Test-Case Protocol Template – Prospective Research

Use of this template is required for all NESTcc Real-World Evidence Test-Cases involving prospective research studies.

Prospective Study and Clinical Trial Methodology has been adopted from the ***NIH-FDA Phase 2 and 3 IND/IDE Clinical Trial Protocol Template Version 1.0-040717*** with the enhancement of Real-World Data and Real-World Evidence Application.

R2B36 - Efficacy and Safety of ICD Remote Monitored Exercise Testing to improve Heart Failure Outcomes: REMOTE HF-ACTION (Pilot Randomized Controlled Trial)

Protocol Number: 6292-2020-R2TCB36
National Evaluation System for health Technology coordinating center (NESTcc)
ID Number: R2B36
Lead Principal Investigator: Brett D. Atwater, MD, William E. Kraus, MD
Sponsor: Duke Clinical Research Institute
Funded by: FDA
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Protocol Amendment History:

Version	Approval/Target Date	Description of Change
1.0	*10SEP2020*	*Original*
2.0	*29SEP2020*	*Incorporated comments from NESTcc*
3.0	*28OCT2020*	*Corrected eConsent will be done through REDCap and corrected exclusion criteria*
4.0	*02MAR2021*	*Changed wearable device brand from Fitbit to Garmin.* *Edited randomization stratification.* *Corrected screen failures*
5.0	*8JUN2021*	*Addition of satisfaction survey at study completion*
6.0	*29JUN2021*	*Increased EF eligibility verification window from 12 months to 24 months*
7.0	*08SEP2021*	*Changed exclusion criteria from any history to CR to CR within the last year*
8.0	*24JUN2022*	*Changed exclusion criteria to <40 or more than 240 min of PA* *Removed wearable device aim*

TABLE OF CONTENTS

Listing of Tables 7
Sponsor Signature Page 8
Investigator Signature Page 9
Protocol Synopsis 10
1 Introduction 13
1.1 Rationale & Background 13
1.2 Disease area, Therapies, and Unmet Needs 13
1.3 Device or Technology of Interest 14
1.4 Evidence Analysis 14
1.5 Risk Class, Regulatory Use, and Effects 14
1.6 Historical and Supporting Literature Analysis 15
1.7 Clinical, Epidemiological, and Public health Significance 15
2 Study Collaborators 16
2.1 Contribuing Institutions and Roles 16
3 Study Objectives 17
3.1 Primary objective 17
3.2 Secondary objectives 17
4 Study Design 18
4.1 Prospective/Retrospective Data Identification 18
4.2 Anticipated Study Design 18
4.3 Treatment Assignment, Randomization, and Blinding 18
4.4 Covariates 18
5 Target Population, Recruitment, and Retention 19
5.1 Target Population & Demographics 19
5.2 Inclusion Criteria 19
5.3 Exclusion Criteria 19
5.4 Screening Failures 19
5.5 Recruitment Source, Clinical Centers and Real World Data Identification 20
5.6 Strategies for Recruitment and Retention 20
5.6.1 Compensation Framework 21
6 Criteria for Participant Withdrawal or Study Intervention Discontinuation 22
6.1 Participant Discontinuation or Withdrawal 22
6.2 Replacement of Participants 22
6.3 Lost to Follow-Up 22

6.4 Criteria for Discontinuation of Study Intervention 23
6.5 Criteria for Discontinuation of an Investigational Site 23
7 Participant (Study) Visits 24
7.1 Participant Screening 24
7.2 Consent and HIPAA Authorization Requirements 24
7.3 Informed Consent Form 24
7.4 Participant Study Periods 24
7.5 Discharge of Participant 24
7.6 Follow-Up Visits 24
8 Study Procedures 25
8.1 Study Duration and Timeline 25
8.2 Participant Medical History 25
8.3 Participant Schedule of Events 25
8.4 Study Interventions 26
8.4.1 Baseline 26
8.4.2 Treatment 26
9 Study Outcomes 28
9.1 Aims 28
9.2 Definitions 28
9.2.1 Abbott ICD and CRT-D device measured PA 28
9.2.2 Garmin measured daily step counts ..... **Error! Bookmark not defined.**
9.2.3 KCCQ and NYHA Scores 28
9.2.4 Adverse Events of Special Interest 29
9.3 Exploratory Outcomes of Interest 29
10 Data Quality 30
10.1 Data Collection Procedures and Data Elements 30
10.1.1 Patient reported Data and Device Data 30
10.1.2 Duke EPIC EMR 30
10.2 Data Collection and Management 30
10.2.1 Pattern Health App Data 30
10.2.2 REDCap 30
10.3 Monitoring Plans 31
10.4 Data Quality Assurance 31
11 Statistical Analysis Plan (SAP) 32
11.1 Overall Statistical Approach and Analysis Population 32

11.1.1 Hypotheses 32
11.1.2 Overall Statistical Approach 32
11.1.3 Analysis population/datasets 32
11.2 Baseline Descriptive Statistical ANalysis 33
11.3 Study Success and Failure Criteria 33
11.4 Sampling Procedure, Sample Size and Power Calculation 33
11.5 Computation of Derived Variables 33
11.6 Acceptance Criteria 34
11.7 Tables, Graphs, Statistical Models and Tests for Analysis 34
11.8 Endpoint Analysis 34
11.8.1 Primary Endpoint Analysis 34
11.8.2 Secondary Endpoint Analysis 34
11.8.3 Multiplicity 35
11.9 Learning Curve Effects 35
11.10 Interim Analysis Plan 35
11.11 Sensitivy Analysis 35
11.12 Confounding Variables, Missing Data and Bias 35
12 Study Administration 37
12.1 Study Conduct, Regulatory and Ethical Considerations 37
12.1.1 Ethical Conduct of the Study 37
12.1.2 Ethics Approval 37
12.2 Study Registration 37
12.3 Investigator Responsibilities 37
12.3.1 Reporting Requirements 37
12.3.2 Source Documentation 37
12.3.3 Record Retenton 37
12.3.4 Financial Disclosure and Obligations 37
12.4 Key Roles and Study Governance 38
12.5 Safety Oversight 38
12.6 Clinical monitoring 38
12.7 Termination of Study 39
13 Institutional Review Board (IRB) 40
14 Management of Protocol Amendments, Deviations and Adverse Events 41
14.1 Protocol Deviations, AMendments and Violations 41
14.2 Adverse Events (AEs) and Serious Adverse Events (SAEs) 41

14.2.1 Definition of an Adverse Event 41
14.2.2 Definition of a Serious Adverse Event 41
14.2.3 Classification of an Adverse Event 42
14.2.4 Adverse Event Reporting 42
14.2.5 Serious Adverse Event reporting 43
14.2.6 Reporting of Events to Participants 43
15 Risk Benefit and Confidentiality 44
15.1 Risk/Benefit Assessment 44
15.2 Confidentiality and Mitigation Plan 44
16 Results and Dissemination Plan 45
17 References 46
18 Appendices 49
18.1 Participant Schedule of Events 49
18.2 List of Abbreviations 49
18.3 Additional Appendices 51
18.3.1 Informed Consent Form 51
18.3.2 Kansas City Cardiomyopathy Questionnaire 51
18.3.3 NYHA Questionnaire 51
18.3.4 PHQ-9 Questionnaire 51

LISTING OF TABLES

Table 1: Contributing Institutions and Roles 16
Table 2: Study Duration 25
Table 3: Key Roles 38
Table 4: SAE reporting timeframes 43
Table 5: Schedule of Events 49

SPONSOR SIGNATURE PAGE

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki;
- International Council for Harmonisation (ICH) harmonized tripartite guideline E6 (R1): Good Clinical Practice, where applicable;
- Human subject research requirements set forth by the Institutional Review Boards (IRBs) of the institutions conducting the study;
- All other applicable laws and regulations, including without limitation, data privacy laws and compliance with appropriate regulations, including human subject research requirements.

Brett D. Atwater, MD Director of Cardiac Electrophysiology Inova Heart and Vascular Institute	Date

William E Kraus, MD PI Professor of Medicine Duke University School of Medicine	Date

INVESTIGATOR SIGNATURE PAGE

I confirm that I have read and that I understand this protocol, the investigator brochure, and other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki;
- ICH harmonized tripartite guideline E6 (R1): Good Clinical Practice, where applicable;
- Human subject research requirements set forth by the Institutional Review Boards (IRBs) of the institutions conducting the study;
- Regulatory requirements for reporting of serious adverse events (SAEs) defined in Section 14.2 of this protocol; and
- Terms outlined in the Clinical Study Site Agreement between the study sponsor and academic research institution(s) conducting the study;
- All applicable laws and regulations, including without limitation, data privacy laws and regulations.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in this protocol, where necessary.

