OptiVol for Precision Medical Management of Heart Failure
(OPTIMED-HF) Protocol

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1. PURPOSE OF STUDY

To demonstrate that a multidisciplinary team intervention using pre-specified standard of care medication dosing guided by ICD-derived data will increase the rate of change in Guideline Directed Medical Therapy (GDMT) medication dosing in the intervention group compared to usual care at 6 months in cardiomyopathy patients who have received an ICD for primary prevention.

2. BACKGROUND AND RATIONALE

Most patients with ischemic and non-ischemic cardiomyopathies do not receive optimal Guideline Directed Medical Therapy (GDMT) at the time of ICD implantation. Our data from the Rochester ICD Registry show that >60% of patients who are implanted with an ICD do not receive all guideline-recommended medications for heart failure (HF) at the time of device implantation and >90% do not receive an optimal dose of the recommended drugs[1]. Furthermore, most HF patients do not receive prescription for a regular exercise program, despite the fact that activity was shown to be associated with improved morbidity and mortality in this population [2]. Accordingly, there is a ~30% higher relative risk of adjusted mortality rate for patients not on GDMT [3]. In addition, the relatively low rates of patient activation and engagement in their care is associated with reduced outcomes and increased cost of care [4].

Current medical management regimens are limited due to the fact that individual continuous functional and physiologic data are not available to the patient's health care providers, leading to reduced rates of guideline-directed medications, dose adjustments, and lack of appropriate exercise prescription. Physiologic and functional data from Cardiac Implantable Electronic Devices (CIEDs), including information on heart rate, activity, and fluid status derived from the OptiVol monitor, together with a concurrent patient engagement strategy through remote interactions, can be used to optimize the medical management of HF patients implanted with an ICD.

We hypothesize that continuous use of the standard CIED functional and physiologic data currently available to clinicians, integrated in the OptiVol-Monitor algorithm (Medtronic) and additional device features, can be used by an active remote multidisciplinary team directed GDMT to optimize medical management in patients with ischemic and non-ischemic cardiomyopathy (NICM) who have an implanted ICD.

We will show that the incorporation of Cardiac Compass data with pre-specified medication

regimens will result in optimization of GDMT medications compared to usual care and we will demonstrate the safety and utility of using CIED data for patient management. Furthermore, we would like to provide evidence that remote interactions, encouraging patient engagement via virtual visits and mobile device based quality of life questionnaires, can be used to improve functional and clinical outcomes in heart failure patients.

We chose to focus this pilot study on both ischemic and non-ischemic cardiomyopathy since patients in both groups have potential for improvement following medical optimization.

Objectives

To demonstrate that a multidisciplinary team intervention (see administrative organization section) using pre-specified medication dosing standards guided by CIED-derived data will increase the rate of change in GDMT medication dosing in the intervention group compared to usual care at 6 months in cardiomyopathy patients who have received an ICD (Medtronic) for primary prevention.

The secondary objectives are:

1) To characterize the correlation between Cardiac Compass-guided optimization and improved functional capacity and activity
2) To show that ICD-derived physiologic data, including arrhythmia and activity, are associated with clinical outcomes.
3) To validate a personalized framework for optimizing GDMT based medication dosing using time-dependent CIED and wearable sensor derived physiologic and functional data.
4) To characterize the correlation between wearable wristband sensors derived activity data and functional capacity and show that activity is associated with improved clinical outcomes.
5) Characterize health care utilization, defined as unplanned clinic visits, emergency department utilization, and hospitalization between CIED guided GDMT and usual care.
5) To develop a risk stratification scheme for adverse events within the total study population using time-dependent CIED and wearable sensor-derived physiologic and functional data.
6) To demonstrate that remote monitoring with a concurrent patient engagement strategy, using optional journal entries, is associated with improved clinical and functional outcomes and reduced health care utilization.
7) Quality of life (measured by Kansas City Cardiomyopathy Questionnaire) from enrollment to 6 months.

3. ADMINISTRATIVE ORGANIZATION

The study will take place at the University of Rochester Medical Center facilities. The investigators are both within the Department of Medicine-Cardiology. The PI and Investigators will lead the study and be responsible for study execution, safety, and data analysis. A Project manager, a Registered Nurse and Research Coordinators will have an active role throughout the study process.

4. STUDY DESIGN

The study is a randomized pilot clinical trial. The Coordination and Data Center (CDC) is at the University of Rochester. Each site will directly interface with the subjects for activities such as consent, testing, study team virtual and in person-visits.

