PROTOCOL TITLE: Hózhó (Heart Failure OptimiZation at Home to Improve Outcomes) Trial for HF Patients Receiving Care through the Indian Health Service in Navajo Nation

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Protocol Synopsis

TITLE	**Hózhó (Heart Failure OptimiZation at Home to Improve Outcomes) Trial for HF Patients Receiving Care through the Indian Health Service in Navajo Nation**
SPONSOR	University of Pennsylvania and Indian Health Service
FUNDING ORGANIZATION	Indian Health Service Quality Improvement Innovation Award
NUMBER OF SITES	1 (Gallup Service Unit)
RATIONALE	Heart failure morbidity and mortality disproportionately impact racial minorities, and inequitable care delivery based on race is pervasive in the United States. The American Indian/Alaska Native (AI/AN) population is one of the populations that suffers most from health disparities. AI/AN patients with heart failure receiving care through the IHS (IHS) face tremendous barriers to accessing quality care, particularly specialized cardiac care. Guideline-directed recommended therapy (GDMT) can significantly lower mortality, hospitalizations and improve quality of life in heart failure with reduced ejection fraction (HFrEF). However, GDMT utilization rates are low nationally. AI/AN patients are at particular risk of not receiving appropriate GDMT. Innovative models to improve uptake of GDMT may help improve quality of care in this patient population. Models that incorporating telemonitoring and strategies to support primary care physicians could be implemented to reach AI/AN patients with HFrEF that face barriers to accessing quality cardiovascular care, particularly those that receive care through the IHS, the federal healthcare agency responsible for providing medical and public health services to this population. A strategy to identify HFrEF patients and get them on appropriate therapy with telemonitoring should be evaluated through a pragmatic clinical trial as a strategy to ensure high-quality heart failure care for AI/AN patients,

	especially those living remotely and receiving care through the IHS, where cardiology care is often unavailable. The proposed pragmatic clinical trial aims to improve the quality of care of AI/AN patients with heart failure with reduced ejection fraction receiving care through the IHS. We will perform a pragmatic trial clinical that will use a stepped wedge randomized design to implement and evaluate the effectiveness of a strategy that leverages the electronic medical record to find HFrEF patients not on appropriate therapy, and initiates/optimizes GDMT through telemonitoring in the Navajo Nation.
STUDY DESIGN	This is cluster stepped wedge randomized control trial, with randomization at the patient level
PRIMARY OBJECTIVE	To evaluate if there is an increase in rates of guideline-directed medical therapy with implementation of the heart failure telemonitoring model
SECONDARY OBJECTIVES	To evaluate if there is an increase in the dose of the guideline-directed medical therapy with implementation of the heart failure telemonitoring model
NUMBER OF SUBJECTS	80-100 HFrEF patients
SUBJECT SELECTION CRITERIA	Inclusion Criteria: This care delivery model will be applied to adult patients (age >18 years) with heart failure with reduced ejection fraction seen cared for in the Gallup Service Unit in Navajo Nation (Gallup Indian Medical Center and Tohatchi Helath Center) with at least 1 clinical encounter in past 12 months (including telemedicine), and has 1 active prescription at an IHS pharmacy in the last 12 months Exclusion Criteria: Anyone not willing to participate, anyone that their primary care physician opts out as feels is inappropriate to participate, anyone on hospice care.
EFFICACY EVALUATIONS	
PRIMARY ENDPOINT	The proportion of patients who have an increase in the number of prescribed evidence-based therapies for HFrEF (betablockers, ACE-I/ARB/ARNI, MRA, SGLT2i) at 30 days post implementation. This endpoint is based on filling of the prescription.
SECONDARY ENDPOINTS	Secondary outcomes will include: percentage of patients prescribed each medication class (i.e. percentage on beta-blockers, percentage on ACE-I/ARB, percentage of ARNIs, percentage on SGLT2i, and percentage on MRAs), medication doses (all at 30-days as well as post-implementation at 6 months); HF hospitalizations at each time point, 6-month mortality, referrals, cardiac procedures, adverse events (to include hypokalemia [K<3.0