William E. Kraus, MD	Date
Professor of Medicine	
Duke University School of Medicine	

PROTOCOL SYNOPSIS

Protocol Number:	6292-2020-R2TCB36
Protocol Date:	24JUN2022
Test-Case ID/Title:	R2B36 Efficacy and Safety of ICD Remote Monitored Exercise Testing to improve Heart Failure Outcomes: REMOTE HF-ACTION (Pilot Randomized Controlled Trial)
Investigator(s):	William E. Kraus, MD; Brett D. Atwater, MD
Study Description:	This pilot study will be a single center randomized controlled trial involving 50 medically stable outpatients with HF, reduced ejection fraction, and previously implanted ICD or CRT-D devices followed longitudinally on the Abbott Medical Merlin remote patient monitoring network. Patients will be randomized in a 1:1 fashion to usual care plus a remotely administered home based weekly prescription for aerobic exercise (intervention) or usual care alone (control). Usual care will include regularly scheduled visits with the clinical heart failure care team and medical therapy as prescribed by that team. The exercise prescription will be created by an exercise physiologist after incorporating remotely collected data from a patient directed smartphone app assessing HF symptom severity, vital signs, weight, and blood sugar, implantable device measures of physical activity, heart rate, heart failure volume status and heart rhythm, and Garmin measures of physical activity. We aim to determine if a remotely administered exercise prescription results in increased device measured physical activity and improvement in HF symptoms over a 12 week follow up interval.
Summary and Objectives:	**Primary Objective:** Compare the median Abbott ICD and CRT-D device measured daily PA obtained over the 1 month before randomization (baseline) and 12 weeks after randomization among patients randomized to remote cardiac rehabilitation (CR) versus usual management. **Secondary Objective(s):** Compare baseline and 12 week Kansas City Cardiomyopathy Questionnaire (KCCQ) HF symptom severity scores among patients randomized to remote CR versus usual management.
Study Design:	This pilot study will be a single center randomized controlled trial involving 50 medically stable outpatients with HF, reduced ejection fraction, and previously implanted ICD or CRT-D devices followed longitudinally on the Abbott Medical Merlin remote patient monitoring network. Patients will be randomized in a 1:1 fashion to usual care plus a remotely administered home based weekly prescription for aerobic exercise or usual care alone. **Inclusion Criteria** • Patients have a MERLIN patient registry record for an ICD or CRT-D implantation between 01/01/2010-12/31/2020 • Age ≥ 18 years

	• Left ventricular ejection fraction < 50% • Ongoing NYHA class II, III, or IV HF symptoms • Ongoing use of beta-blocker and ACE-inhibitor or angiotensin receptor blocker or willingness to start them • Life expectancy > 12 months • To allow for a post-surgical adjustment period, patients must be >30 days out from device implantation **Exclusion Criteria** • Prior participation in CR within the last year • Unwillingness to sign informed consent form • Currently performing <40 or >240 minutes of device detected daily PA • Lack of a smartphone or unwillingness to use an App or Garmin device • Prior left ventricular assist device (LVAD) implantation or heart transplantation • ICD tachyarrhythmia therapies programmed off • Inherited arrhythmia condition with contraindication to exercise (eg Lamin A mutation or ARVC) • No transmissions through Merlin.net in past 12 months
Endpoints:	**Aim 1:** Compare the medain Abbott ICD and CRT-D device measured daily PA obtained over the 1 month before randomization (baseline) and 12 weeks after randomization among patients randomized to remote CR versus usual management. **Aim 2:** Compare baseline and 12 week Kansas City Cardiomyopathy Questionnaire (KCCQ) HF symptom severity scores among patients randomized to remote CR versus usual management. **Aim 3:** (Safety) Report Adverse Events of heart failure hospitalization, fracture, myocardial infarction, serious adverse arrhythmia, and ICD therapy. **Aim 4:** Measure the correlation between change in daily PA measured by the Abbott ICD or CRT-D device between baseline and end of follow up and change in KCCQ HF symptoms severity score measured between baseline and end of follow up.
Statistical Methods:	Multilevel Modeling (MLM), Wilcoxon rank-sum tests and Pearson's correlation will be used to compare outcomes across treatment assignment. The expected sample size will be 50 subjects.
Target Population:	We will enroll patients followed in the Duke Health System Abbott Medical Merlin remote monitoring dataset who have heart failure and prior implantation of an ICD or CRT-D device. Patients will be ≥18 years of age. No enrollment restrictions will be based on gender or race.
Description of Sites/Facilities:	This will be a single center study performed at Duke University Health System.

Description of Study Intervention:	The study intervention will be a patient directed exercise prescription based on device measured physical activity and provided by a smart phone application.
Study Duration:	11 months
Participant Data Duration:	12/30/2020 to 11/15/2021
Additional Data Captured:	N/A

1 INTRODUCTION

1.1 RATIONALE & BACKGROUND

Cardiac rehabilitation (CR) improves survival and reduces hospitalizations in patients with heart failure (HF) and reduced physical activity (PA).[1] While supervised CR has been shown to be cost effective [2], participation in CR requires significant resources including hours of time commitment from patients and specially trained providers and dedicated facilities and equipment. A small minority of eligible Medicare beneficiaries are referred for CR. Women, minorities, those with limited financial resources, and those living in rural areas are less likely to be referred to CR, potentially contributing to the poorer HF outcomes observed in these groups.[3]

The HF-Action trial randomized patients with NYHA class II-IV HF to usual medical care versus usual medical care plus 3 in-person cardiac rehabilitation sessions per week over a 12-week period.[1] After completing in-person CR, patients randomized to CR were prescribed an at-home exercise regimen including exercising to 70% of their heart rate capacity for 40 minutes a day, 5 days a week. Patients randomized to usual care were encouraged to exercise to moderate intensity 30 minutes a day without supervision.

The study showed that CR participants had no increase in adverse events including ICD shocks, hip fracture, or hospitalization after PA and a modest reduction in all-cause mortality or HF related hospitalization (HR for primary endpoint 0.93, 95% confidence interval [CI] 0.84-1.02, p = 0.13). After randomization the CR group and usual care group had significant differences in the frequency of atrial fibrillation, depression, left ventricular ejection fraction, and baseline exercise capacity. After adjusting for these differences, there was a significant reduction in the primary endpoint in patients randomized to CR (HR 0.89, 95% CI 0.81-0.99, p = 0.03). Based largely on these results, the Center for Medicare and Medicaid Services (CMMS) issued a payment decision to reimburse up to 36 in person CR sessions for patients with HF and no recent hospitalizations. One of the significant limitations of the study was the inability to assess adherence to the study prescribed exercise regimens in both the CR and usual care arms. In the CR arm the median duration of exercise was highest during the first 2 months of study participation and had decreased to only 50% by the end of 3 years. The usual care arm likely exercised more than the prescribed 30 minutes per day, limiting the power of the trial to detect a difference in the unadjusted analysis of the primary endpoint. This pilot study design incorporates the use of two new technologies that will allow us to track adherence to exercise recommendations. Part of the design of this pilot will allow us to determine the correlation between physical activity measurements acquired by a wearable device (Garmin) and implanted devices (ICD and CRT-D devices) and to determine if one is superior for prediction of improvement in HF symptoms with PA.

1.2 DISEASE AREA, THERAPIES, AND UNMET NEEDS

Over 6 million Americans suffer from HF[4] and HF was a contributing cause of 1 in 8 deaths in 2017. HF cost the US over $30 billion in 2012[4] and the annual costs attributed to HF continue to climb. The number of hospitalizations attributed to HF tripled between 1979 and 2004[5] Angiotensin-converting enzyme (ACE) inhibitors, β-blockers, aldosterone antagonists, anticoagulation for atrial fibrillation, and therapy with implantable cardioverter-defibrillator (ICD), and cardiac resynchronization therapy (CRT) devices reduce all-cause mortality by 20% to 40% when used appropriately in patients with HF.[5-14] Their

use is recommended in the most recent American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of HF.[15]

Exercise training in patients with HF is safe and has been shown to reduce mortality, improve functional capacity and exercise duration, reduce HF hospitalization, and improve quality of life.[16] The 2013 ACC/AHA guidelines for the management of HF recommend exercise training and participation in cardiac rehabilitation (CR) to improve functional status, exercise duration, quality of life, and mortality.[15] Unfortunately a small minority of patients with HF participate in CR and disparities exist between sex, races, and socioeconomic status for the likelihood of referral for CR.[3]

Most cardiac implantable electronic devices (CIEDs) including ICD and CRT devices track patient physical activity and the newest generation devices are capable of reporting this to the patient through their smart phone. At home, remotely administered exercise training may improve patient compliance, reduce disparities and reduce costs for patients with HF. No evidence exists regarding the usefulness of CIED derived measures of PA for guiding at home exercise training. This study seeks to determine if a remotely administered CIED based exercise prescription results in increased CIED measured PA and improvement in HF symptoms over a 12 week follow up interval.

1.3 DEVICE OR TECHNOLOGY OF INTEREST

The devices of interest are currently FDA approved ICD and CRT-D CIEDs manufactured by Abbott Medical. PA data collected in the Abbott Medical remote monitoring system will be incorporated into a patient facing smartphone App made by Pattern Health and provided to the patient along with an exercise prescription. These devices are existing approved devices and this study will aim to provide an indication expansion for provision of remotely administered exercise training for patients with symptomatic HF and reduced ejection fraction.