The study will enroll approximately 30 subjects with ischemic and non-ischemic cardiomyopathy previously implanted with an ICD for primary prevention of sudden cardiac death. Subjects are followed for 6 months. Clinical, functional, and digital biomarker data will be captured related to: activity, heart rate, blood pressure, weight, blood biomarker BNP, quality of life status, and clinical events. Electronic health records will be monitored for 12-month period to collect/record study data.

Study data will be entered by site staff using a web-based data entry system at the University of Rochester for data management, analysis, and coordination of logistics.

The study duration is 2.0 years: including an estimated 3-month initiation phase; an estimated 8-month enrollment phase; and an estimated 6-month follow-up phase; with subsequent data analysis.

Primary Endpoint

The primary outcome of this study is the rate of change in medical management with beta-blockers, diuretics and Sacubitril/Valsartan (defined as initiation, termination, switch, or dosing adjustment) in the intervention group compared to usual care at 6 months.

Secondary outcomes

- Recurrent changes to medication type and dosing reflecting ongoing personalized optimization.
- Mean changes in functional status (measured by 6-minute walk distance) in the intervention vs. control groups.
- Percentage change in average daily activity level between the first month following discharge and the last month of the study (6th month) will be compared between intervention and control groups.
- Quality of life (measured by Kansas City Cardiomyopathy Questionnaire) from index discharge to 6 months after discharge in the intervention vs. control groups.
- Healthcare utilization as determined by unplanned office visits and hospitalizations.
- Cardiac hospitalizations and all-cause mortality.
- Laboratory biomarkers.

Screening

Potential subjects will be screened using electronic records to ascertain prior ICD implantation per inclusion/exclusion criteria. The potential subject's health care provider will be contacted for permission to approach the patient for further screening and if eligible, obtain consent.

Patients are randomized 2:1 into:

An Intervention Group

The clinical management of the intervention group will be comprised of the following:

- A study care-team, comprised of a Cardiologist, an Electrophysiologist, a Registered Nurse, and study coordinator who will receive monthly physiologic and functional reports derived from Medtronic CIEDs incorporating Cardiac Compass and OptiVol monitoring.

- The study team will also be provided with patient-specific data derived from patient reported outcomes that include symptoms, quality of life scores, and PROMIS data if available. PROMIS®, a tool developed for use by the National Institutes of Health provides quality of life data, and is part of standard clinical care at the University of Rochester Medical Center Cardiology Department for patients. This is a survey patients have the option of filling out at clinic visits and available through the electronic medical record.
- The Datos app platform will be used to conduct a separate Quality of Life study survey and weekly e-survey REDCap may also be used as an additional resource..
- A pre-specified management regimen based on standard clinical practice will be provided to the study team in which medical management including medication dosing (focusing on beta-blockers and diuretics) will be monitored and modified using CIED and OptiVol data (see Figure 1 and footnote* at end of document). This is based on current and accepted clinical practice.
- The study team will contact the patients on a monthly basis for 4 monthly virtual visits. Based on CIED and patient engagement data, the study team will adjust medications and dosages, and optimize activity/ exercise steps. All medication changes resulting from the virtual visits will be updated in the subject's electronic medical record and communicated by medical chart messaging or URMC email based on the patient physician's preference.
- All study team contacts with the patients will be virtual, using telecommunication or E-communication. These options include URMC approved Zoom portal (currently used for URMC telemedicine clinical care), phone, or email. If the telemedicine call (preferred method) is disconnected, phone or email will be utilized. These e-communications will occur using an existing HIPAA compliant platform to improve efficiency, patient engagement, and reduce study costs while preserving data quality.
- In-person clinic research visits will be scheduled at 3 and 6 months, if feasible (if in-person visit is not feasible, Zoom or telephone visit will be conducted). Medication changes may occur based upon study physician judgement, assessment including NYHA class, in- person device interrogation, and patient reported symptoms.
- Garmin wearable wristband sensor data, such as number of steps, heart rate, and oxygen saturation, is passively captured and not used for patient management.
- CIED functional and physiologic data, as well the OptiVol monitor information and wristband sensor data will be captured in the study digital biomarker core-lab to better understand risk stratification in the total study population following study completion (see secondary aims above).

A Conventional Management Control Group

The clinical management of the control group will be comprised of the following:

- In-person clinic research visit, if feasible (if in-person visit is not feasible, Zoom or telephone visit will be conducted)will be scheduled at 3 and 6 months, similar to the intervention group. The 3 and 6-month visit includes: in-person device interrogation, NYHA class, any changes to medication or new events.
- To control for patient contact, patients in the conventional management group will receive 4 monthly virtual visits from the same study team. The study team will ask questions about symptoms, changes in activity levels, medication changes by their non-study

physician, and any adverse events. The study team however will not be provided with any patient specific Optivol data, survey results or PROMIS® data.