	mEq/L], hyperkalemia [K >5.5 mEq/L], AKI [defined as Cr increase >0.5 from baseline], Hyponatremia [Na<130 mg/dl], volume overload [urgent clinic visit/ ER visits for lower extremity edema, dyspnea, with clinical evaluation consistent with volume overload], hypotension (SBP <90mmHg), bradycardia (HR <50 bpm). Outcomes determined by review of medical, hospital, and billing records.
OTHER EVALUATIONS	None
SAFETY EVALUATIONS	Adverse events (to include hypokalemia [K<3.0 mEq/L], hyperkalemia [K >5.5 mEq/L], AKI [defined as Cr increase >0.5 from baseline], Hyponatremia [Na<130 mg/dl], volume overload [urgent clinic visit/ ER visits for lower extremity edema, dyspnea, with clinical evaluation consistent with volume overload], hypotension (SBP <90mmHg), bradycardia (HR <50 bpm).
PLANNED INTERIM ANALYSES	At 30-days after implementation for cluster 1, we will evaluate for safety. Serious adverse events will be monitored by the research team on an ongoing basis throughout the study.
STATISTICS **Primary Analysis Plan**	To assess the effectiveness of our intervention, measurement of rates of GDMT, including each specific medication of ACE inhibitors, ARB, ARNI, beta-blockers, MRA, SGLT2 inhibitors will be performed at baseline, at each cross-over time point, and at the conclusion of 6 months after the implementation of the intervention. The main analysis of our stepped wedge design will be based on a logistic mixed-effects model which will contain a random intercept to account for between-cluster variability, a fixed effect parameter for time, and a group indicator variable for the treatment for each subject and time to capture treatment differences over time.
Rationale for Number of Subjects	We anticipate there is approximately 100 patients with HFrEF actively engaged in care at GIMC. Our goal to enroll all patients given ethical concerns with withholding implementation to all patients.

SECTION 1: BACKGROUND

Statement of Purpose:

Heart failure is the leading cause of hospitalization among older adults and has a 5-year mortality of up to 50%.[1][2]. There are well-established evidence-based guidelines for treating heart failure with reduced ejection fraction (HFrEF), a major subset of HF. The background of guideline-directed medical therapy (GDMT) for HFrEF now includes 4 classes of therapy: a beta-blocker, an angiotensin-converting enzyme inhibitor (ACE) inhibitor/angiotensin receptor blocker (ARB) or preferably an angiotensin receptor-neprilysin inhibitor (ARNI), a mineralocorticoid receptor antagonist (MRA), and a sodium glucose transporter 2 (SGLT2) inhibitor [3-7]. There is a cumulative risk reduction for mortality of >75% among HF patients receiving combined therapy with a beta-blocker, ARNI, MRA and SGLT2 inhibitor.[3] Therefore, the American College of Cardiology/American Heart Association guidelines recommend treatment with all 4 of these agents and titration to highest-tolerated dose (or target dose) to maximize clinical benefit.[8] However, despite clear evidence-based interventions for HF, suboptimal care is a major driver of poor HF-related outcomes in the U.S.[9] Guideline-directed therapies for HFrEF are underutilized among all patients in the U.S.[10]. AI/AN patients receiving care through the Indian Health Service, in particular, are at high risk of not receiving appropriate GDMT given barriers to accessing appropriate care.[11]

The reasons for underutilization of appropriate GDMT in HF are multifactorial. In the Indian Health Service, access to cardiology care is severely limited, and HF care is provided primarily by primary care providers. We surveyed primary providers at two Indian Health Service sites to identify the primary barriers to getting HFrEF patients on appropriate GDMT. The primary barriers identified were include lack of knowledge/comfort among providers about guidelines and appropriate management, clinical burden, time constraints during the visit. Given this we hypothesized that a model that identified HFrEF patients not on appropriate therapy, and initiated missing recommended therapy by the study team would be an effective way to improve HF quality of care and uptake of GDMT. In addition, given the rurality of the Navajo patients cared for at these two IHS sites, and the barriers to accessing care, we hypothesized that a telemonitoring model in which patients had GDMT initiation and uptitration at home, with home BP monitoring would be preferable.

We therefore, in discussion with community members and primary providers at two IHS sites in Navajo, designed a model to identify HFrEF patients cared for in the system, identify gaps in their therapy, and initiate appropriate therapy by the study team with home BP and HR monitoring for initiation and titration of GDMT. We propose a stepped wedge randomized trial to compare the implementation of this model compared to usual care over a 6 month period with 5, 30-day cross over periods. The primary outcome for the trial will be the proportion of patients who have an increase in the number of prescribed evidence-based therapies for HFrEF (betablockers, ACE-I/ARB/ARNI, MRA, SGLT2i) 30 days post implementation. This endpoint is based on filling of the prescription. In addition to addition of missing GDMT, we will also consider a change from an ACEI/ARB to an ARNI consistent with increase in the ‘number’ of GDMT given their demonstrated benefit. Secondary outcomes will include: percentage of

patients prescribed each medication class (i.e. percentage on beta-blockers, percentage on ACE-I/ARB, percentage of ARNIs, percentage on SGLT2i, and percentage on MRAs), medication doses, all at 30-days as well as post-implementation at 6 months; HF hospitalizations at each time point, 6-month mortality, adverse events (to include hypokalemia [K<3.0 mEq/L], hyperkalemia [K >5.5 mEq/L], AKI [defined as Cr increase >0.5 from baseline], Hyponatremia [Na<130 mg/dl], volume overload [urgent clinic visit/ ER visits for lower extremity edema, dyspnea, with clinical evaluation consistent with volume overload]. Outcomes determined by review of medical, hospital, and billing records.