1.4 EVIDENCE ANALYSIS

In contrast to the former belief, exercise training in HF has proven to be safe and has no adverse effect on left ventricular remodeling.[17] Currently, exercise prescriptions are based on (sub) maximal exercise capacity, measured with a symptom-limited cardiopulmonary exercise test (CPET). The CPET gives information on the degree of cardiac impairment and objectively measures the VO2 peak. Based on the results of CPET testing exercise physiologists may determine the appropriate training intensity, determine risk and prognosis, and retest after starting exercise training to objectively identify improvement in exercise capacity.

This study seeks to initiate and maintain an exercise training program without in-person instruction and without the use of CPET testing. The study seeks to understand the safety and benefit of a completely remotely administered exercise training program. Based on the low frequency of adverse events occurring in supervised and unsupervised exercise training in patients with HF[18], we anticipate the benefits will outweigh the risks for participation in the study.

1.5 RISK CLASS, REGULATORY USE, AND EFFECTS

The ICD and CRT-D CIEDs used in this study are FDA approved class III devices.

The Pattern Health App is not FDA approved and is not being investigated under an IDE. It is clinically used in the Duke Health System.

1.6 HISTORICAL AND SUPPORTING LITERATURE ANALYSIS

Physical activity (PA) predicts cardiovascular events and all-cause mortality in patients with heart failure (HF) [19-24]. Baseline PA, whether assessed via self-reported questionnaires, pedometers, or remote monitoring data from implantable devices has been associated with short- and long-term outcomes in patients with chronic HF [21-23, 25-33]. Increased PA as part of a comprehensive cardiac rehabilitation (CR) program has been shown to improve survival in patients with HF and cardiac ischemia [1] with evidence of a dose response relationship between PA and outcomes [34, 35]. Among many other potential benefits, a comprehensive CR program develops an exercise program aimed at increasing PA in patients with HF and ischemia in a safe environment with extensive cardiac monitoring and access to immediate correction of exercise-induced arrhythmia.

1.7 CLINICAL, EPIDEMIOLOGICAL, AND PUBLIC HEALTH SIGNIFICANCE

Safe and effective home exercise training performed without the need for in-person instruction and testing could improve patient adherence, reduce costs, and extend the benefits of increased physical activity to patient groups who currently experience disparities in care. Home exercise training would not be limited by safer at home orders and comply with current needs to maintain social distancing. The program's integration with wearable and implantable electronic devices can provide insight into the value of these devices for augmenting patient outcomes. We seek to determine if this integration can be leveraged to maximize patient safety.

2 STUDY COLLABORATORS

2.1 CONTRIBUING INSTITUTIONS AND ROLES

Table 1: Contributing Institutions and Roles

Contributing Institutions	**Team Member**	**Contributing Role**	**Date of Protocol Review & Signoff**
Inova Heart and Vascular Institute	Brett Atwater, MD	Thought Leadership, protocol development	
Duke University Health System	William E Kraus, MD Brian Dusha	Site PI Contributor	
Duke Clinical Research Institute	Marjan Cobbaert, MPH Sathya Amarasekara, MS	Project Leader Statistician	
Abbott Medical	Yelena Nabutovsky, MS	Contributor, data source	
Pattern Health	Ed Berber	Contributor, data source	

3 STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVE

The primary objective is to test the efficacy of a weekly patient tailored remotely administered exercise prescription to increase the CIED measured weekly physical activity level in patients with HF and previously implanted cardioverter-defibrillator (ICD) or cardiac resynchronization therapy defibrillator (CRT-D) CIEDs manufactured by Abbott medical.

The PA data will be gathered by the CIED and provided to the study database in a structured format by Abbott Medical. The primary endpoint data will be recorded daily for the entire enrollment period of 16 weeks. Weekly averages will be calculated and compared across groups. Clinical and demographic information gathered at baseline will be used to ensure randomization was effective at balancing patient comorbidities. Adjusted analyses will be used to adjust for residual differences.

3.2 SECONDARY OBJECTIVES

- Baseline and follow up KCCQ quality of life survey scores will be compared between treatment groups.
- To assess safety of the intervention, we will report AEs between treatment groups.

No adjusted analyses will be performed for comparisons of secondary outcomes.

4 STUDY DESIGN

4.1 PROSPECTIVE/RETROSPECTIVE DATA IDENTIFICATION

All primary and secondary endpoints, including Abbott ICD and CRT-D device measured PA, KCCQ score, , and AEs (safety) will be collected prospectively.

Identification of possible study subjects will be performed by retrospective review of the medical records of patients at Duke University Health System with prior implantation of an Abbott Medical ICD or CRT-D device and active follow-up in remote monitoring.

4.2 ANTICIPATED STUDY DESIGN

The study will be an unblinded prospective randomized controlled trial of a remotely administered exercise training program developed using ICD or CRT-D measures of PA.

4.3 TREATMENT ASSIGNMENT, RANDOMIZATION, AND BLINDING

Treatment assignment will be randomized in a 1:1 fashion. Randomization will be performed in the Pattern Health App. Neither the patient nor the study team will be blinded to treatment assignment. Randomization will be stratified based on patient sex and non-ischemic versus ischemic cardiomyopathy etiology.

4.4 COVARIATES

The covariates of interest include CIED device measured PA, KCCQ quality of life score, and adverse events.

Covariates that will be collected include demographics (age, sex, race and ethnicity), medical history including atrial fibrillation, hypertension, coronary artery disease, peripheral artery disease, prior myocardial infarction, diabetes, chronic obstructive pulmonary disease, smoking history, dyslipidemia, depression, NYHA class, most recent left ventricular ejection fraction, device type (ICD vs CRT-D) and baseline daily PA duration in minutes. For a complete list of medical history covariates, refer to section 8.2.

5 TARGET POPULATION, RECRUITMENT, AND RETENTION

5.1 TARGET POPULATION & DEMOGRAPHICS

We will enroll patients followed in the Duke Health System Abbott Medical Merlin remote monitoring dataset who have heart failure and prior implantation of an ICD or CRT-D device. Patients will be ≥18 years of age.

We expect to enroll 30-50% women and 30% underrepresented minorities in accordance with the general makeup of our remote monitoring clinic. We will not enroll vulnerable subjects including pregnant patients, those with mental handicap, minors, or patients who are incarcerated.

5.2 INCLUSION CRITERIA

- Patients have a MERLIN patient registry record for an ICD or CRT-D implantation between 01/01/2010-12/31/2020
- Age ≥ 18 years
- Left ventricular ejection fraction < 50% by echocardiogram, nuclear cardiology scan, cardiac magnetic resonance imaging, or invasive left ventriculography within the past 24 months.
- Ongoing NYHA class II, III, or IV HF symptoms by questionnaire
- Ongoing use of beta-blocker and ACE-inhibitor or angiotensin receptor blocker or willingness to start them- assessed by Duke Epic EMR screening.
- Life expectancy > 12 months
- To allow for a post-surgical adjustment period, patients must be >30 days out from device implantation

5.3 EXCLUSION CRITERIA

- Prior participation in CR within the last year- by patient questionnaire
- Unwillingness to sign informed consent form
- Currently performing < 40 or > 240 minutes of device detected daily PA- by ICD/CRTD remotely collected data.
- Lack of a smartphone or unwillingness to use an App or Garmin device
- Prior left ventricular assist device (LVAD) implantation or heart transplantation
- ICD tachyarrhythmia therapies programmed off
- Inherited arrhythmia condition with contraindication to exercise (eg Lamin A mutation or ARVC)
- No transmissions through Merlin.net in past 12 months

5.4 SCREENING FAILURES

Patients with an active Merlin account will be pre-screened and complete a screening questionnaire. Eligibility will be re-verified before Garmin shipment.

Participants who initially meet enrollment criteria during pre-screening but are found to have become ineligible between pre-screening and signing of the informed consent form will be considered screen failures.

5.5 RECRUITMENT SOURCE, CLINICAL CENTERS AND REAL WORLD DATA IDENTIFICATION

All subjects will be enrolled from Duke University in the US. All subjects will be recruited from the remote cardiac monitoring clinic at Duke University Health System.

Real-World Data will be acquired from 4 sources for use in the study:

1. **Abbott Medical ICD or CRT-D implantable devices**: Heart rate, daily physical activity, physical activity intensity, and heart failure severity data will be recorded by the device, transmitted automatically to Merlin.net, collated into an analyzable format by data scientists at Abbott Medical and provided to the study team on a weekly basis for creation of personalized exercise prescriptions and for inclusion in the study database for analysis.

2. **Pattern Health Patient App**: Patient weight and height, heart failure symptom severity, questionnaire responses, blood pressure and blood sugar data will be entered into the app by the patient. Questions will include a review of current medications, any recent hospitalizations, and the presence of symptoms including resting shortness of breath or chest pain. The data will be transferred automatically from Pattern Health to the REDCAP database in .csv format. For patients randomized to the CR study arm, the data will also be reviewed by the exercise physiologists for creation of the weekly exercise prescription which will be presented to the patient in the smartphone app along with feedback about their performance in the prior weeks of study participation.

3. **Duke EPIC EMR**: The Duke EMR will be used to review data including echocardiograms, ECGs, and will be used to ascertain eligibility. After enrollment, the EMR will be used to verify the patient's medical history and to review if the patient has experienced any study related adverse events.

