PROTOCOL AND STATISTICAL ANALYSIS PLAN

Protocol Title: Assessing the Efficacy of Digital Health Technology in the Management of Congestive Heart Failure: An Evaluation of Three Novel Digital Health Products

NCT: NCT04394754

HRP-503B – BIOMEDICAL RESEARCH PROTOCOL
(2017-1)

Protocol Title: Assessing the Efficacy of Digital Health Technology in the Management of Congestive Heart Failure: An Evaluation of Three Novel Digital Health Products

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INSTRUCTIONS
This template is intended to help investigators prepare a protocol that includes all of the necessary information needed by the IRB to determine whether a study meets approval criteria. **Read the following instructions before proceeding:** 1. Use this protocol template for a PI initiated study that includes direct interactions with research subjects. Additional templates for other types of research protocols are available in the system Library. 2. If a section or question does not apply to your research study, type "Not Applicable" underneath. 3. Once completed, upload your protocol in the "Basic Information" screen in IRES IRB system.

SECTION I: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.
   The purpose of this study is to determine the efficacy of three novel digital health technologies versus usual care in the management of congestive heart failure, as assessed by a primary outcome of improvement in quality of life, and a variety of secondary outcomes that include metrics measuring patient and provider satisfaction, clinical efficiency, and patient outcomes.

2. **Probable Duration of Project:**
   We anticipate the duration of the study to be 12 months. Three months will be spent developing all study-related materials including protocols, consents and recruitment materials, and completing training of site coordinators and providers. Eight months will be spent recruiting patients and performing follow up visits. The last month will be spent performing data analysis activities.

3. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

   Heart failure is the most common cause of mortality and morbidity in the United States and in Western Europe.[1] It is a complex and chronic illness, and patient etiology and prognosis varies considerably. However, to date, guidance about how to best treat patients has relied on large clinical international trials that do not represent contemporary patients and only include snapshots of the syndrome—at the few times when the patients interact with the health care system.[2] Patient participation in clinical research in the US is also extremely low, approximated at 3% in cancer and far lower for chronic disease states such as heart failure.[3] Furthermore, as with many chronic diseases, there is lack of patient engagement in care.

   Insights from behavioral economics have the potential to improve patient engagement in self-management and clinical research as well as increase uptake of guideline recommended medical therapies in heart failure.[4] Whereas several medical studies have examined the application of behavioral economic principles in helping patients lose weight, quit smoking, and adhere to medications, there are limited data on applying these concepts to the management of chronic diseases, such as heart failure.[5] Therefore, there is an unmet need to test the hypothesis as to whether behavioral interventions can improve self-care and engagement with the health care system in heart failure, thus leading to better clinical outcomes.

   Digital health technologies also have the potential to streamline and optimize clinical management of heart failure.[6] The types of digital health interventions range from apps (applications) to devices that might provide patients and providers with information about their cardiovascular health. As was seen with the Apple Heart Study and others, these technologies can be integrated with health care systems and allow for true patient engagement in management of their disease.[7] To date, no prior study has comprehensively examined the ability of digital health products that collect a variety of key physiological measures to improve self-management of heart failure, nor have subsequent downstream impacts on clinical outcomes been assessed.

   To this end, the proposed study seeks to measure the efficacy of three digital health technologies to improve the management of care and quality of life of patients with congestive heart failure (CHF). Patients who are enrolled in a general heart failure clinic within the Yale health system specializing in the treatment of heart failure will be eligible for the study and approached for consent. Subjects will be randomized into either a control (usual care) group, or to one of three intervention arms assessing three digital health technologies

(described below). These technologies are either devices that measure and relay to the provider key physiological parameters in patients with CHF or are data-driven communication applications that provide either live or automated personalized coaching. All technologies can be used on a daily basis by patients at home and are meant to both increase patient engagement in the management of their disease as well as provide physicians with additional information that can be used in the clinical decision-making process. Patients will be followed for 6 months. Our primary outcome will assess changes in quality of life, while secondary outcomes will measure various parameters of clinical efficiency, patient and provider satisfaction, and patient outcomes (i.e. mortality, hospital visits, etc).