- CIED functional and physiologic data, as well the OptiVol monitor information and wearable wristband sensor data, for the control group will be captured in the study digital biomarker core-lab for the development of a risk stratification scheme in the total study population following study completion (see secondary aims above).
- The non-study physician will receive CIED/OptiVol data (as in usual care) and its use and the management strategy will be left to his/her discretion.
- The wearable wristband sensor data is passively captured and not used for patient management. Only the data currently available in remote monitoring from the ICD is being used which is same as current usual care.

Addition or removal of heart failure medications and changes in medication dosage will be left to the discretion of the treating physician. Upon completion of 6 month follow up the subjects will no longer require study visits and will return study equipment. We plan to collect study data from the electronic heath record through 12 months at which time no further data will be collected.

4.1. SUBJECT POPULATION

Approximately 30 subjects total will be enrolled in this study following a 2:1 ratio (intervention: control). The study will be conducted at the University of Rochester Medical Center. Over 250 patients are newly implanted with a defibrillator per year and over 1,000 patients are followed within the system.

- Gender and Age of Subjects**:** Male and female subjects aged 18 years to 85 years. We expect to enroll about 25% women.

- Racial and Ethnic Origin: There are no restrictions on race or ethnicity in this study. We expect to enroll about 25% minority subjects.

Inclusion Criteria

- 18 to 85 years of age on the date of randomization
- ICD implantation for primary prevention in patients with ischemic and non-ischemic cardiomyopathy ≥3 calendar months from date of enrollment
- SMART Phone or tablet with Bluetooth capability with internet access
- No other identifiable reversible cause explaining the left ventricular dysfunction

Exclusion Criteria

- CRT implanted.
- LVEF>45% in the last echocardiogram or other clinic imaging performed.
- Medtronic device generator and/or device components not implanted
- Unstable clinical condition, life threatening arrhythmia
- Heart failure hospitalization within the preceding 3 calendar months
- Cognitive impairment
- Severe renal dysfunction (eGFR < 30 ml/min/m2)

- Serious known concomitant disease with a lift expectancy of < 12 calendar months
- Non-ambulatory NYHA class IV
- Pregnancy

Inclusion of Vulnerable Populations:

- Vulnerable populations: Women of childbearing potential are included if they are currently on the medications to be optimized (beta-blockers, diuretics and Sacubitril/Valsartan).

4.2. STUDY INTERVENTIONS

Please see section 7 entitled Study Procedures for integrated description that includes the study interventions.

Devices

Implantable Cardioverter Defibrillator: This study is not studying devices but will utilize data already clinically used and available from implantable defibrillators (ICD). Patients qualify for this study once they and their clinical team has decided to have an ICD implanted for primary prevention of sudden death as part of standard of care. All ICDs are FDA approved and will be used per the FDA indications.

Wristband Sensors: The study will also use a commercially available wearable wristband sensor (Garmin) to collect functional data. The Garmin Vivo Smart wristbands will be used to passively collect data. This data will not be used for optimizing the Guideline directed medical management. These wristbands use 3D accelerometers and other sensors to measure basic human function such as movement and heart rate patterns and provides high resolution raw data for research purposes. The URMC investigators have evaluated the actual device and found it ideal for the proposed study. It is wrist-worn, fully waterproof watch like band that has been scientifically validated in both adults and children. They are compact, wrist-worn, rechargeable battery- operated whose physical characteristics are similar to a small wristwatch attached at subject's wrist. The following technical specifications have been provided by the manufacturer.

- The Garmin Vivo Smart utilizes an accelerometer to monitor the occurrence, degree of and duration of motion. The sensor integrates the degree and speed of motion and produces an electrical current that varies in magnitude. An increased degree of speed and motion produces an increase in voltage. The device stores this information as activity counts. The shape of the sensor makes it most sensitive to motion in certain orientations. It also measures heart rate, and other basic physiologic variables as well as time. However, it is sensitive to motion in all directions.

- The Garmin wearable wristband data can also be downloaded and programmed to provide the needed data. Both wristband sensors are similar in form factor attached to the

subject's wrist. It then accumulates subject activity as counts for a specific period of time known as the *epoch length*.

Datos App: The Datos App is commercially available in the app store marketplace and will be free to use by study subjects

1. Activity data collected by the Garmin watch will be transmitted via Bluetooth/Wifi to a smart device (tablet or smartphone with installed app). The app collects subject activity data passively from the Garmin watch.
2. Survey data, including the Weekly e-Survey and KCCQ will be performed using the Datos app platform to make the surveys convenient and user-friendly for subjects. REDCap may also be used as an alternative for the surveys if Datos is unavailable.

