates such as age, race, education, and rurality. To address correlation arising from repeated measurements on the same subject over time, a random subject effect will be included in the model. For the primary endpoint, we will compare intervention effect at 3 months and at 6 months using contrasts (model-based t-tests) at a significance level of 0.025 (Bonferroni adjustment of alpha level of 0.05 for 2 comparisons). We will also use multiple imputation methods to address missing data (see below). Since scores > 70 on the standardized scale have been used to indicate adequacy of self-care using a similar approach to the above, we will also analyze data as a binary endpoint in a repeated measures logistic model based on a generalized linear model framework.

Secondary Outcomes, including other patient centered, caregiver, and health system outcomes, will similarly be modeled using an ANCOVA approach. Hospital admissions and adverse events will be analyzed as proportion with unplanned admissions in the next 6 months and event rates using logistic models and models based on Poisson calculations or Negative Binomial to handle potential over-dispersion issues, and mortality and time to first unplanned hospitalization will be compared using survival methods such as log-rank tests and Cox proportional hazards models.

Evaluating heterogeneity of the treatment effect is a key consideration for Aim 2 since we want to identify which patients benefit most. The objective of the HTE analyses is evaluate whether the interventions produce differential benefits for subsets of participants. This will be investigated by including an interaction between baseline factors and intervention group (i.e., race x group) to the model above, and comparisons made using contrasts (model-based t-tests). The analytical approach taken is known as moderator analysis. Baseline factors include the demographic information as well as others measures, such as baseline self-care management score, age, race, rurality, gender, education, time since initial HF diagnosis, HF severity, depression, self-care confidence, etc. Factors with small subgroups (<20% of the sample size) will not be investigated. If the arm x time interaction is significant, we will include 3-way interactions to investigate if the intervention effect differs by subgroup at each time point. When there is not a significant interaction with time, we will investigate how the arm effect differs for subgroups averaged across time. The proposed measures will be considered moderators if it meets the eligibility and analytic criteria described by Wang & Ware (2013).[37] Using the model mentioned above, we will also analyze data as a binary endpoint (adequacy of self-care >70 vs. <70) in a repeated measures logistic model; with this approach we can also give the probability of achieving adequacy of self-care for various subgroups in addition to odds ratios.

Investigation of mediators (SCI-2) will be done by examining whether changes in self-care confidence, self-efficacy to manage symptoms, self-efficacy to manage medications & treatment, or HF knowledge mediate the effect of the mHealth intervention on patient outcomes (e.g., self-care of HF index). We will use the method proposed by Hayes (2016)[38] for evaluating mediation effects via a regression modeling approach which reflects the change scores in the mediators. Baseline measurement of the potential mediator and baseline outcome measure (e.g., self-care of HF index) will be included as covariates to provide a precise estimate of mediation effects. The test of mediation evaluating the indirect effect of the invention on outcome will be based on a product of coefficients approach. The modeling and testing for mediation as described by Hayes (2016) will be done for each mediator separately. As a sensitivity analysis for the mediation analyses, we plan to use a non-parametric bootstrap approach. Both the indirect effect of each mediator along with 95% bootstrap confidence intervals will be reported.

Sensitivity analyses to determine the impact of key assumptions. In the event that continuous endpoints are skewed or key distributional assumptions are not met, we will investigate transformations (e.g., log) and compare findings based on parametric and non-parametric tests (e.g., Wilcoxon rank-sum test & robust regression techniques), as a sensitivity analysis to confirm findings. To address the impact of missing data, multiple imputation methods will be investigated.

Plans to address missing data. Data collection procedures will be designed so that measures/instruments will not allow subjects to skip questions and assistance will be available to help complete the survey, if needed (e.g. may need to read to some participants if vision is problematic). We have built in travel resources to visit participants' homes to complete a measurement interval (baseline,-3,-6 month), and/or can split this task within 2 days if participants become fatigued, as needed. See Data Collection Procedures. Sensitivity analyses will be conducted to investigate the impact of missing data (in the case of attrition) on estimates. The above analyses based on mixed models assume data are missing completely at random, but we will also use multiple imputation techniques to model missing data patterns, which is appropriate when data are not missing at random. These results will be reported as well in keeping with an intent-to-treat approach which uses data from all randomized participants, even those lost to follow-up. We anticipate that up to 10% of participants may die by six months. To address any differential dropout rates between interventions, the composite endpoint approach[39] will be assessed similar to what was done for QOL outcomes in the ELITE study;[40] one-sided tests are required for the approach so we will split our alpha accordingly assuming the alternative hypothesis is that the enhanced mHealth care model results in better outcomes.

Ethical Considerations

This study will be conducted in accordance with all applicable government regulations and University of Arkansas for Medical Sciences research policies and procedures. This protocol and any amendments will be submitted and approved by the UAMS Institutional Review Board (IRB) to conduct the study.

Informed Consent & HIPAA Authorization

The formal consent of each subject, using the IRB-approved consent form, will be obtained before that subject is submitted to any study procedure. All subjects for this study will be provided a consent form describing this study and providing sufficient information in language suitable for subjects to make an informed decision about their participation in this study. The person obtaining consent will thoroughly explain each element of the document and outline the risks and benefits, alternate treatment(s), and requirements of the study.

The consent process will take place in a quiet and private room in-person or verbally by telephone, and subjects may take as much time as needed to make a decision about their participation. Participation privacy will be maintained and questions regarding participation will be answered. No coercion or undue influence will be used in the consent process. This consent form will be signed (written or Electonic consent) by the subjects if this is an in-person interaction, and by the person obtaining the consent. If this is a telephone consent, the Research Assistant will document “telephone consent” on the form.

A copy of the signed, or telephone informed consent document and HIPAA authorization will be given, emailed, or mailed to the participant, and the informed consent process will be documented in the research record.

In light of the COVID-19 pandemic, we may need to perform informed consent and obtain HIPAA authorization on some subjects verbally, using the telephone. For example, because of COVID-19, caregivers are most often not in the patient’s hospital room and may only be allowed to pick up the patient outside of the building, we would not have a in person interaction with the caregiver at all. Additionally, if the HF patient is recommended to quarantine, although he/she would be in the hospital, we may need to contact the participant by telephone to limit the in-person interaction time.

The verbal consent & HIPAA authorization of subjects, using the IRB-approved telephone script, will be obtained before the subject is allowed to participate in any study procedure. The person obtaining consent and HIPAA authorization will thoroughly explain each element of the documents, especially outlining the risks and benefits, alternate treatment(s), and requirements of the study. Subject consent and HIPAA

authorization will be documented on the informed consent process note in the subject research file.

The research team member obtaining consent and HIPAA authorization will document the consents by indicating a proxy signage of the "*telephone consent*" of "*participant name"* by "*research team member's name",* with "time and date". A copy of these forms will be mailed to the participant. (This alternative to an in-person consent will also limit contact with potentially contaminated documents and reduce burden on patient participant and caregiver.)

Dissemination of Data

Results of this study may be used for presentations, posters, or publications. The publications will not contain any identifiable information that could be linked to a participant. The study will be listed on clinicaltrials.gov in accordance with (journal or FDA) requirements. The final, anonymized dataset will be made publicly available through PCORI.

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Appendices