4. Research Plan:

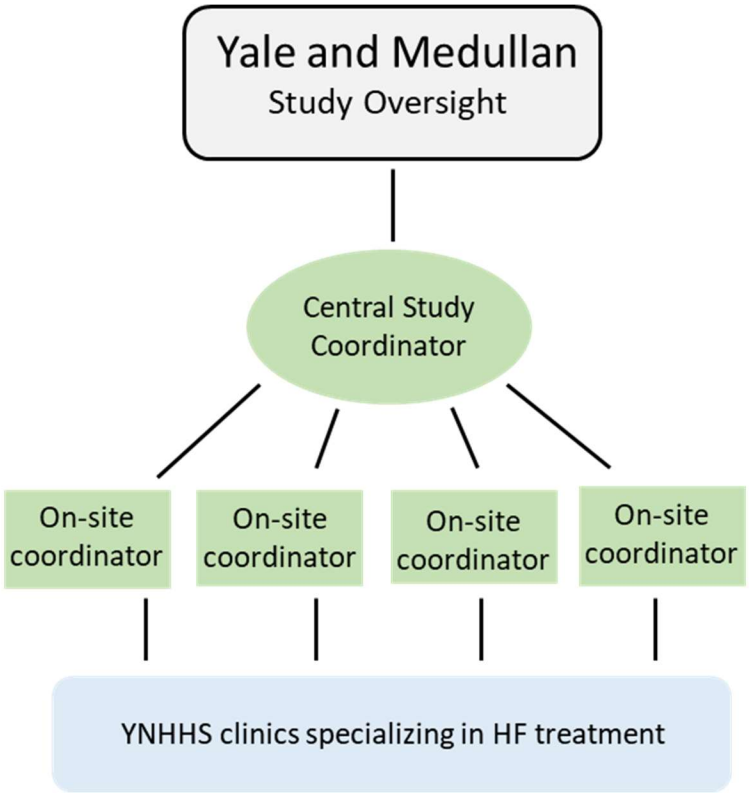
Study Overview:

This study will be an unblinded, 4-arm parallel group, randomized controlled trial designed to determine the efficacy of three digital health products versus usual care in improving quality of life metrics in patients with congestive heart failure (CHF). This will be a joint project between Yale's Program of Applied Translational Research, Boehringer Ingelheim (BI), and Medullan Inc. While this protocol has been developed together with BI and Medullan, and these third parties will contribute to data collection and storage, all decisions regarding data analysis, presentation and publication reside with the Yale investigators.

Patients with CHF who are enrolled at one of several outpatient clinics with the Yale New Haven Health system specializing in the treatment of heart failure will be eligible for this study. These clinics are located across the state of Connecticut, in New London, Norwich, North Haven, New Haven, Greenwich, Trumbull and Bridgeport, allowing us to capture a broad and diverse patient population.

Rollout of the study will be conducted in 2 distinct phases. Initial rollout will occur in three clinics (in New Haven, North Haven, and Trumbull) so that we can perform any necessary quality assurance and troubleshooting prior to a larger rollout. This will be followed by expansion to three additional clinic sites in New London, Bridgeport, and Greenwich. At day 45 of our study, we will perform an interim enrollment assessment to determine enrollment rates and trajectories, and we will expand to the final clinics as needed to achieve our sample size target within our anticipated timeframe.

The overall structure of the study is as follows:



Yale and Medullan will provide central oversight and responsibility of all aspects of the study. Further, each site will have a trained physician and trained registered nurse who will oversee the study at their specific location. Four on-site coordinators will be specially trained and responsible for patient screening, recruitment, education, survey administration and data collection at each of the nine clinic sites. A Yale-based study coordinator will oversee the study at large, ensuring quality control between all sites, performing virtual patient screening and recruitment, administering training to site coordinators, and providing assistance across all sites as needed via regular site visits and phone calls. We describe the roles of the on-site and central study coordinators in more detail below.