2 STUDY RATIONALE

Treatment with GDMT for HFrEF with the 4 classes of recommended therapy significantly reduces heart failure hospitalization and overall mortality [3-8]. However, these therapies are underused among all patients nationally, but particularly among marginalized patient groups and racially minoritized patients, which is one of the factors that drives racial disparities in cardiovascular outcomes. Therefore, strategies to engage with marginalized patient groups in order to increase rates of recommended therapy are critically needed to improve cardiovascular outcomes and reduce disparities. American Indians are one of the most marginalized patient groups in the United States and the majority receive care through the Indian Health Service, where cardiology care is not readily available. Therefore, this study will evaluate if a model that leverages the electronic medical record to get American Indian patients with heart failure on appropriate therapy, and supports primary care providers with telemonitoring, is an effective way to ensure high-quality heart failure care for American Indian patients receiving care through the Indian Health Service in Navajo Nation.

2. 1 Risk/Benefit Assessment

This study will evaluate the effectiveness of a heart-failure care delivery model to improve rates of guideline recommended medical therapy through a stepped wedge randomized control trial. Therefore, the primary objective of this study is to evaluate if the implemented model is effective in increasing rates of medications that are already recommended by guidelines. All patients will only be started on medication after chart review by the research team which includes a cardiologist. Thus, patients will be started on appropriate therapy, as strongly recommended by current American College of Cardiology/American Heart Association Guidelines [4][8]. Since this model is being tested through a stepped wedge trial as a way to improve standard of care for heart failure patients, this study represents minimal risk to participants. The benefit is significant as increased use of guideline-recommended therapy and these medications has been demonstrated to reduce heart failure hospitalization and mortality

3. STUDY OBJECTIVES

3.1 Primary Objective

The primary objective is to assess the clinical efficacy of a heart failure care delivery model as measured by the rates of patients with an increase in the number of classes of rates of guideline directed medical therapy over the study period.

3.2 Secondary Objectives

The primary objective is to assess the clinical efficacy of a heart failure care deliver model as measured by the change in rates of each GDMT therapy, the doses of each therapy, differences in HF hospitalizations, referrals, cardiac interventions, and adverse events over the study period.

4. STUDY DESIGN

4.1 Study Overview

This is a single 'center' (Gallup Service Unit- which includes two ambulatory clinics), stepped wedge cluster randomized design with 5 clusters planned. We will randomize each patient to 1 of 5 clusters, each of which has a different enrollment time point, separated 1 month apart. Each patient will receive intervention with the heart failure care delivery model at time of enrollment. Evaluations will be taken at each cross-over time point and at conclusion of 6 months. Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be entered into the study. Prior to enrollment for ech patient, a message will be sent in that patient's chart through the EHR to the patient's primary provider who has 7 days to opt out if they think patient should not be enrolled.

Probable Duration of Project: Total duration of subject participation will be 6 months.

4.2 Study Setting

This study is being conducted at the ambulatory clinics in the Gallup Service Unit at Gallup Indian Medical Center (GIMC) and Tohatchi Health Center. GIMC is located in Gallup, New Mexico and is a 99-bed hospital that serves the Navajo Nation, the largest U.S. Indian tribe [12]. GIMC is part of the Indian Health Service-which is a federally-funded agency within the U.S. Department of Health and Human services, is responsible for providing health services to AI/AN patients. GIMC. has one of the highest clinical volumes in the IHS—250,000 outpatient encounters and 5800 inpatient admissions annually—and the largest staff of all Navajo IHS facilities. GIMC is associated with a primary care ambulatory clinic. With a 50-mile radius catchment area, it serves as the major Navajo referral hospital and ambulatory clinic for the Navajo Nation [13][14]. Tohatchi, is a smaller health center located 45 minutes north of GIMC, in a more rural remote area on the Navajo Nation, in Tohatchi, NM.

4.3 Study Design

Stepped-wedge designs are increasingly being utilized to evaluate interventions within routine care and are recommended where there are limited numbers of clusters [13]. In this study, we will perform a prospective stepped-wedge randomized control trial, where randomization will occur at the patient level with 5 patient clusters.

The randomization procedures will be managed independently at the University of Pennsylvania Cardiovascular Outcomes, Quality, and Evaluative Research Center. Physicians will be randomized through a SAS-based computer-generated randomization scheme developed by the study PI. Using a stepped-wedge design, each patient cluster will begin the study as a control

site, providing treatment as usual to participants (Control). Clusters will then progressively commence the heart failure care delivery model and will begin contributing to the intervention arm of the study in a stepped fashion (Intervention; see **Figure 1**). An independent statistician at University of Pennsylvania Cardiovascular Outcomes, Quality, and Evaluative Research Center will randomly generate the clusters and the order of the patient cluster. CONSORT procedures will be followed including using an intention to treat analysis.