The study team will have access to the patients' activity data, however these data are passively collected and not used in clinical decision-making. These data are collected for future data analysis. These data will be coded by study subject number. The Datos app can be used on iOS and Android operating platforms. All data will then be synced to a secured cloud database via Internet connection as indicated in the Electronic Data Security Assessment Form. Study subjects will delete the Datos app when instructed to do so by study staff.

PHYSICAL PROPERTIES OF WRISTBAND WEARABLES

Parameter	**Value**
Sampling rate	10-100Hz
Battery type	Rechargeable (Garmin)
Battery life	Rechargeable (Garmin)
Accelerometer sensitivity	+-8g
Waterproof	Yes to 10 meters
Frame cover	plastic
Wrist band	Nylon or compatible

- The accelerometer wristband and any monitoring equipment that needs to have data downloaded will be done remotely to minimize number of research visits.

- The devices will be assigned to the subject by a study team member. Devices will be stored in a locked office that only the study team has access to. Subjects will be asked to return the devices upon completion of the study. Medical- grade disinfectingwipes will be used to clean the wristband wearable monitors after each subject use.

5. RECRUITMENT METHODS

This study will identify potential subjects for recruitment using the UR CTSI Research Participant Registry, STUDY00001978, and by local referrals to URMC electrophysiology lab or clinic patients or patients who have recently undergone an ICD device implant with cardiomyopathy. Investigators have routine access to medical records that will be screened.

Subjects who meet inclusion will be identified by or referred to the investigator. The initial contact via study team will be by way of the clinical service treating provider obtaining permission for the study team to approach patient. Phone contact will occur if the initial contact has been made by the clinical team first. The study team will introduce and gauge interest about participating in the study. The investigator will notify the research coordinator if the patient is interested to continue the informed consent process.

The research coordinator will discuss the study details with patient either in clinic or via phone depending on patient preference. The consent form may be taken home from clinic or mailed so the patient will have adequate time to think about study and/or discuss with family if applicable. Consent will be obtained in person or via mail consent by coordinator or investigator at the study site.

6. CONSENT PROCESS

The site investigator and/or study coordinator will consent subjects in this study. The consent document will be used as a guide for the verbal explanation of the study and will be the basis for a meaningful exchange between the investigator and the potential subject. The subject's signature provides documentation of agreement to participate in a study but is only one part of the consent process. The consent document will not serve as a substitute for discussion and the potential subject will be invited to ask any questions or concerns that will be answered by the study team members. Once a participant indicates that he or she does not want to take part in the research study, this process stops. The potential subject will be given sufficient opportunity to consider whether or not to participate. Refusal to take part or withdraw from the study at any time will not interfere with the future medical treatment.

The consent will be archived in study binders with consent checklist and kept at study center offices at the enrolling site. The subject will be provided with a copy of the signed original consent form for their records. Subject enrollment log will be maintained throughout study.

7. STUDY PROCEDURES

After consent, subjects will undergo/agree to the following study-related procedures (Consent and Enrollment may be done at separate visits):

- Garmin wearable wristband is provided for daily wear. Subjects should wear the wristband as often as possible. Subjects will return the Garmin wristband at 6 months.
- Quality of life questionnaire: KCCQ and a 3-question weekly electronic survey (e-survey) will be completed via the commercially-available Datos app platform. The survey

asks questions about how you are feeling, have you felt any symptoms, and the quality of your health status. The KCCQ should take 10 minutes to complete and the 3-question weekly e-survey should take 3 minutes to complete. Research staff will follow up with subject if weekly e-survey has not been completed for 2 weeks. REDCap may also be used as an alternative.

- Electronic medical record data regarding clinical history, medications, device implantation, and follow-up data will be collected for 12-month period.
- PROMIS data collected from medical record for 12 months, ICD data, medications, and other office visits/ hospitalizations/ unplanned visits standard of care will be available for chart review.
- Will participate in virtual visits, with phone visits occurring in the event a virtual visit is not possible. For those subjects in the intervention group, medications will be adjusted to optimize to medical guidelines; for those in the control group, no medications will be adjusted, but the subject will have the opportunity to share any changes in their medical status and any questions for the study staff. The control group will only receive their usual care and will not have their medications optimized by the research team. Visit time is approximately 30 minutes.
- Virtual Visit Overview with Subjects: Study staff will provide basic instruction to the subject on the use of Zoom. Study staff will show subject an example of a Zoom virtual visit to help them better understand the Zoom program before the first monthly virtual visit. Subjects will be invited, via e-mail link, to the Zoom meeting from the URMC HIPAA secured Zoom portal. They will then click on the invite link and will be directly connected with the study staff member. The Zoom Help Center (https://support.zoom.us/hc/en-us) may also be used as an online resource to help troubleshoot the virtual visit.
- Blood samples may be taken as part of the study if a subject is randomized to the intervention group and the study team adjusts diuretic medications as clinically indicated. These blood samples are for patient safety and are routinely ordered to assess kidney function when a patient is taking diuretics. Labs will be ordered via a paper requisition and billed to the study. Research study staff will follow up within 3 days of result return.
- Future Use Blood Sample (optional)