On-site coordinators and providers will be trained and educated prior to study commencement by members of both Yale and Medullan teams via a virtual training session. Training will include an overview of the study, use of the various technologies, screening and recruitment protocols, e-consent processes, and training for Case Report Form completion and data collection in RedCap.

Subject Eligibility and Recruitment

Eligible patients will be prospectively identified via electronic medical chart review for enrollment into our study. We will have two avenues for subject screening and recruitment, using both a central study coordinator and four on-site study coordinators.

1. On-site study coordinators will perform prospective identification of eligible patients via daily review of a patient dashboard we will create. Patients will be screened based on the inclusion and exclusion criteria outlined below and eligible patients will then be approached by a site study coordinator for consent at one of their regular clinic visits.
2. The central study coordinator will perform off-site eligibility screening of patients across all sites. Responsibilities of the central coordinator may include: 1) Notifying on-site coordinators of upcoming

clinic visits of eligible or already enrolled patients 2) Contacting potentially eligible patients to give them information about the study prior to their clinic visit and discussion with an on-site coordinator 3) Contact eligible patients that were missed by on-site coordinators for virtual recruitment and consent 4) Make clinic visits for in -person patient recruitment and consent should onsite coordinators be unable to do so.

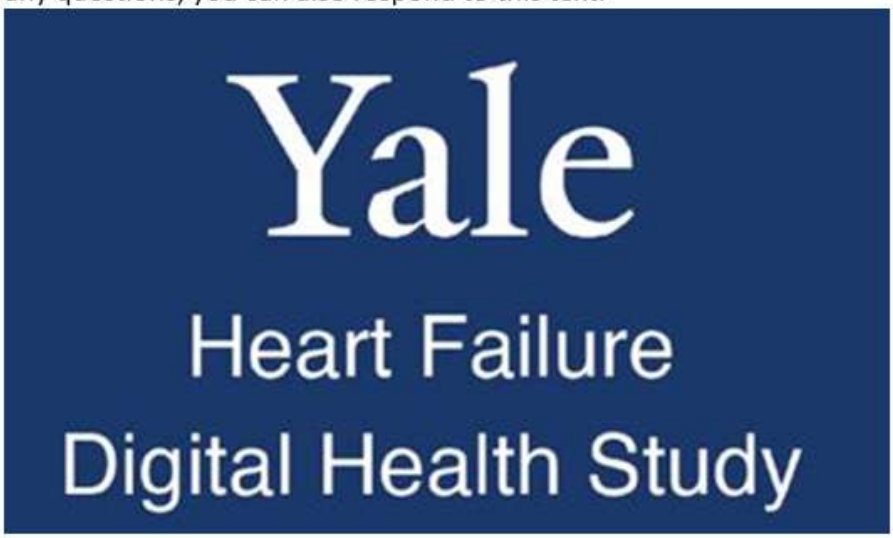
When an eligible patient is identified during a clinic visit, they will be approached by a study coordinator who will thoroughly explain the study, provide informational pamphlets, answer any questions, and ensure patient understanding of the study, each device, and their expectations. All study coordinators will have study tablets on which they can access our study website containing an entirely electronic patient enrollment platform, including baseline assessments and consent forms. Interested patients will be given this tablet and asked to review the information and study details and be given ample opportunity to ask any questions they may have. When ready, patients will be asked to read through and sign an e-consent document. Finally, they will be directed to create an account and profilee on our study website.