5.6 STRATEGIES FOR RECRUITMENT AND RETENTION

Eligible patients will be identified by screening the Duke Epic EMR record of all patients currently followed longitudinally in the Duke/Abbott Merlin remote monitoring network. This network of real-world data, maintained by Abbott medical is used by health systems around the world for management of remotely collected data from patients with pacemaker, ICD, or CRT-D devices manufactured by Abbott medical. While the network contains data from patients with prior implantation of devices across the world, only patients actively followed at Duke will be included in this study. Patients will be enrolled without regard to their sex, race, ethnicity, or socioeconomic status.

We anticipate screening up to 500 subjects to identify 50 eligible subjects who are willing to participate. Subjects will be recruited by an invitation letter sent to them by Duke MyChart EMR message, physical mail, and follow up phone call in accordance to the recruitment plan provided by Duke Health Recruitment Innovations and approved by the Duke IRB.

We anticipate completing enrollment of the 50 subjects within 1 month of opening enrollment.

To maximize participant retention, the study team will keep the participant engaged through messages via the Pattern Health App, in combination with text messages and phone calls.

5.6.1 COMPENSATION FRAMEWORK

Patients will not be compensated for being in the study. Patients will be provided a Garmin device for use during participation in the study protocol. They will be allowed to keep the device at the study conclusion.

6 CRITERIA FOR PARTICIPANT WITHDRAWAL OR STUDY INTERVENTION DISCONTINUATION

6.1 PARTICIPANT DISCONTINUATION OR WITHDRAWAL

Each enrolled subject shall remain in the clinical investigation until completion of the required follow-up period; however, a subject's participation in any clinical investigation is voluntary and the subject has the right to withdraw at any time without penalty or loss of benefit. Conceivable reasons for discontinuation may include, but not limited to, the following:

- Subject death
- Subject voluntary withdrawal
- Subject lost to follow-up as described below

The sponsor must be notified of the reason(s) for subject discontinuation. The site will provide this information to the Sponsor. Investigators must also report this to the IRB.

No additional follow-up will be required or data recorded from subjects once withdrawn from the clinical investigation, except for the vital status (deceased/alive).

However, if a subject withdraws from the investigation due to problems related to safety, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical investigation.

6.2 REPLACEMENT OF PARTICIPANTS

Subjects who withdraw or are lost to follow-up before completion of the first study intervention (first exercise prescription) will be replaced. Subjects who withdraw after the first study intervention do not need to be replaced. For patients lost to follow-up we will censor data collection at the last known date of contact.

6.3 LOST TO FOLLOW-UP

If the subject missed two consecutive scheduled follow-up time points and the attempts at contacting the subject detailed below are unsuccessful, then the subject is considered lost to follow-up. Site personnel shall make all reasonable efforts to locate and communicate with the subject (and document these efforts), including the following, at each contact point:

- A minimum of two reminder messages through the Pattern Health App.
- A minimum of two text messages to the patient's smart phone.
- A minimum of two telephone calls on different days over the specified follow-up windows to contact the subject should be recorded in the source documentation, including date, time, and initials of site personnel trying to make contact.
- If these attempts are unsuccessful, a letter (certified) should be sent to the subject.
- If a subject misses one or more non-consecutive follow-up contact time points, it will be considered a missed visit. The subject then may participate in subsequent visits. If the subject missed two consecutive time points and the above mentioned methods of communicating with the subject are unsuccessful, the subject will be considered lost to follow-up.

6.4 CRITERIA FOR DISCONTINUATION OF STUDY INTERVENTION

The study intervention will be discontinued if the occurrence of AEs exceeds the estimate used to calculate the risk benefit of study participation. The risks of participation are similar to those taken during exercise training occurring remotely currently at Duke University Health System.

6.5 CRITERIA FOR DISCONTINUATION OF AN INVESTIGATIONAL SITE

N/A

7 PARTICIPANT (STUDY) VISITS

7.1 PARTICIPANT SCREENING

Subject screening will begin after IRB approval, likely in December 2020.

Adult patients who are active in the Duke University Health System and with an Abbott Medical ICD or CRT-D device implanted between 01/01/2010 and 12/31/2020 will be screened by the study team for physical activity measures within the target range. In addition, the Duke EMR will be used to screen for EF measurement, medication use, and prior participation in CR. HF severity (NYHA class) and willingness to use a smartphone for study participation will be assessed using a survey or phone call to potentially eligible subjects.

7.2 CONSENT AND HIPAA AUTHORIZATION REQUIREMENTS

The nature of the study and its risks and benefits will be explained to the patient by the investigator or designated study personnel. The patient must voluntarily provide electronic informed consent on an ethics-approved informed consent form (ICF), prior to performing any study-related procedures.

Informed consent will be administered electronically through REDCap. The patient's electronically signed ICF will be stored in the study database.

7.3 INFORMED CONSENT FORM

See appendix 18.3.1

7.4 PARTICIPANT STUDY PERIODS

A patient will spend a total of 13 weeks in the study protocol: 1 week of baseline PA measurement prior to randomization and 12 weeks of intervention or control care. The study visit table is below in section 8.3

7.5 DISCHARGE OF PARTICIPANT

Prior to discharge from the protocol participants will complete the NYHA assessment and KCCQ QOL assessment, an assessment of AEs, a remote monitoring transmission, and a review of medications.

The subject will be encouraged to use the Garmin device to continue to achieve similar PA thresholds to what were accomplished in the last follow up period.

7.6 FOLLOW-UP VISITS

All follow-up visits will occur through the Pattern Health App. Any AEs will be self reported and further details will be acquired by telephone call as needed.

8 STUDY PROCEDURES

8.1 STUDY DURATION AND TIMELINE

Table 2: Study Duration

	Deliverable	**Proposed Submission Date**
1	Planning/IRB Approval	11/30/20
2	Last Patient Enrolled	12/30/20
3	Last Patient Last Visit	5/31/21
4	Database Lock	6/30/21
5	Final Analysis Complete	7/30/21
6	Manuscript Submission	8/31/21

8.2 PARTICIPANT MEDICAL HISTORY

Targeted Medical History will be collected at baseline.

The following elements of past medical history will be collected to describe the patients and ensure randomization was effective at balancing covariates of interest:

- Etiology of HF (ischemic versus non-ischemic)
- LVEF
- Baseline NYHA Class
- Previous Revascularization
- History of MI
- Moderate or Severe Valvular Disease (Aortic or Mitral)
- Baseline Medications (ACE Inhibitor, Beta blocker, ARNI, digoxin, loop diuretic, statins)
- Diabetes
- Hypertension
- BMI
- A fib or A flutter
- PHQ-9 Depression Screen
- Baseline Systolic and Diastolic BP (measured by cuff at home)
- Device type (ICD versus CRT-D)
- Baseline daily PA duration (minutes)
- Baseline day and night heart rate

8.3 PARTICIPANT SCHEDULE OF EVENTS

See appendix 18.1

8.4 STUDY INTERVENTIONS

8.4.1 BASELINE

After confirmation of eligibility and Informed Consent, the participant will receive a Garmin wearable device and download the CR app (Pattern Health). The Garmin device will be linked to the CR App, and patients 1 month prior to randomization will be used to collect a baseline physical activity level.

Following the baseline month, patients will be randomized 1:1 to either remote CR or usual care through the CR app.

8.4.2 TREATMENT

Remote CR: Patients randomized to remote CR with usual care will receive the complete suite of Duke Health remote CR features. They will be asked to use the app a minimum of 3 times a week but can use it more often if they prefer. A typical CR session will involve a series of questions screening for symptoms including chest pain or shortness of breath at rest. Patients will be asked to input their morning weight, resting blood pressure (from a home cuff,) and their morning blood glucose level (if diabetic). After this data is provided, patients will be given an exercise prescription provided by a certified exercise physiologist based on the patient inputs, resting heart rate, prior prescriptions, and mean physical activity measured by the ICD or CRT device over the past 1 week.

The exercise prescription will change each week based on refreshed data from the prior week. Abbott devices are capable of measuring not only the total daily exercise time but also the intensity of the exercise performed (categorized as none, light, moderate, and vigorous). Total time in each intensity bin is logged in the device and transmitted to Merlin. The exercise physiologist will create the prescription to increase not only the total amount of exercise time but also the intensity of exercise, such that patients gradually increase the amount of time spent in each exercise intensity bin.

Instructional videos for each exercise are provided in the app. Patients will not be told to perform the exercise at a particular time. Instead they will be asked to complete a certain amount of exercise per week at whatever time is convenient for them. Exercises will be prescribed to accommodate certain disabilities. Examples include walking for a patient with normal ambulation, resistive arm exercises for patients who require the use of a cane or walker for ambulation, etc. Patients will be asked to wear the Garmin throughout the day and are free to track their own heart rate and step count, but no step count goal will be provided. The Garmin account will initially be set up by the study team and Garmin data will be cataloged and used for study endpoints. At the conclusion of the study the Garmin account will be turned over to the patient and they will be given the Garmin as a gift for participation in the study. Patients randomized to remote CR will also receive App based reminders to take their medications, resources to guide healthy eating habits, and other behavioral health advice as is done as standard of care in both remote based and clinic based CR. Each week they will receive visual feedback on the smartphone app summarizing their progress in CR. Presented data will include their change in physical activity compared to the prior weeks and change in weight from prior weeks. At the beginning of week 1 and the end of week 12 the smartphone app will also perform the KCCQ quality of life questionnaire.