Method of Assigning Subjects to Treatment

Study enrollment using the electronic data capture system that is available 24/7 to all study personnel. Patients will be randomized in a 2:1 fashion to either intervention or conventional management. Randomization will be conducted using a computer random number generator.

Follow-up Schedule (See also Table 1)
Following enrollment, all subjects will have scheduled follow-up visits (phone, electronic or telemedicine) by the study team at monthly intervals following enrollment and baseline testing.

CIED-derived physiologic and functional reports will be available to the study team only for patients assigned to the GDMT-medical optimization intervention group.

All subjects will be followed for a time-period of 6-months. Medical record data will be collected for a 12-month period.

The following time-points will be assessed:

- *Enrollment (V0):* Baseline clinical characteristics, existing echocardiographic measures and NYHA class will be recorded. Additional tests will include a 6-minute walk test and KCCQ questionnaire. Garmin wristband is provided.

- *Randomization (V1):* subjects will be randomized to an intervention arm of CIED-based medical optimization vs. conventional management.

- *Monthly virtual visits by research team (V1a):*

    - Conventional group: questions about symptoms, changes in activity levels, medications and adverse events. No additional CIED data provided to the subjects' usual clinical care providers since they will follow their own standard routine for CIED-monitoring.

    - Intervention group: virtual visits for medical optimization and prescription changes to medications based on CIED-reports and decision flowchart.

- *3-months (V2):*

    - Intervention group: office visit for clinical assessment, including physical exam and NYHA class. Clinical and adverse events.

    - Control group: office visit for device interrogation, medical record review, report any changes in standard care, NYHA class.

- *6-months (V3):*

    - Intervention group: Physical exam, NYHA class, 6-minute walk test, KCCQ, clinical and adverse events.

    - Control group: office visit for device interrogation, medical record review, report any changes in standard care. NYHA class, perform 6-minute walk test and KCCQ.

The CIED and Garmin wearable wristband physiologic (activity, heart rate, oxygen saturation) and functional data will be continuously captured by the study's core lab for all patients throughout follow-up. The Garmin Wristband sensor data will not be used for intervention. The

lab/data capturing process is HIPAA compliant and Garmin wristband is identified through a study ID number and patient name is not registered into with wristband.

Timeline	Consent/ Enrollment (may be separate visits)	Performed Weekly	1m +- 7d	2m +- 7d	3m +- 7d	4m +- 7d	5m +- 7d	6m - 7d/+14d	Thru Month 12 Chart Review No Visits
Informed Consent	✓								
Randomization	✓								
Medical History	✓								✓
Vital Signs: BP, weight, RR	✓				✓			✓	
Review Inclusion/Exclusion Criteria	✓								
Medication List	✓		✓	✓	✓	✓	✓	✓	✓
Blood Sample Repository: Optional	✓								
Remote CIED data acquisition	✓	**Data Acquired remotely throughout study**							
Remote Wearable data (Garmin) acquisition	✓	**Data Acquired remotely throughout study**							
QOL: KCCQ	✓							✓	
Weekly E-Survey	✓	✓							
6MWT	✓							✓	
Virtual Visit	✓		✓	✓		✓	✓		
In-person Clinic Visit: **Physical Exam** **NYHA Class** **CEID Interrogation**	✓				✓			✓	