Figure 1: Stepped-Wedge Implementation of HF Care Delivery Model

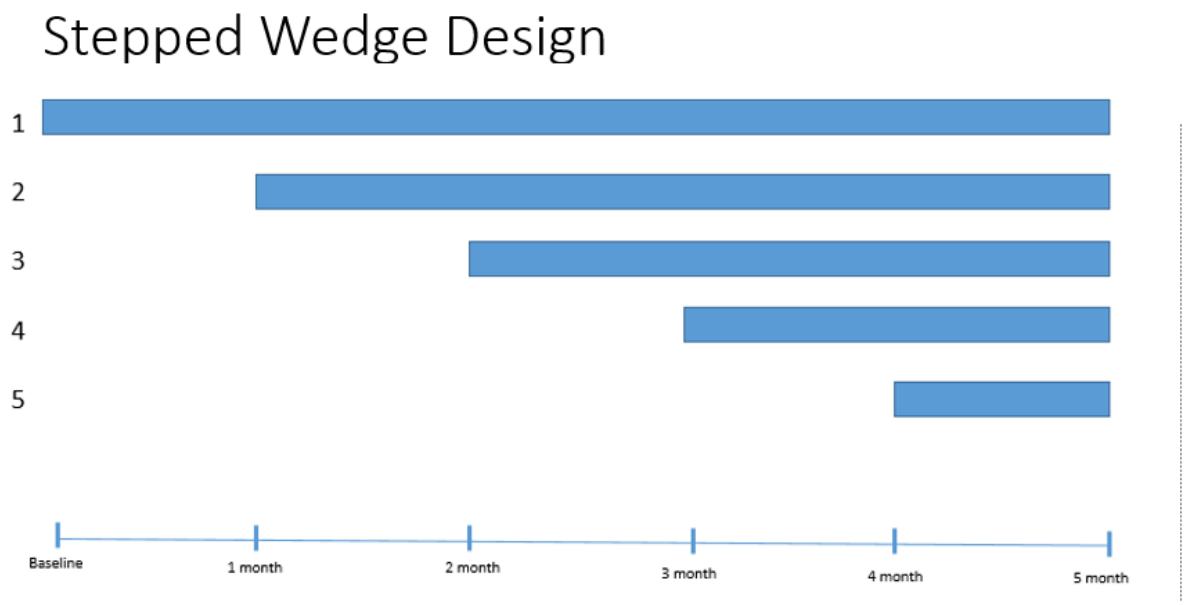


Figure 1. Stepped wedge randomized controlled study design. Participants in the control condition will receive treatment as usual. Participants in the intervention condition will receive the heart failure care delivery model as described below. The patient clusters and order of intervention will be randomly allocated.

4.4. Randomization

Randomization in this study will occur at the level of the patient. This is a stepped wedge trial design, and patients will be randomized to 1 of 5 clusters. Every cluster will have the model implemented, but the time point of implementation will vary based on cluster, in 30 day increments. Cluster 1 will have the model implemented at time 0, cluster 2 at 30 days, cluster 3 at 60 days, etc (as shown in Figure 1). Prior to implementation, patients in pre-implementation time points will receive usual care. In addition, all providers received a lecture regarding updated ACC/AHA/HFSA guidelines and expert consensus prior to implementation of the model. Given the stepped-wedge design, all patients will eventual benefit from implementation of the model, but it also allows us to evaluate the effect of secular trends towards better care over time (and ensure the model rather than trends in care are not responsible for improving care).

5. CRITERIA FOR EVALUATION

5.1 Primary Efficacy Endpoint

The primary outcome for the trial will be the proportion of patients who have an increase in the number of prescribed evidence-based therapies for HFrEF (betablockers, ACE-I/ARB/ARNI, MRA, SGLT2i) 30 days post implementation. This endpoint is based on filling of the prescription. In IHS pharmacies, we are able to differentiate between active prescriptions that are filled/picked up, and those that are "not picked up". We will only include filled prescriptions in the primary and secondary endpoints. In addition to addition of classes of GDMT, we will also consider a change from an ACEI/ARB to an ARNI consistent with increase in the 'number' of GDMT given their demonstrated superior benefit.[5]

5.2 Secondary Efficacy Endpoints

Secondary endpoints will include percentage of patients prescribed each medication class (i.e. percentage on beta-blockers, percentage on ACE-I/ARB, percentage of ARNIs, percentage on SGLT2i, and percentage on MRAs), medication doses of each therapy, all at 30-days as well as post-implementation at 6 months; HF hospitalizations at each time point, 6-month mortality, referrals, cardiac procedures. Outcomes determined by review of medical, hospital, and billing records.