Patients randomized to remote CR will complete a self-administered satisfaction survey through the app at the end of week 12. Results of the survey will be used for program improvement and feasibility.

Usual Care: Patients randomized to usual care will receive the App and Garmin device but will not be provided with the full suite of features. They will be asked to log into the app at least 3 times a week. They will be given the same series of questions as patients randomized to remote CR screening for symptoms including chest pain or shortness of breath at rest. Patients will then be asked to input their morning weight, resting blood pressure (from a home cuff, if they own one) and their morning blood glucose level (if diabetic). No further information will be presented to the patient but they will be encouraged to continue to pursue a healthy lifestyle and to contact their physician if they are experiencing worsening symptoms of heart failure. At the beginning of week 1 and the end of week 12 the App will also perform the KCCQ quality of life questionnaire.

9 STUDY OUTCOMES

9.1 AIMS

Aim 1: Compare the mean Abbott ICD and CRT-D device measured daily PA obtained over the 1 week before randomization (baseline) and 12 weeks after randomization among patients randomized to remote CR versus usual management. This objective was chosen to determine if it is possible to objectively measure a clinically meaningful change in PA using an ICD or CRT-D device. Further, the primary objective assesses whether a remotely administered exercise training program can increase the observed PA over a relatively short time interval.

Aim 2: Compare baseline and 12 week Kansas City Cardiomyopathy Questionnaire (KCCQ) HF symptom severity scores among patients randomized to remote CR versus usual management. This objective was chosen to determine if the remotely administered exercise training is associated with subjective improvement in HF symptoms. This endpoint has been used previously in studies of exercise training in patients with HF, so we should be able to compare the direction and magnitude in change in our study to results obtained in prior studies.

Aim 3: (Safety) Report Adverse Events of heart failure hospitalization, fracture, myocardial infarction, serious adverse arrhythmia, and ICD therapy among patients randomized to remote CR versus usual management. This objective is important since little data are available regarding the safety of starting an exercise training program without a prior CPET study. We will determine if patients randomized to exercise training experience excess risk.

Aim 4: Measure the correlation between change in daily PA measured by the Abbott ICD or CRT-D device between baseline and end of follow up and change in KCCQ HF symptoms severity score measured between baseline and end of follow up. This objective will allow us to determine what change in device measured PA is associated with an improvement in QOL.

The results of this study (Aims 1-4) will be used to design a larger pivotal randomized controlled study evaluating whether remotely administered CR reduces the combined clinical endpoint of HF related hospitalization or death. Providing CR using a smartphone app coupled to an existing implantable device may result in significant cost savings and improved availability, particularly to vulnerable populations. This study would support label expansion for ICD and CRT-D devices to include provision of remotely administered CR and would be used in support of a new coverage for implantable device guided remotely administered CR.

9.2 DEFINITIONS

9.2.1 ABBOTT ICD AND CRT-D DEVICE MEASURED PA

Physical activity is defined as a force measurement of 25 mg as measured by the Abbott Medical ICD or CRT-D implantable device. The accelerometer within the Abbott medical cardiac electronic implantable device detects both the frequency and amplitude of patient motion to calculate a force measurement. A force measurement of 25 mg is equivalent to walking 2 miles per hour.

9.2.2 KCCQ AND NYHA SCORES

The Kansas City Cardiomyopathy Questionnaire (KCCQ) will be completed by the participant via the Pattern Health CR App prior to starting intervention and after 12 weeks of intervention.

The KCCQ is a 23-item, self-administered, validated and reliable questionnaire,[36, 37] measuring the patient's perception of their HF symptoms and how their HF affects their quality of life. KCCQ scores ranges between 0 and 100, with 100 representing the least burden of symptoms. The NYHA scale is well validated and reproducible. We will use a previously validated version in the study.

9.2.3 ADVERSE EVENTS OF SPECIAL INTEREST

AEs of special interest (AESIs) defined for this trial include: heart failure hospitalization, fracture, myocardial infarction, serious adverse arrhythmia, and ICD therapy. Certain disease-related events (DREs) that are common within the study population will not be reported. This includes chest pain, hyper or hypotension, hyper or hypoglycemia, muscle or joint pain, shortness of breath or breathlessness, fatigue, diaphoresis, or depression.

9.3 EXPLORATORY OUTCOMES OF INTEREST

N/A

10 DATA QUALITY

10.1 DATA COLLECTION PROCEDURES AND DATA ELEMENTS

Data will be extracted from the implanted ICD or CRT-D device. Patient-reported outcomes (PROs) will be collected via the Pattern Health smartphone App. Patients will report study-related AEs through the App. Any reported AEs will be followed up with a phone call and screening in the EMR. At study conclusion, the EMR will also be screened for any unreported AEs.

10.1.1 PATIENT REPORTED DATA AND DEVICE DATA

Patient reported data collected via the Pattern Health Patient App include weight, questionnaire responses, blood pressure and blood sugar, review of current medications, recent hospitalization and the presence of symptoms (shortness of breath or chest pain).

Devices used in this study will be integrated with the Pattern Health App and the data collected will be passively uploaded to the Duke EMR.

Device data for this study include:

- Abbott Medical ICD or CRT-D implantable device: heart rate, daily physical activity, physical activity intensity, and heart failure severity

All AEs will be gathered electronically through the Pattern health smartphone application. The study coordinator will request addition information through the App on an individual basis. In the event that a subject fails to respond to requests for data through the App, a follow-up telephone call will be placed by a study coordinator. All AEs will be recorded in the eCRF.

10.1.2 DUKE EPIC EMR

The Duke EMR will be used to collect the results of recent testing (echocardiograms, ECGs) and will be used to ascertain if the patient has experienced any study related adverse events.

10.2 DATA COLLECTION AND MANAGEMENT

10.2.1 PATTERN HEALTH APP DATA

Data will be de-identified at the earliest opportunity, and PHI will be stored only for purposes of subject identification by the PI and study staff as necessary during the course of the study. The data collected by the Pattern Health Patient application will be stored on HIPAA compliant Pattern Health server.

Pattern Health research data will be transferred directly to the DCRI statistical team via Duke Box.

10.2.2 REDCAP

The Electronic Data Capture (EDC) used for this study is REDCap. Data will be entered electronically by site study staff into REDCap. The study site is expected to enroll all participants into REDCap and enter data within 72 business hours of enrollment or each subsequent study visit/procedure/contact. Corrections to eCRFs should be performed using REDCap, which will track modifications in the audit history. The audit history contains the date, time, field name, and username of the individual who modified the study data.

REDCap is a secure, web-based application for building and managing online databases, hosted by the Duke Office of Clinical Research (DOCR). REDCap provides automated export procedures for seamless data downloads to Excel and common statistical packages (SPSS, SAS, Stata, R), as well as a built-in project calendar, a scheduling module, ad hoc reporting tools, and advanced features, such as branching logic, file uploading, and calculated fields.

All REDCap users are expected to be trained and to be able to perform project responsibilities within the REDCap before obtaining access to the live study.

10.3 MONITORING PLANS

Due to the short time between trial startup and completion along with the single center study design and relatively small number of enrolled subjects, no DSMB will be convened for the project

10.4 DATA QUALITY ASSURANCE

This study will be conducted under Good Clinical Practice (GCP) and all applicable regulatory requirements. To ensure compliance, the sponsor or designee may conduct a quality assurance audit.

Actions to ensure the accuracy and reliability of data include the selection of qualified investigator and appropriate study center; the review of protocol procedures with the investigator and study personnel prior to study start; the design of suitable source documents with appropriate instructions for use (where applicable); the internal audit of source data according to GCP and internal procedures to ensure their accuracy, completeness, and verifiability.

11 STATISTICAL ANALYSIS PLAN (SAP)

11.1 OVERALL STATISTICAL APPROACH AND ANALYSIS POPULATION

11.1.1 HYPOTHESES

Hypothesis for Primary Endpoint 1 (P1): We hypothesize that the change in median of physical activity from baseline to 12 weeks as measured by Abbott ICD and CRT-D device will be larger (more physical activity) among patients randomized to remote CR versus usual management. Our null hypothesis is that there is no difference in the two groups.

Hypothesis for Secondary Endpoint 1 (S1): We hypothesize that the change in KCCQ HF symptom severity score mean from baseline to 12 weeks as measured by KCCQ questionnaire will be lower (less severity) among patients randomized to remote CR versus usual management. Our null hypothesis is that there is no difference in the two groups.

Hypothesis for Secondary Endpoint 3 (S3): We hypothesize that the change in PA measured by the Abbott ICD or CRT-D device between baseline and end of follow up and change in KCCQ HF symptoms severity scores during same time period will be negatively correlated. With greater increases in PA measurements being correlated with greater reduction in KCCQ HF severity scores.