Eligible patients who have been missed during an in-clinic visit will be contacted by one of the study coordinators by phone. This may be via a phone call or, if unable to reach the patient, via text messaging and/or via e-email through a MyChart message. The following text messaging script will be sent to an eligible patient:

You have been selected by your Yale physician to participate in our Yale Heart Failure Digital Health Study. If eligible, you will be:

- compensated for your time
- getting access to new digital tools at no charge to you
- helping us make decisions on what types of tools to offer HF patients

We need your help! Please click on the following link to learn more:
https://yale.digitalhealthstudy.org/about-study
A study team member will be reaching out shortly to provide you with more information. If you have any questions, you can also respond to this text.



The following MyChart message will be sent:

If you attend one of Yale's Congestive Heart Failure Clinics and are between the ages of 18 and 79, you may be eligible to participate in a free and confidential research study investigating the use of digital health technologies in the care of patients with heart failure. If you enroll, you will potentially receive free access to new digital health tools at no cost to you, and you will be compensated up to $180 for your time and participation. To learn more or to see if you are eligible to participate, click on "I am interested" or call the Yale Heart Failure Digital Health Study line at 203-350-6124. You can also visit our website at yale.digitalhealthstudy.org for more information.

No action by you is required. You may ignore this message or click "not interested." Thank you very much for considering being a part of research at Yale.

To learn about future research opportunities, you may also create a volunteer profile through the Research Tab in MyChart.

To opt-out of all future research communications, please call the Yale Clinical Trials Office at 1-877-978-8343 and select #3.

During an enrollment phone call, the coordinator will discuss the study and instruct the patient through the enrollment process outlined above. The patient will access our study website through a link that will be sent to them via email, text messaging, or other electronic means acceptable to the potential enrollee.

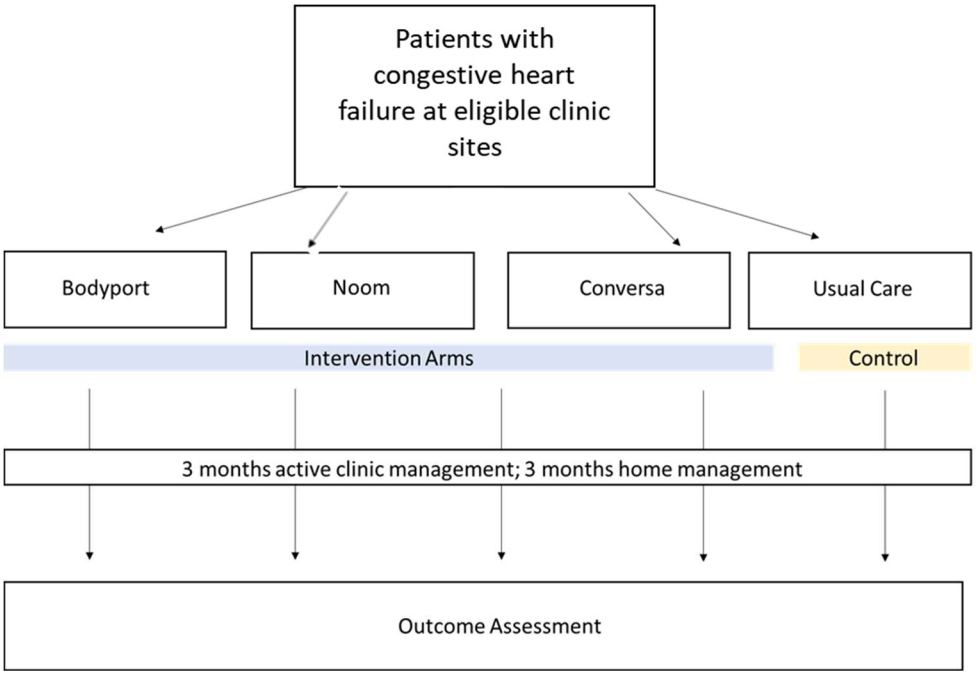
Once a patient has electronically consented and created a study profile, an email will be sent with next steps, and will also contain an electronic copy of the signed consent form. They will be directed to complete the KCCQ questionnaire and a medication adherence survey for baseline data collection towards our primary and secondary outcomes, as well as a health literacy assessment and a technology literacy assessment to track any improvements over the course of the study.