Medication Optimization – Management Regimen

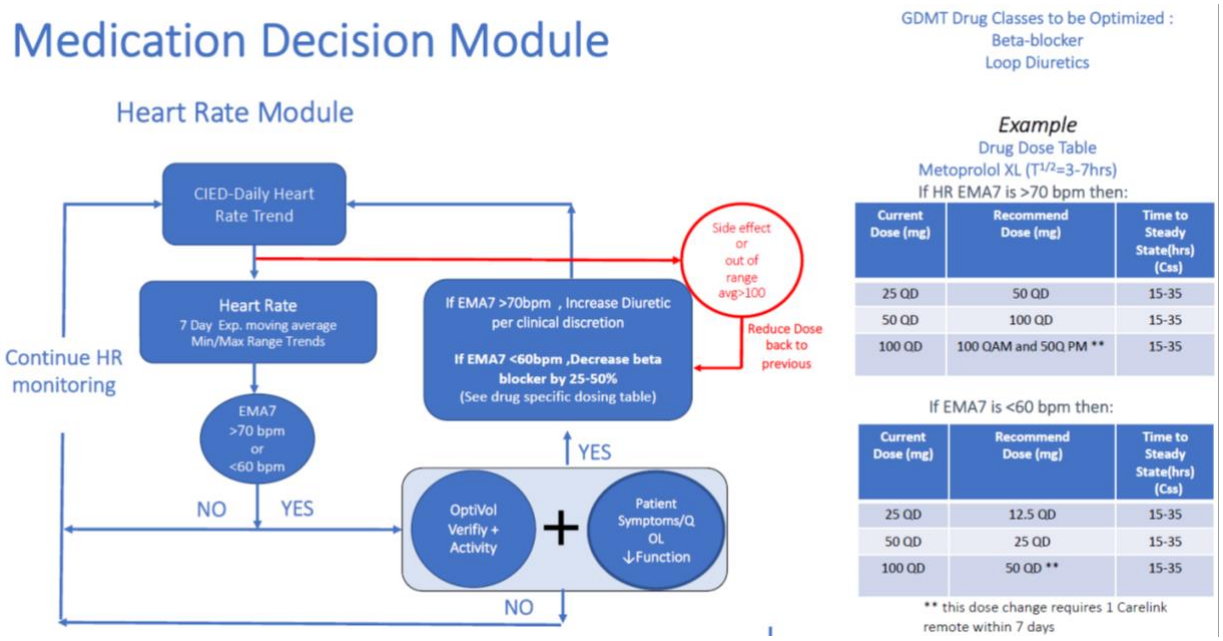
The clinical research team managing the intervention group will follow standard clinical discretion in adjusting medications as appropriate and will use the medication flowchart (Figure 1) that includes considering the clinical physiologic data that is available in ICD devices and used clinically.

The medication adjustment flowchart reminds clinicians to consider any device data such as heart rates and activity etc. as well as patient reported outcomes to optimize medication dosing to meet guideline directed medical therapy which is associated with long term survival benefit.

Dose adjustment will be based upon the monthly reporting of data acquired from the CIEDs focusing on the following medications: Loop diuretics (e.g., furosemide, bumetanide, torsemide) unless the subject is not indicated, is contraindicated, or is intolerant of loop diuretics; and beta-blockers unless the subject is not indicated, contraindicated, or is intolerant of beta-blockers. The choice of selective or non-selective beta-blockers use is left to the clinician Investigator's discretion. Blood work may be ordered to assess kidney function within 1-2 weeks of changes to diuretic medications.

Additional virtual follow up after dose adjustments is not prohibited and left to investigator team discretion as needed.

Figure 1: Medication Flowchart



Medication Optimization Guideline

- If Average HR > 70 bpm+ Stable OptiVol + Stable per patient symptoms, Then increase BB per the recommendation (drug dosage table)
- If Average HR < 60bpm + Stable OptiVol + Stable per patient symptoms, Then no change in BB until next follow up
- If Average HR > 70 bpm + increased volume per OptiVol + reduction in capacity per patient symptoms, then adjust diuretics first and subsequently (in the next virtual visit BB if HF still >70 bpm)
- If Average HR < 70 + increased volume per OptiVol + reduction in capacity per CIED activity and patient symptoms, then, adjust diuretics without BB
- Similar flow process for Activity guided exercise prescription which would look to optimize daily activity/exercise steps upward toward target if OptiVol, HR, patient reported symptoms are consistent that no acute decompensation is occurring or imminent.

Clinical Discretion applies to all medication adjustments

Plans for return of research results:

- A summary of the study research results will be provided to all patients after completion of the study, analysis and publication of a peer-reviewed publication. Raw data and individual will not be available.
- For both groups, if there are life-threatening incidental findings during the study which require clinical intervention, the subject's primary clinical team will be notified in a time frame appropriate for the clinical event, via eRecord, secured email, or in person as applicable. It is understood that the usual care control group will have significantly less monitoring and data will not be analyzed at the same frequency as the intervention group.

8. RISKS TO SUBJECTS

This is an interventional study in subjects who are qualified for a standard-of-care implantation of an ICD device. The study is not evaluating any medical device. The intervention is to include the use of currently available device data to guide medication management and optimize guideline directed medical therapy.