11.1.2 OVERALL STATISTICAL APPROACH

All tests will be tested in no particular sequence. There will be no interim analysis. As this is a hypothesis generating study, we will not employ a mechanism to address alpha spending (multiplicity) within the secondary endpoint family.

For P1 and S1-S2, we will be reporting 95% confidence intervals, mean at baseline, mean at terminal timepoint, Multilevel Model estimates over the timepoints of interest, and related p values.

For the S3, we will be reporting the strength of the correlation and related p values.

Additionally, alpha levels will be set at 0.05, and all tests will be two sided unless otherwise stated. All these statistics will be obtained via SAS 9.4 or higher. Please see Section 11.2 for how continuous and categorical variables will be reported. Values obtained from scheduled measurement time points will be included in data summaries tables and listings. We will utilize the Shapiro-Wilk or goodness of fit tests to assess normality.

11.1.3 ANALYSIS POPULATION/DATASETS

Effectiveness will be assed in the Intent-To-Treat (ITT) population and in the Per-Protocol (PP) population. Both analysis populations will be examined for all objectives, however, the success of the trial will be based on the analysis of the ITT population.

Intent-to-Treat (ITT) Population: All participants who were randomized. Subjects will be analyzed according to the treatment group to which they were randomized, regardless of whether they received that intervention. This population will include participants who may have received the wrong intervention and have protocol violations.

Safety Analysis (SA) Population: All participants who had at least one session on the study app.

As-Treated (AT) Population: The treatment assignment of this population will be based on the actual treatment patients received, not the treatment the patients were randomized to receive. Deviations related to treatment compliance with randomized intervention: Participants not meeting the adherence requirement of completing at least 2/3 of expected app check in sessions will be considered a protocol deviation and excluded from the PP analysis population.

Any additional exclusion of any subject from a data presentation, other than those described above and in the section on handling of missing data, will be considered on a case-by-case basis, and will be described in the final study report.

11.2 BASELINE DESCRIPTIVE STATISTICAL ANALYSIS

For the baseline descriptive summaries, continuous variables will be summarized using number of observations (n), mean, standard deviation (SD), median, 25th and 75th percentiles, minimum, and maximum.

All categorical variables will be summarized using frequency counts and percentages. The calculation of percentages will be based on the number of patients with non-missing measurements for that time point in the corresponding category. P values for Wilcoxon rank sum test or Pearson chi-square test or Fisher's exact test will also be reported.

11.3 STUDY SUCCESS AND FAILURE CRITERIA

The success of the study will depend on finding a statistically significant difference in the change in mean from baseline to week 12 in:

Physical activity as measured by Abbott ICD and CRT-D devices for the ITT population.

11.4 SAMPLING PROCEDURE, SAMPLE SIZE AND POWER CALCULATION

Sample size was determined based on the following power calculations:

For aim 1, a sample size of 28 subjects with 1:1 randomization were each measured at 4 time points provides 81.1% power to detect a 15 minute per day difference in PA between groups with a standard deviation of 19 minutes per day within each group anda within subject correlation of 0.7. A test based on a mixed-model analysis is anticipated at a significance level of 0.05.

For aim 2, a sample size of 50 subjects with 1:1 randomization provides 80.2% power to detect an 8% difference in KCCQ score between groups with a standard deviation of 10 in KCCQ score within each group and an alpha of 0.05.

11.5 COMPUTATION OF DERIVED VARIABLES

Weekly averages:

1. Baseline mean: Average of all measurements in a month prior to randomization.
2. Week 4 mean: Average of all measurements in week 4.
3. Week 8 mean: Average of all measurements in week 8.
4. Week 12 mean: Average of all measurements in week 12.
5. Change from baseline to Week 12 mean: Difference of week 12 mean from baseline mean.
1.

11.6 ACCEPTANCE CRITERIA

Subjects will be screened and selected based on methods described in Section 5. All subjects who were enrolled will be classified based on the analysis populations described in Section 11.1. Missing data will be dealt with as described in Section 11.12.

11.7 TABLES, GRAPHS, STATISTICAL MODELS AND TESTS FOR ANALYSIS

Please refer to the Statistical Analysis Plan for tables, graphs, models and tests.

11.8 ENDPOINT ANALYSIS

11.8.1 PRIMARY ENDPOINT ANALYSIS

General statistical approach to primary endpoint: This endpoint will be analyzed in both the ITT and PP populations. Missing data will be handled as described in Section 11.12.

Analysis strategy for P1:

The outcome variable for this objective is the median Abbott ICD and CRT-D device measured daily PA obtained over the 1 week before randomization (baseline) and week 4, week 8, and week 12 after randomization. This endpoint represents a summary measure. The hypothesis test will evaluate whether the trajectory of the mean Abbott ICD and CRT-D device measured in the remote CR treatment group is different from the trajectory in the usual management group. The test will be a multilevel modeling (aka mixed models) on trajectories of the outcomes over the study period.

P1: Compare the trajectory of the median Abbott ICD and CRT-D device measured daily PA obtained over the 1 week before randomization (baseline) and week 4, week 8, and week 12 after randomization among patients randomized to remote CR versus usual management.

Reporting for P1: Descriptive summaries of the median physical activity at baseline and 4 weeks, 8 weeks, and 12 weeks after randomization will be presented by treatment group. The estimated differences in slopes of trajectories from CR and usual care treatment groups will be presented, along with the p-values by comparing the trajectories over study period. If differences are noted with regard to baseline covariates adjusted analyses will be performed for the primary endpoint.

11.8.2 SECONDARY ENDPOINT ANALYSIS

General statistical approach to secondary endpoints: These endpoints will be analyzed in both the ITT and PP populations. We will not be using methods to account for multiplicity (alpha sharing plan) as this is a hypothesis generating rather than a confirmatory study. Missing data will be handled as described in Section 11.12.

Analysis Strategy for S1: Will be similar to what is described for P1 with different endpoints.

S1: Compare the change in mean HF symptom severity scores at baseline and 12 week as measured by Kansas City Cardiomyopathy Questionnaire (KCCQ) among patients randomized to remote CR versus usual management.

Reporting for S1: Will be similar to what is described for P1 with different endpoints. If differences are noted with regard to baseline covariates adjusted analyses will be performed for the secondary endpoints.

S2: (Safety) Report Adverse Events of the combination of heart failure hospitalization, fracture, myocardial infarction, serious adverse arrhythmia, and ICD therapy.

Reporting for S2: A listing of Adverse Events will be produced for the study population.

Analysis Strategy for S3: This analysis strategy will be implemented for the S4 analyses. The outcome variable for this objective is the HF symptoms severity score as measured at baseline through end of follow up. This endpoint represents repeated measures. The hypothesis test will evaluate whether there is a correlation between these treatment groups. If data are normally distributed, the test will be a Pearson correlation test. Otherwise, we will use a Spearman correlation test.

S3: Investigate the correlation between change in daily PA as measured by the Abbott ICD or CRT-D device between baseline and end of follow up and change in HF symptoms severity scores as measured by KCCQ during same time period.

Reporting for S3: We will be reporting the strength of the correlation and related p values.

11.8.3 MULTIPLICITY

Since this is an exploratory/pilot/hypothesis generating study, we will not adjust alpha level for multiple tests. All tests will have an alpha level of < 0.05.

11.9 LEARNING CURVE EFFECTS

NA

11.10 INTERIM ANALYSIS PLAN

NA

11.11 SENSITIVY ANALYSIS

The sensitivity Analysis will be considered for P1 ITT analysis:

Multilevel modeling after imputing missing data using MI: This sensitivity analysis will be performed with the same method as the main analysis, but with imputation for missing data as described above.

Multilevel modeling assumption not met: This sensitivity analysis will be performed if the Multilevel modeling assumptions severely violated and data transformation needed. If that is the case, we will run multilevel model on the transformed data and the p-value will be compared to the main results. The estimated differences in slopes of trajectories and respective p-values will be presented.

11.12 MULTILEVEL MODELING OF ENDPOINTS P1 AFTER ADJUSTING FOR BASELINE DATA: THIS SENSITIVITY ANALYSIS WILL BE PERFORMED SAME AS ORIGINAL ANALYSIS ADJUSTING FOR THE BASELINE MEAN IN THE MODEL AS A COVARIATE. THE SIGNIFICANCE OF THE TREATMENT ASSIGNMENT VARIABLE WILL BE TESTED. THE ESTIMATED ADJUSTED DIFFERENCES IN SLOPES OF TRAJECTORIES AND RESPECTIVE P-VALUES WILL BE PRESENTED AND COMPARED TO THE MAIN RESULTS. CONFOUNDING VARIABLES, MISSING DATA AND BIAS

Confounding: patients entering weight loss programs which promote exercise, surgeries which reduce body fat by significant degree, getting a physical trainer during course of study.

Missing Data: When using weekly averages (P1), will take the median of the existing values for that week and use that value to impute the missing values for patients.

Weekly missing values will be handled using Multiple Imputation (MI) approach.Bias: The study sample size is reasonably small introducing the possibility of selection bias. To minimize this risk, we are employing simple, straightforward inclusion and exclusion criteria and minimizing the total number of criteria to make our study population as similar to a general HF population as possible. Other sources of bias, including misclassification bias will be minimized by the direct electronic dataflow from randomization to data capture from the Pattern Health App, and direct data streams from Abbott medical to the Pattern Health app. Recall bias will be minimized because questions regarding symptoms will be asked to reflect the current symptoms, not a recollection pf prior symptoms. Observer bias will be minimized by the objective nature of the physical activity measurement used in the primary endpoint.