While patients are typically followed for approximately three months in several of these heart failure specialty clinics, this is not always the case. Even when patients have continued visits past the three month point, patients may still not have optimized care. We will reach out to any eligible patient within one month of a visit to the clinic, regardless of the length of time they have been attending clinic visits. Should we not enroll a patient during this initial call, we will continue to attempt to enroll either until a patient declines consent or until they are no longer within a month of a clinic visit.

Subject Randomization and Intervention

At this point, all consented patients will be enrolled and randomized, via a stratified permuted block randomization scheme, to one of the 4 study arms. An independent statistician will create randomization lists stratified by clinic.

Our study flow is as follows:



Three of the four study arms will be intervention groups where patients will be randomized to receive one of three digital health devices or experiences designed to enhance patient care, reduce symptoms and improve disease management, provide health coaching, and/or detect abnormalities in patients living with CHF, and overall improve the quality of life for this patient population.

Patients in each of these three groups will be encouraged to interact with their device on a daily basis. It is important to note that no formal protocol is being mandated for any of the devices (for example, patients will not be obligated to step on the BodyPort scale everyday as part of a specified protocol). They will be given information about the product, what information it provides, and how it can be helpful for them, and then will simply be encouraged to use it regularly, but may use it as often or as little as they like.

Any clinical data that is collected directly by the device, or any clinical information put into the device directly by the patient (e.g. a daily weight) will be accessible to the patient's physician via device-specific clinician dashboards available to the health care team. Importantly, we do not outline any standardized protocols for physicians to follow regarding use of this data. We will make it clear to all participating physicians that data collected from any device is purely informational and a supplement to regular clinical care. The collected data should not be used on its own to make any clinical decisions. Data must be used by providers in the context of all other clinical information available using their own clinical judgement. Further, the use of these devices should not disrupt usual clinic care in any way. Subjects will continue to see their provider as they would outside of the context of this study and will receive their usual care.

While physicians will have access to all clinical data collected via the devices, we have outlined a limited number of device-specific "triggers", such that when a key datapoint reaches a particular pre-specified threshold, the physician will be notified and asked to follow a standardized protocol in which the healthcare team calls the patient to check in and asks a series of standardized questions to assess the patient's condition and document the responses. We will not provide any pre-specified or standardized protocols beyond these "check-ins" and leave further care decisions up to the discretion and clinical judgement of the patient's

healthcare team. Any decisions made by the provider should be based on all clinical information available in addition to any data provided by a device. These triggers were selected based on the type of information collected by the device and the importance of these data points in the assessment of a CHF patient's status (as determined by our heart failure experts).

The three devices are described below, including the type of data collected and how it is stored, and which clinical data points will be used as triggers to notify the health care team.

Device Based Interventions:

- BodyPort: A novel data-driven smart scale that provides advanced cardiac monitoring and risk assessment data that feed directly to an analytics platform visible to providers. The scale also provides limited patient instruction and educational materials.

  Patients will be encouraged to step on the scale on a regular basis. They may also use an optional BodyPort Patient Portal to track view their measurements, track their symptoms, and complete educational modules. The following data will be collected by BodyPort for use in our study and stored by Medullan in a HIPAA-compliant manner. All clinical data will be available to physicians in the provider dashboard provided by BodyPort. We have included both the physician and patient user manuals in this application. We have also included a document outlining both the patient and provider dashboards that includes what elements each can see and actions each can take within the portal.