5.3 Safety Evaluations

Secondary safety endpoints: Secondary safety endpoints include adverse events (to include hypokalemia [K<3.0 mEq/L], hyperkalemia [K >5.5 mEq/L], AKI [defined as Cr increase >0.5 from baseline], Hyponatremia [Na<130 mg/dl], volume overload [urgent clinic visit/ ER visits for lower extremity edema, dyspnea, with clinical evaluation consistent with volume overload].

6. SUBJECT SELECTION

6.1 Study Population

All adult patients (>18 years old) with ICD code I50* (given ICDI50.2 may not always be selected) and echo with LVEF <=40% within the last 24 months (24 months was chosen rather than 12 months given limited echo availability, particularly during COVID-19). Only patients with active prescription through IHS and engaged in care at our centers (clinical visit within last 12 months) will be included. Patients will be randomized to 1 of 5 clusters (which determines time of implementation). For ethical considerations, we aim to enroll all patients who meet eligibility criteria at GIMC and THC. Subjects who will be enrolled are those with a diagnosis of

HFrEF (LVEF ≤ 40%) who are seen in an outpatient internal medicine or family medicine IHS clinics at GIMC or THC.

6.2 Inclusion/Exclusion Criteria

Inclusion

- Age >=18 years
- Seen at internal medicine or family medicine clinic at GIMC or THC in last 12 months
- Left ventricular ejection fraction ≤40%
- Prescription at IHS pharmacy in last 12 months

Exclusion

- Primary providers opted out of inclusion for that particular patient
- Hospice care

Eligibility: Eligibility of patients will be assessed by the study team based on the patient's medical record. However, as detailed, if provider feels patient is inappropriate for enrollment, they can also opt out of enrollment. Those who meet criteria will have a EHR message sent through the chart to the primary provider. Primary providers have 1 week to opt out. If they do not opt out, patient will be automatically enrolled and placed into a randomization cluster group.

Exclusion criteria have been kept to a minimum to ensure that the study can examine the effectiveness of using this heart failure care model within a 'real world' setting.

6.3 Subject Recruitment

Eligible patients are identified as above. All primary providers will be sent a message through the EHR in the patient chart reporting that their patient is planned to be enrolled in the study. Providers can sign to consent to patient enrollment, or otherwise, can opt out of the study if their feel patient enrollment not appropriate. If a primary provider does not opt out within 7 days, then patient will be enrolled.

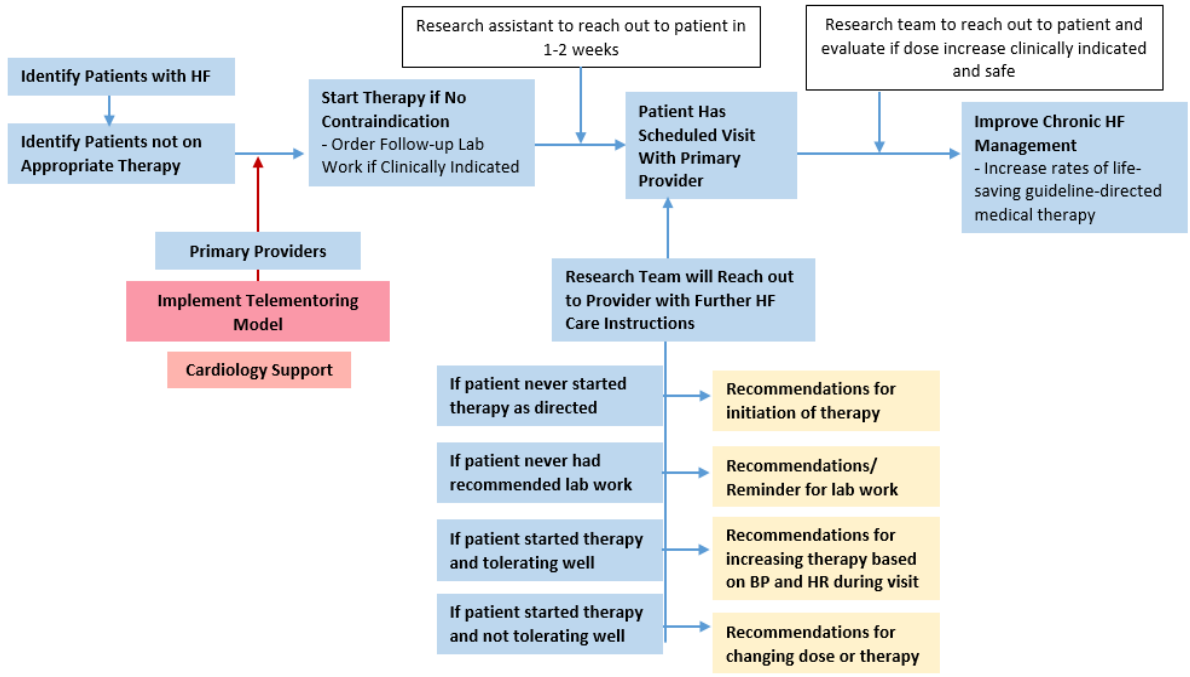
Eligible patients are identified through a query through iCARE, a EHR based data system through the IHS EHR. Patients with ICD10 diagnostic criteria for HF will be identified, and then all those patients will have their chart reviewed to confirm LVEF less than or equal to 40% on echo within last 24 months. The inclusion criteria will be all adults ≥18 years, who have a prescription in the IHS system in the last 12 months, and have had a clinical visit at GIMC or THC in the last 12 months. As this is an intervention assessing a model to improve uptake of standard of care, we cannot inform patients of their participation in the study at the time of enrollment, as this would contaminate the randomized exposure. As this study presents minimal risk to patients, we requested a waiver of informed consent at the patient level.