There is some risk of associated with the use of any medication. It is important to note that in this study, we are using standard of care and recommended guideline directed medications already indicated in this population of heart failure patients; which are often associated with reduced mortality and improved outcomes. We are not testing new medications. Medications inherently may be associated with side effects. The clinical research team is experienced in cardiovascular trials and the clinical management of patients with heart disease/heart failure and will be monitoring for any adverse effects and adjust medications accordingly.

The study team may be notified if you receive other health care services at URMC or its Affiliates (e.g., visit to the emergency room). In addition, the following individuals may know you participated in research and may see results of testing conducted for this study:

- Staff at the University of Rochester Medical Center and its Affiliates (e.g., Strong Memorial Hospital, Highland Hospital, URMC primary care, specialist physician offices) who have a reason to access your electronic health record.
- Health care providers who are involved in your care at a facility that is not part of the University of Rochester Medical Center and its Affiliates and who have reason to access your electronic health record.
- Individuals who request a copy of information from your health record for activities such as treatment or payment (e.g., medical insurance companies, worker's compensation).

All study data will be deidentified using a unique study ID number. The study ID number will also be stored in a separate document (study log) that is linked to identifying information about you such as your name.

10. POTENTIAL BENEFITS TO SUBJECTS

There are no direct benefits that the subject can expect to receive as a result of participating in this study. It is possible that there may be a benefit to participating in the intervention group as these subjects will have a comprehensive study team managing their medications and possibly adjusting medications based on reported symptoms.

11. COSTS FOR PARTICIPATION

There are no additional costs to the subject. All medication optimization follows standard of care guidelines. Medication changes are billed to subject's insurance per standard of care.

12. PAYMENT FOR PARTICIPATION

Subjects will be paid up to $100.00 for taking part in this study. Subjects will receive $50.00 for each completed in-clinic follow up visit. Subjects will not be paid for visits that they do not complete. Compensation is paid by check and may take 4-6 weeks to process.

If subjects withdraw from the study prior to the 3-month visit, then subjects will not receive any compensation.

Additionally, subjects will be reimbursed for parking fees via a URMC parking voucher at the "in-person" research-related clinic visits.

13. SUBJECT WITHDRAWALS

Subjects will be advised in the written informed consent forms that they have the right to withdraw from the study at any time without prejudice. Subjects may be withdrawn as lost to follow-up by the investigator if their data on ICD interrogation and survival are not available for 7 months from last device interrogation. These subjects will not undergo any additional study activities after withdrawal. If a subject becomes pregnant during the course of a study, they will continue to be monitored but no longer be part of the interventional arm. Data collected will be used up to the date of withdrawal.

14. PRIVACY AND CONFIDENTIALITY OF SUBJECTS AND RESEARCH DATA

Data collected during this study will be obtained for research purposes and derived from study procedures. Data will be captured using a dedicated website containing a number of electronic case report forms (eCRF's). Data captured is de-identified upon entry. Identifiable information on individual subjects will be accessible only to the investigators and study staff. Electronic data will be de-identified and stored securely in a password protected EDC system maintained by the Clinical Cardiology Research Center (CCRC) at the University of Rochester. Study coordination, database management, and statistical analysis will be performed by CCRC. Research data will be stored indefinitely. All study binders with subject data will be stored securely in the locked Clinical Cardiology research offices. A paper enrollment log will be maintained in Regulatory binder and stored securely in the locked Clinical Cardiology Research offices.

Once the study is closed, all patient binders and regulatory binders will be boxed up, labeled (so easily identified), and taken to a specific locked storage room that all study files are kept.

Datos App: This is smart device app used via the subject's personal smart device. Password or PIN number is required for use of the app. Data transferred from Datos server running on

the Google Cloud Platform located on the East coast of the US and is encrypted. The use of this app and data transmissions have been vetted by University of Rochester IT.

15. DATA / SAMPLE STORAGE FOR FUTURE USE

Data will be stored with the UR research system for future use and used for research purposes and identified using study subject number. Data will be stored indefinitely. The PI and authorized research personnel working on the project will have access to the data. Restricted areas of any study website will be protected by user login. University of Rochester is protected by a dedicated firewall limiting the traffic source and type entering the University, which imposes restrictions on network protocols to reduce the risk of common vulnerabilities. SQL Server relational database enables central management, data acquisition, and data flow coordination and is used to design, manipulate, and protect data and build applications. Using a journaling audit trail option, we will track data changes. Prior to merging or extracting any data into or from the database, merge/extraction routines will be developed and thoroughly tested.

Blood samples for future research.

Purpose of blood samples.

Patients will have the option of providing blood sample for future research.