12 STUDY ADMINISTRATION

12.1 STUDY CONDUCT, REGULATORY AND ETHICAL CONSIDERATIONS

12.1.1 ETHICAL CONDUCT OF THE STUDY

The investigator will conduct the study in accordance with GCP and all applicable regulations, including, where applicable, the Declaration of Helsinki. The study will also be carried out in keeping with applicable national and local laws and regulations. This may include an inspection by the sponsor's representatives and/or regulatory authority's representatives at any time.

12.1.2 ETHICS APPROVAL

The investigational site's IRB must meet all relevant regulatory requirements. The study protocol and ICF will be reviewed by the IRB prior to enrolling participants into the study. The investigator is responsible for submitting all protocol or ICF changes and SAE reports to the IRB according to local procedures.

In accordance with applicable local regulatory requirements, the investigator may be obligated to provide periodic safety updates on the conduct of the study at his or her research site and notification of study closure to the IRB. Such periodic safety updates and notifications are the responsibility of the investigator.

12.2 STUDY REGISTRATION

The study team will register the study with ClincialTrials.Gov prior to enrollment of any subjects.

12.3 INVESTIGATOR RESPONSIBILITIES

12.3.1 REPORTING REQUIREMENTS

By participating in the study, the principal investigator agrees to submit reports of any serious adverse events (SAEs) incidences according to the specific timeline as outlined in Section 14.3.6. The investigator will also agree to submit reports to the IRB as appropriate. As required by NESTcc, the investigator will provide accurate reporting to both the sponsor organization and NESTcc for preliminary scientific results, final scientific results, progress reporting and all other reporting requirements as outlined in the Scope of Work.

12.3.2 SOURCE DOCUMENTATION

The Investigator of the study will agree to maintain satisfactory case histories for study participants that have received treatment or been involved in a study intervention. Also, the investigator agrees to maintain accurate source documentation as part of the case histories.

12.3.3 RECORD RETENTON

The investigator shall maintain the records required for this investigation for a period of 5 years after the date on which the investigation is terminated or completed. The research data collected in this study will be kept indefinitely.

12.3.4 FINANCIAL DISCLOSURE AND OBLIGATIONS

The investigator of this study is required to provide financial disclosure information to allow the sponsor of the study to submit the complete and accurate certification or disclosure documents under 45 CFR 45, if applicable.

12.4 KEY ROLES AND STUDY GOVERNANCE

Table 3: Key Roles

Principal Investigator	
Name, degree, title	Brett D Atwater, MD, Director of Electrophysiology., Inova Heart and Vascualr Institute William E Kraus, MD, Professor of Medicine, Duke University School of Medicine
Institution Name	Duke University School of Medicine
Address	P.O. Box 17969, Durham, NC 27715
Phone Number	919-239-0127
Email	*brett.atwater@inova* org. *william.kraus@duke.edu*

The endpoint Committee will be composed of a specialist in cardiac electrophysiology, a specialist in exercise physiology, and a specialist in advanced heart failure.

12.5 SAFETY OVERSIGHT

Due to the short time between trial startup and completion along with the single center study design and relatively small number of enrolled subjects no DSMB will be convened for the project.

The likelihood of serious adverse events occurring as a result of participation in this study is minimal. Project Aim 4 is designed to assess the safety of remotely administered CR. Data sources to ascertain the combination safety endpoint will include answers to questionnaires administered through the patient smartphone application, review of the Duke EMR and review of electrogram data from the implantable device.

12.6 CLINICAL MONITORING

Monitoring of the study site will be performed by the sponsor's designated monitor(s). No on-site visits are scheduled. Eligibility, ICF and safety outcomes will be monitored remotely.

By signing the protocol, the investigator agrees that, within local regulatory restrictions and institutional and ethical considerations, authorized representatives of the sponsor, a regulatory authority, and/or an IRB may visit the site to perform audits or inspections, participant charts and source documents, and other records related to study conduct. The purpose of the sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether the study-related activities were conducted, and data recorded, analyzed, and accurately reported according to the protocol, the site's standard operating procedures, GCP guidelines of the ICH, and any applicable regulatory requirements. The investigator should contact the sponsor immediately if contacted by a regulatory agency regarding an inspection.

12.7 TERMINATION OF STUDY

The sponsor reserves the right to temporarily suspend or prematurely discontinue this study at any time and for any reason. If such action is taken, the sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. The sponsor will promptly inform any other investigators and/or institutions conducting the study, if the study is suspended or terminated for safety reasons and will inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator will inform the IRB promptly and provide the study participants with the reason for the suspension or termination. If the study is prematurely discontinued, all study data will be returned to the sponsor.

13 INSTITUTIONAL REVIEW BOARD (IRB)

The Duke IRB will function as the IRB of record for this protocol.

Institutional Review Board (IRB) approval for the CIP and the ICF will be obtained by the PI prior to screening, consenting and enrolling patients in the clinical investigation. The approval letter must be received by the Sponsor. The IRB will be responsible for assuring the CIP and ICF comply with applicable regulatory requirements (e.g., 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56) and ICH GCP.

Any amendments to the CIP as well as associated ICF changes will be submitted to the IRB and written approval obtained prior to implementation, according to IRB requirements.

No changes will be made to the CIP or ICF or other written information provided to the patient without appropriate approvals, including the IRB and the Sponsor.

Until the clinical investigation is completed, the PI will advise his IRB of the progress of the clinical investigation, per IRB requirements. Written approval must be obtained from the IRB yearly to continue the clinical investigation, according to the IRB requirements.

No investigative procedures other than those defined in the CIP will be undertaken on the enrolled subjects without the agreement of the IRB and the Sponsor.

14 MANAGEMENT OF PROTOCOL AMENDMENTS, DEVIATIONS AND ADVERSE EVENTS

14.1 PROTOCOL DEVIATIONS, AMENDMENTS AND VIOLATIONS

A study deviation is defined as an event within the study that did not occur according to the Clinical Investigative Plan (CIP). Investigators are not allowed to deviate unless it is necessary to protect the safety, rights, or well-being of a subject in an emergency or in unforeseen situations beyond the investigator's control. Any significant protocol deviation will be reported to the IRB as soon as possible. If the investigator anticipates, contemplates, or makes a conscious decision to deviate, in other situations, the study sponsor should be notified and asked for approval in advance.

All study deviations must be reported to NESTcc and the Sponsor with an explanation for why the deviation occurred. In the event a deviation occurred to protect the life or physical well-being of a subject in an emergency, the deviation must be reported to the IRB and to the sponsor within five (5) working days. Reporting of all other deviations should comply with the IRB policies and be reported to the sponsor as soon as possible. The sponsor and PI will review all reported deviations on a periodic basis, assess their significance, and identify any corrective or preventive actions (eg. amend the CIP, conduct additional site training, or terminate the investigation).

We do not anticipate any protocol deviations, however during the course of the study patients may accidently be provided inaccurate information through the Pattern Health app that breaks the randomization or is not in compliance with the exercise prescription as provided by the trained physiologist. To avoid this, the app functionality has safeguards in place limiting the flow of data to the patient's smartphone to only the components approved in the study protocol.

Treatment non-compliance with the prescribed exercise regimen has the potential to reduce the observed effect size from randomization. To reduce the effect of non-compliance and patient withdrawal, we will carefully assess the patient's willingness to exercise and periodically engage with the smart phone application during the baseline phase prior to enrollment. Patients who are reluctant to participate in the full 12 week trial will be excluded.

14.2 ADVERSE EVENTS (AES) AND SERIOUS ADVERSE EVENTS (SAES)

14.2.1 DEFINITION OF AN ADVERSE EVENT

An adverse event is defined as any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

14.2.2 DEFINITION OF A SERIOUS ADVERSE EVENT

An adverse event (or a suspected adverse reaction) is considered "serious" if it has been determined by either the investigator or sponsor that a particular event results in the following outcomes: a life-threatening adverse event, significant or persistent state of incapacitation (or severe disruption of normal daily functions), a congenital anomaly/birth defect, inpatient hospitalization (or lengthened hospitalization) or death. In the event important medical events that do not result in death (but require hospitalization or is life threatening) can be classified as a serious adverse event with appropriate medical judgement when interventions related to the study jeopardize the study participant (and

require medical or surgical intervention to prevent any of the outcomes listed in the definition of a serious adverse event).

14.2.3 CLASSIFICATION OF AN ADVERSE EVENT

The following categories will be used to classify AE in the protocol.

- **Mild –** Events that will require minimal or no treatment intervention and does not interfere with the participant's daily activities.
- **Moderate –** Events that could result in a low-level inconvenience or concern with the prescribed therapeutic measures. A moderate event may cause interference with normal functioning.
- **Severe –** Events that can interrupt a study participant's typical daily activity and would require systemic drug therapy or another intervention/treatment. Severe events can pose as potentially life-threatening or incapacitating. Note, the terms severe and serious are not necessarily equal.