7. INTERVENTIONS

7.2 Intervention: Heart Failure Telemonitoring Care Delivery Model

This project was implemented as an Indian Health Service Innovations Award to improve quality of care for patients. Once patients are at their intervention time point, they receive implementation of our designed HF QI model. As part of this model, all patients are given a home BP cuff (Omron 5 arm cuff) for home BP monitoring. Protocols for each step of this model are detailed in the supplement. However, in brief, as part of the intervention, these protocols allow the study team to identify which, if any recommended guideline-directed mediations are missing, identify any contraindications to therapy, and initiate therapy as directed if no contraindications are identified. Prescriptions for the therapy are made, appropriate follow-up lab testing ordered if needed, and patients are called by the study team to discuss the therapy and recommendations. Getting patients are low doses of all 4 therapy (or all therapies they are eligible on) is prioritized by the study protocol, and then doses could be secondarily uptitrated per recent HF Expert Consensus Statement.[8] There are protocols for overall model, and initiation and titration of all medications. Utilizing home blood pressure monitoring, medications were added and titrated as directed by study protocols, with patients coming in for lab work as recommended by the study protocol. All medication changes, lab work, home BP and HR readings, will be documented in the EHR and sent to the PCP. Please see supplement for flowcharts utilized in this study. Overall model is shown in Figure 2.

Figure 2. Overview of Model to Improve Heart Failure Care in Navajo Nation



7.3 Control Condition- treatment as usual

Participants in the Control Condition will continue to receive medical treatment as usual as directed by their primary care physician. All physicians at THC and GIMC will receive a lecture at the start of the study on updated ACC/AHA/HFSA guidelines on optimal therapy for GDMT.

8. STUDY TREATMENTS

8.1 Method of Assigning Subjects to Intervention Group

Patients will be randomized assigned to 5 clusters cluster and timing group using a SAS-based computer-generated randomization scheme developed by the study PI. The investigator or designee will complete a randomization worksheet, as detailed in the Study Protocol.

8.2 Blinding of Intervention

Patients will be informed that they are enrolled in a new quality improvement program to get them on optimal therapy and thus will not be blinded to their randomization status or participation in this trial. Provider subjects will, obviously, not be blinded to the intervention as they are receiving the alert and will be consenting to participate in the study. We will engage in both pre-trial and periodic teaching and discussion with all participating care providers to inform clinicians about the nature of the study and to discuss specific factors that are being measured. The study team is not blinded to the cluster assignment as they are implementing the model. However, the outcomes will be pulled from the EHR from study members that are blinded to randomization/cluster status of the patient.

9 STUDY PROCEDURES AND GUIDELINES

9.1 Clinical Assessments

9.1.1. Baseline Medications

All baseline medications and their doses will be documented at enrollment of a patient's physician, as well as at each assessment cross-over time point. Dose, route, unit frequency of administration, will be captured. We only consider a patient to be on a medication if they have an filled prescription for the medication.

9.1.2. Demographics

Demographic information (date of birth, sex, race) will be recorded at start of the study.

9.1.3. Medical History

Relevant medical history, including comorbidities, LVEF from echo, prior cardiac imaging and ischemic evaluation (coronary angiography, stress testing) will be captured at start of the study from the EHR.

9.1.4 Vital Signs

Most recent blood pressure, pulse will be extracted from the chart from the most recent clinic visit which is closest to enrollment.

9.1.5 Clinical Laboratory Measurements

Most recent laboratory evaluation will be extracted from the chart from the most recent lab check that closest to enrollment.

9.1.4. Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates), severity/grade, outcome, treatment and relation to guideline-directed medical therapy will be recorded.