The study will collect blood samples and these will be stored at the University of Rochester at the time of enrollment for future research use, indefinitely. Providing blood samples for future research is optional for subjects. Samples will be stored at the University of Rochester Medical Center, but may also be sent to specialized labs for future genetic research with initial plans to assess polymorphisms and mutation in alpha and beta-adrenergic receptors systems, G-protein signaling pathways, ion-chanelopathies, markers of fibrosis, myocardial damage, inflammatory markers and genetic biomarkers to determine their contribution to the individual patient response or lack of response to guideline directed medical therapies. These analyses will be exploratory and purposefully not included in the primary specific aims in light of limited data supporting their usefulness in predicting clinical events.

Description of the repository

In subjects who consent to blood sample collection, 3 tubes of blood will be collected at baseline. The samples will be de-identified and are to be labeled with the subject ID number given at enrollment, an anonymous bar code from the blood sample kit, and the date collected. The University of Rochester Central Laboratory will store the samples in a -80°C environment. The blood samples are coded and linked to a study key with subject identifiers which is protected from non-study personnel and will allow correlation of clinical data with biomarkers in the future. Subjects will not be contacted for the future use of their samples, nor will they be informed of the results of the research on their donated specimens.

Risks and Benefits

There is a very slight but small risk that the subject donating a sample could be identified. The risk is mitigated by coding the sample with the study subject ID number and use of an anonymous code. Subjects will be informed that contributing an anonymous specimen offers no direct benefit to subjects, nor will they be informed of any results.

16. DATA AND SAFETY MONITORING PLAN

An adverse event is any unexpected symptom, sign, illness, or experience that develops or worsens during the course of the study and is possibly or definitely related to study procedures.

Adverse Event Reporting

Investigators shall report to their local IRB, and report in the electronic data collection system within five business days of PI awareness only real or suspected, serious and unanticipated adverse events that are related to participation in the study (i.e. anaphylaxis to medication) Events related to standard of care such as medications side effects do not need to be reported unless severe as defined below. Death of a subject must be reported as an adverse event, per the serious adverse event definition below. The PI is aware that investigators are responsible for reporting to and following the guidance of any other applicable oversight bodies, including the Institutional Review Broad (IRB).

Serious Adverse Event Definition

This population is at baseline increased risk of heart failure, death, and poor clinical outcomes. A serious adverse event is defined as any adverse medical experience that results in any of the following outcomes:

- death;
- is life-threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in permanent impairment of a body structure or a body function;
- requires medical or surgical intervention to prevent permanent impairment or damage;
- leads to fetal distress, fetal death or a congenital abnormality or birth defect.

Data Safety Monitoring Board

A data and safety monitoring board (DSMB) will be appointed to independently monitor the conduct and the outcome of the trial. The DSMB will be responsible for monitoring the safety and well-being of the patients participating in this study and ensuring the ethical conduct of the trial. Since this study is a pilot project enrolling approximately 30 patients using data already routinely used by clinicians and since the safety endpoints focus on optimizing current standard of care medications, the main focus of DSMB activity will be to monitor for potential increase in unexpected complications during the trial. For patients in the conventional treatment arm, data on clinical events including adverse events, cardiovascular hospitalizations, and death will also be collected and provided to the DSMB for evaluation of risks associated with drug therapy.

The board will meet every three months either in-person or via conference call to review the data. The DSMB will consist of 2 physicians with expertise in cardiology and one expert in biostatistics.

17. DATA ANALYSIS PLAN

Statistical Methods

Primary Statistical Hypothesis

To test the hypothesis that a multidisciplinary team intervention using pre-specified medication

dosing regimens guided by Cardiac Compass-Optivol data will increase the rate of change in beta-blocker and/or diuretic prescription (defined as initiation, termination, or dose adjustment) in the intervention group compared to usual care at 6 months.

Statistical Test Method and Sample Size Considerations

The primary outcome of this study is the rate of change in medical optimization (changes in heart failure medications and dosing) guided by CIED physiologic and patient engagement app data that are used together with pre-specified medication dosing regimens over 6 months. The rate of change in HF medications (beta-blocker, diuretic, and Sacubitril/Valsartan) will be compared between the multidisciplinary team intervention guided by CIED physiologic digital data group and usual care control group using chi-square analysis. We estimate that the rate of medication change will be 10% in the conventional group based on our URMC ICD database, as compared to 60% in the intervention group. Accordingly, a sample of approximately 30 patients will be required to provide a power of 80% and a 2-sided alpha of 0.05, accounting for 10% drop out rate. The comparison of the rate of recurrent medication adjustments between the two study groups will be assessed using negative binomial regression analysis and is expected to result in greater that 80% power (possibly 99%) based on the expected rate of multiple medical changes (at the monthly virtual visits) in the intervention group.

18. REFERENCES

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