Relatedness: AEs that result from the presence, application, or performance of the remotely administered exercise regimen will be considered system related. AEs that are not temporally related, that affect organ systems or body-sites that are not affected by the exercise regimen, or that can be attributed to another cause will be considered unrelated.

Adverse Event relationships to the study intervention will be classified as either related to study participation or not related to study participation. Expected and unexpected AEs will be clearly delineated from one another. Expected AEs include worsening HF symptoms, orthopedic injury (including fracture, sprain, or tear of bone or soft tissue), myocardial infarction, serious arrhythmia, and ICD therapy. All other AEs will be considered unexpected.

14.2.4 ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information for clinical studies are crucial for the protection of subjects. Reporting and analysis of safety data are mandated by regulatory authorities worldwide. AE CRF's will be collected for all AEs that are potentially study-related and all serious AEs regardless of their relationship to the study. For AEs that require immediate reporting, initial reporting may be done by phone, fax, email or on the CRF completing as much information as possible. The AE CRF must be completed as soon as possible. For any changes in status of a previously reported adverse event (i.e. change in actions taken, change in outcome, change in relatedness), an update to the original AE must be completed. All reported AEs must be followed until the AE has been resolved, is unresolved with no further actions planned, the subject dies or exits the study, or until study closure, whichever occurs first. In the event that a subject is exited from the study prior to study closure, all efforts should be made to continue following the subject until all unresolved system related AEs, as classified by the investigator, are resolved or they are unresolved with no further actions planned. At the time of study exit, all collected AEs with an outcome of "Unresolved, further actions or treatment planned" must be reviewed and an update to the original AE must be reported. At a minimum, if there are no changes to the description, relatedness, test and procedures or actions taken, the outcome must be updated to reflect "Unresolved at time of study closure."

All AEs will be reported to the sponsor and the IRB within 10 working days of the event.

14.2.5 SERIOUS ADVERSE EVENT REPORTING

Regulatory reporting of AEs/device deficiencies will be completed according to local regulatory requirements. Refer to Table 4: SAE reporting timeframes for a list of required investigator reporting requirements and timeframes. The investigator is required to report all SAE's to the Sponsor immediately, and to the IRB per local requirements. The sponsor is also required to report these events to the local regulatory authority based on their requirements. It is the responsibility of the investigator to abide by any additional AE/device deficiency reporting requirements stipulated by the IRB responsible for oversight of the study. For AEs/device deficiencies that require immediate reporting, initial reporting may be done by contacting the study sponsor per the sponsor contact information provided in this document.

Table 4: SAE reporting timeframes

Serious Adverse Events	
Investigator submit to:	
Sponsor	Immediately
IRB	Per local IRB requirement
NESTcc	Immediately
Sponsor submit to:	
Regulatory authorities	Per local requirement
IRB	Per local IRB requirement

All SAEs will be followed and tracked until there is a satisfactory resolution or the site investigator uses their medical judgement to classify the participant as stable or suffering from a chronic illness.

According to 21 CFR 312.32(c)(2), "the FDA must be notified of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information."

14.2.6 REPORTING OF EVENTS TO PARTICIPANTS

Due to the short timeline that we expect to use to enroll and complete the study, little time will be available to fully investigate suspected SAEs and AEs, however, if an AE or SAE does occur and it is determined to be related to study participation, subject participants who have not yet completed study procedures will be notified through the Pattern Health application. Contact information will be provided for additional details which will be provided by the study team through a scheduled phone call or letter.

15 RISK BENEFIT AND CONFIDENTIALITY

15.1 RISK/BENEFIT ASSESSMENT

Study subjects randomized to the intervention study arm will perform more PA than normal for the 12 weeks of study participation. During this time, they may be subject to increased risks of muscle or joint strain, fracture, fall, or soft tissue swelling or pain. Additionally, study subjects may have a higher risk of heart failure hospitalization, myocardial infarction, serious adverse arrhythmia, and ICD therapy. There are no expected long-term risks. Risks will be minimized by designing an exercise regimen that provides small incremental increases in physical activity and further increases will be guided by feedback provided by subjects through the Pattern Health application.

Participation in the research study may have potential benefit. Prior retrospective studies suggest that increased PA is associated with improved 1-5 year survival and reduced risk of hospitalization in patients who meet study inclusion criteria. Further work suggests that increased PA is also associated with reduced frequency and severity of depressive symptoms.

15.2 CONFIDENTIALITY AND MITIGATION PLAN

The Sponsor respects and protects personally identifiable information collected or maintained for this clinical investigation. The privacy of each subject and confidentiality of his/her information will be preserved in reports and when publishing any data. Confidentiality of data will be observed by all parties involved at all times throughout the clinical investigation. All data will be secured against unauthorized access.

All subjects will be provided with a subject identification number. A spreadsheet linking each subject ID to the patient's name and medical record number will be kept at the clinical site in a locked and encrypted file and will not be provided to the sponsor. All data transferred from the patient application will contain the subject ID number. Data will be stored in a REDCAP database and stored behind the Duke Firewall. The study PI, statistician, clinical research coordinators, and study coordinator will have access to the REDCAP database which will contain no PHI. Only the site PI and the site Clinical Research Coordinator will have access to the key linking the subject ID back to PHI.

The study database will be kept in a secure location for at least 5 years after study completion per IRB requirements.

16 RESULTS AND DISSEMINATION PLAN

The project team will publicly share the study design including the sources of study data and the method for linking the sources together for inclusion in the study database. This information will be included on clinicaltrials.org. Because the total study duration is expected to be short (with patient involvement lasting no more than 4 months) little time will be available to provide interim study updates.

The PI will be responsible for writing and submitting the scientific manuscript describing the results of the primary outcome. The PI may share responsibilities for publication of the secondary objective(s). The entire study team will be included as authors on publications. All co-authors will be provided access to the final results prior to manuscript publication. The study database will be stored in a repository at the Duke Clinical Research Institute after study completion. The study results will be made available to the study participants. If the active arm has improved outcomes relative to the controls, the controls will be offered participation in remote CR as part of their routine clinical care at Duke. This may not be directed by their implantable device PA data.

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18 APPENDICES

18.1 PARTICIPANT SCHEDULE OF EVENTS

Table 5: Schedule of Events

	Screening / Baseline	Randomization	Initial Remote Physical Activity Session	Follow up Sessions	13 Weeks post Randomization (Completion)
Frequency	1	1	1	11	1
Type of Visit	Chart Review, Written Communication through EMR ± App ± Phone Call	Written Communication through App± Phone Call	Written Communication through App± Phone Call	Written Communication through App± Phone Call	Written Communication through App ± Phone Call
General eligibility criteria	•	•*			
Informed consent	•	•*			
Demographics	•				
Medical history	•	•*	•		
NYHA Assessment	•		•		•
KCCQ QoL Assessment			•		•
Remote Device Interrogation			•	•	•
Medication Review	•		•		•
Adverse Events			•	•	•
Weight, Blood Pressure, Glucose*	•			•	•
Patient Satisfaction Survey**					•

**Diabetes Patients only*

***Remote Cardiac Rehab Patients only*

18.2 LIST OF ABBREVIATIONS

ACC	American College of Cardiology
ACE-inhibitor	Angiotensin-Converting Enzyme inhibitor
AE	Adverse Event
AHA	American Heart Association
ANCOVA	Analysis of Covariance
ARNI	Angiotensin Receptor Neprilysin Inhibitor

BP	Blood Pressure
CFR	Code of Federal Regulations
CI	Confidence Interval
CIED	Cardiac Implantable Electronic Device
CIP	Clinical Investigative Plan
CMMS	Center for Medicare and Medicaid Services
CPET	Cardiopulmonary Exercise Test
CR	Cardiac Rehabilitation
CRF	Case Report Form
CRT	Cardiac Resynchronization Therapy
CRT-D	Cardiac Resynchronization Therapy Device
DCRI	Duke Clinical Research Institute
DOCR	Duke Office of Clinical Research
DSMB	Data Safety Monitoring Board
DUHS	Duke University Health System
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMR	Electronic Medical Record
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HF	Heart Failure
HIPAA	Health Insurance Portability and Accountability Act
ICD	Implantable cardioverter-defibrillator
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intention To Treat
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVEF	Left Ventricular Ejection Fraction
MDIC	Medical Device Innovation Consortium
NESTcc	National Evaluation System for health Technology Coordinating Center
NIH	National Institutes of Health
NYHA	New York Heart Association
PA	Physical Activity
PHI	Protected Health Information
PHQ-9	Patient Health Questionnaire 9
PI	Principal Investigator
PP	Per Protocol
PRO	Patient-Reported Outcome
QOL	Quality of Life
SA	Safety Analysis
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SD	Standard Deviation
US	United States

18.3 ADDITIONAL APPENDICES

18.3.1 INFORMED CONSENT FORM

18.3.2 KANSAS CITY CARDIOMYOPATHY QUESTIONNAIRE

18.3.3 NYHA QUESTIONNAIRE

18.3.4 PHQ-9 QUESTIONNAIRE

18.3.5 PATIENT SATISFACTION SURVEY