9.2 Clinical Laboratory Measurements

9.1.5. Blood Chemistry Profile

After initiation of a recommended medical therapy by the study team, the team will order basic metabolic panel if clinically appropriate based on predetermined protocols (see supplement), which is the typical standard of care when starting certain medications (all but beta blockers). Blood will be obtained at the GIMC lab and will be reviewed by the study team for determination of serum sodium, potassium, chloride, bicarbonate, random glucose, BUN, creatinine.

10. ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

10.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered the treatment arm and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of medication, whether or not related to that therapy. Adverse events will be recorded in the patient chart and a case report form (CRF.) Adverse events will be described by duration, severity, outcome, treatment and relation to GDMT if related (or unrelated). Our Data Safety Monitoring committee will perform an interim analysis of the data after 1 cluster enrollment/implemented at 30 days.

AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. If the experience is not covered in the modified criteria, the guidelines shown in Table 1 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

Adverse Events Description

There are well known side effects of GDMT, which patients will be counseled on prior to initiation of therapy. Common side effects, or adverse events of therapy will be defined as in Table 2.

Table 2. AE Definitions

AE	Definition
Hypokalemia	K <3.0 mEq/L
Hyperkalemia	K >5.5 mEq/L
Hyponatremia	Na <130 mg/dL
Acute Kidney Injury	Increase in creatinine from baseline of >0.5
Hypotension	SBP <90 mmHg
Bradycardia	HR <50 bpm
Urinary Tract Infection (UTI)	Symptoms of UTI and urinalysis/urine culture consistent with infection and/or treated by primary provider for UTI

Candidal vulvovaginitis	Consistent symptoms of infection and/or treated for presumed infection

10.2. Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization
- a significant disability/incapacity

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

10.2.1. Serious Adverse Experience Reporting

The study team will document all SAEs that occur (whether or not related to implementation) per Penn CER guidelines. The collection period for all SAEs will begin after the first patient cluster has enrolled and end 3 months post study period.

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the site investigator will report SAEs to the Navajo Nation Human Research Review Board.

11. STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

11.1. Data Sets Analyzed

All heart failure patients with reduced ejection fraction that have a primary provider that has been randomized into the heart failure care delivery model intervention will be included in each analysis.

11.2. Demographic and Baseline Characteristics

The following demographic variables for each patient upon enrollment will be summarized: race, tribal affiliation, gender, age, BMI.

The following clinical variables and baseline characteristics will be summarized: most recent blood pressure and heart rate, baseline creatinine, baseline potassium, most recent brain

natriuretic peptide, if any heart failure hospitalization in last 12 months, ischemic or non-ischemic cardiomyopathy based on coexisting validated ICD for ischemic cardiomyopathy [ICD codes: ICD 9 414.8, ICD 10 I25.5]), comorbidities to include coronary artery disease, diabetes, chronic kidney disease (including stage, end-stage renal disease), atrial fibrillation, hypertension, hyperlipidemia, left ventricular ejection fraction on most recent echocardiography, and prior cardiac studies including coronary angiography, stress test, or cardiac MRI.

11.3. Analysis of Primary and Secondary Endpoints

To assess the effectiveness of our intervention, measurement of rates of GDMT, including each specific medication of ACE inhibitors, ARB, ARNI, beta-blockers, MRA, SGLT2 inhibitors will be performed at baseline, at each cross-over time point. The main analysis of our stepped wedge design will be based on a logistic mixed-effects model which will contain a random intercept to account for between-cluster variability, a fixed effect parameter for time, and a group indicator variable for the treatment for each subject and time to capture treatment differences over time.

Safety and tolerability data will be summarized by intervention group.

Adverse event rates will be coded by body system and MedDra classification term. Adverse events will be tabulated by treatment group and will include the number of patients for whom the event occurred, the rate of occurrence, and the severity and relationship to newly started therapy.

Statistical Analysis: The primary analysis will utilize the intention to treat principle. A generalized linear model will be used to assess the relationship between randomization cluster status and the primary outcome. The model will use a log-link and independent correlation structure to allow for calculation of adjusted risk ratios. Statistical significance will be based on a P value of <0.05. For categorical secondary outcomes, a similar generalized linear modeling approach will be used. For continuous secondary outcomes, a generalized linear model will be used.

Assessment of contamination: Providers may learn to better treat heart failure as consistent with evidence-based therapies over time. Given we are not clustering by provider, but rather patients, it is possible that providers will take what is being implemented on their patient that is in an active implementation phase, and apply it to a patient in a non-active implementation phase. Therefore, there is a high risk of contamination. However, with the stepped wedge design, we will be able to also see how GDMT rates increase over the study period for those clusters who are not immediately in an active implementation arm. We will be able to better understand if increases in GDMT are related to the intervention or just due to increases over time due to improved knowledge of providers over time.

Interim Analysis: We plan to have interim analyses at 30-days after enrollment of the first cohort. The interim analyses will allow us to stop the trial earlier for ethical considerations, unexpected adverse events. If there is high efficacy, we will continue the trial as all patients will be enrolled as per the stepped wedge design. Earlier stopping will be considered for the reason of safety and efficacy.

11.4. Sample Size

The outcomes of interest measured will be rates of each GDMT therapy. Assuming there are 20 patients per cluster (which is reasonable based on preliminary data from GIMC), five time-points with one baseline measurement, and four clusters, we will have >95% power to detect a change in proportion of patients on appropriate GDMT (one therapy) from 25% to 50%, with Type I error rate of 5%. Given the low documented use of SGLT2 inhibitors and ARNIs (~25%) in preliminary data, the study is primarily powered to detect increase of 25% in those two medications in particular.

12. DATA COLLECTION, RETENTION AND MONITORING

12.1. Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each patient who is started on a guideline-directed medical therapy.

The PI is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator.

12.2. Data Management Procedures

The data will be entered into a validated database, which will be on encrypted computer, password protected, and only available to study personnel. All procedures for the handling and analysis of data will be conducted using good computing practices meeting standard guidelines for the handling and analysis of data for clinical trials. Only data, as collected during set time points from the EHR will be obtained. Data includes medical record elements such as demographics, pharmacy records such as medication prescription and dosing, laboratory values, and administrative codes. All data will be stored without PHI. However, we will retain a linking dataset to be able to re-link individual data to actual patients for future studies and ongoing efforts through the HIS. Access to individually identifiable information will be limited to the PI of the study, and only then via a linking file as aforementioned. All data used for analysis and dissemination to other investigators will be de-identified.

12.3. Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Queries are entered, tracked, and resolved through the system directly. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

12.4. Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

12.5. Availability and Retention of Investigational Records

The Investigator is unable to make data accessible unless indicated by the Navajo Nation Human Research Review Board. All study documents (patient files, signed informed consent forms, Study File Notebook, etc.) must be kept secured for a period of two years following completion of the study.

12.6. Subject Confidentiality

In order to maintain subject confidentiality, only deidentified will be analyzed as detailed above.

12.7 Protection of Human Subjects:

This study is aimed at implementing a model to get patients on appropriate standard of care, guideline directed therapy. Therefore, this poses a minimal risk to patients. We have met with HF experts at the University of Pennsylvania, primary care providers, QI and safety officers at the IHS, nurses to ensure that the design of this study, including the implemented protocols, minimize any risk to the patients. We will restrict the study only to GIMC and THC. Our Data Safety Monitoring committee will perform an interim analysis of the data after 1 cluster enrollment/implemented at 30 days.

Human subjects' involvement, characteristics and design: The studies outlined in this proposal depend on the enrollment of individuals with heart failure. No vulnerable populations are being specifically targeted. We are limiting enrollment to individuals above age 18 years as the etiology and practices surrounding heart failure in pediatrics populations differ significantly from those in adults. All data is transmitted in encrypted and secure fashion, stored on servers with "triple-lock" certification, and is available only to members of the study team, IRB, and any state or federal agencies with auditing power.

Sources of Materials: No biological materials will be obtained or stored as part of these studies.

Over or under treatment: Implementation of the model, and all of the medication changes will be sent to the primary provider. It is possible that not only those patients, but then other patients cared for by those providers may be more likely to be started on evidence based medical therapies. These interventions fall within the standard-of-care and may benefit patients, but it is also possible that additional interventions may not benefit patients and could incur additional costs. However, this is what we are testing as part of this pragmatic trial.

Potential benefits of the proposed research to the subjects and others: Subjects in this study may directly benefit from being started on evidence-based therapies for their heart failure. In addition, providers will be able to see implementation and medication changes, which may improve their education and comfort with updated HFrEF guidelines, leading to improved care for other patients. Additionally, regardless of the outcome for participants, the results of these studies may lead to significant benefit in the IHS and other health systems where access to care, especially

cardiology care is limited. This model could be similarly expanded to other sites and to other disease entities. The risk/benefit ratio, given the minimal risk to study subjects, is more than acceptable in this series of studies.

13. ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the IRB or sponsoring organization. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

13.1. Protocol Amendments

Any amendment to the protocol will be written by the PI. Protocol amendments cannot be implemented without prior written IRB approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

13.2. Institutional Review Boards

The protocol and consent form will be reviewed and approved by the IRB of both the Navajo Nation/IHS as well as University of Pennsylvania. Serious adverse experiences regardless of causality will be reported to the IRBs in accordance with the standard operating procedures and policies of the IRBs, and the Investigator will keep the IRBs informed as to the progress of the study. The Investigator will obtain assurance of IRB compliance with regulations.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRB written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB/IECs unconditional approval statement will be transmitted by the Investigator to the Sponsor prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such

modifications will be submitted to the IRB and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

13.3. Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

13.4. Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor, except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

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