#	Source data	Data type	How Collected	Intended use	Collection Frequency	Data storage (specify where the data is stored and the compliance with HIPPA, ISO and or Hitrust)	Is it Protected Health Information (PHI)?	Additional Comments
1	Body weight	Biomarker data	Own Device	Assess weight of patient	Daily	Stored in Aptible (HIPPA, HITRUST & ISO27001) & Azure Blob Storage (HIPPA, HITRUST & ISO27001)	No	
2	Heart rate	Biomarker data	Own Device	Assess cardiovascular status of patient	Daily	Stored in Aptible (HIPPA, HITRUST & ISO27001)	No	
3	Heart rate variability	Biomarker data	Own Device	Assess cardiovascular status of patient	Daily	Stored in Aptible (HIPPA, HITRUST & ISO27001)	No	
4	Impedance (8kHz)	Biomarker data	Own Device	Assess fluid status of patient	Daily	Stored in Aptible (HIPPA, HITRUST & ISO27001)	No	
5	Impedance (64kHz)	Biomarker data	Own Device	Assess fluid status of patient	Daily	Stored in Aptible (HIPPA, HITRUST & ISO27001)	No	
6	Fluid Index	Biomarker data	Own Device	Assess fluid status of patient	Daily	Stored in Aptible (HIPPA, HITRUST & ISO27001)	No	
7	Ballistocardiograph	Biomarker data	Own Device	Raw data to extract additional biomarkers	Daily	Stored in Azure Blob Storage (HIPPA, HITRUST & ISO27001)	No	
8	Impedance plethysmograph	Biomarker data	Own Device	Raw data to extract additional biomarkers	Daily	Stored in Azure Blob Storage (HIPPA, HITRUST & ISO27001)	No	
9	Electrocardiograph	Biomarker data	Own Device	Raw data to extract additional biomarkers	Daily	Stored in Azure Blob Storage (HIPPA, HITRUST & ISO27001)	No	
10	Center of pressure	Biomarker data	Own Device	Assess balance/sway of patient	Daily	Stored in Aptible (HIPPA, HITRUST & ISO27001)	No	
11	Risk score	Biomarker data	Own Device	Assess overall status of a patient	Daily	Stored in Aptible (HIPPA, HITRUST & ISO27001)	No	
12	Systolic time intervals	Biomarker data	Own Device	Assess cardiovascular status of patient	Daily	Stored in Aptible (HIPPA, HITRUST & ISO27001)	No	
13	Date/Time	Biomarker data	Own Device	Assess Date and time of a measurement	Daily	Stored in Aptible (HIPPA, HITRUST & ISO27001) & Azure Blob Storage (HIPPA, HITRUST & ISO27001)	No	
14	Measurement ID	Biomarker data	Own Device	Uniquely identify measurements	Daily	Stored in Aptible (HIPPA, HITRUST & ISO27001) & Azure Blob Storage (HIPPA, HITRUST & ISO27001)	No	If PII is shared with Bodyport
15	Temperature	Environmental data	Own Device	Assess environmental conditions during measurement	Daily	Stored in Aptible (HIPPA, HITRUST & ISO27001)	No	

16	Humidity	Environmental data	Own Device	Assess environmental conditions during measurement	Daily	Stored in Aptible (HIPPA, HITRUST & ISO27001)	No	
17	Battery voltage	Device data	Own Device	Assess device status (battery status)	Daily	Stored in Aptible (HIPPA, HITRUST & ISO27001)	No	
18	Signal strength	Device data	Own Device	Assess device status (cellular signal strength/coverage)	Daily	Stored in Aptible (HIPPA, HITRUST & ISO27001)	No	
19	Device Status	Device data	Own Device	Assess device status and error conditions	Daily	Stored in Aptible (HIPPA, HITRUST & ISO27001)	No	
20	Height	Demographic data	Own Device	Demographic information used to calculate certain biometric parameters	Adhoc	Stored in Aptible (HIPPA, HITRUST & ISO27001)	No	
21	Gender	Demographic data	Own Device	Demographic information used to calculate certain biometric parameters	Adhoc	Stored in Aptible (HIPPA, HITRUST & ISO27001)	No	
22	Date of Birth (YYYY required, MM/DD optional)	Demographic data	Own Device	Demographic information used to calculate certain biometric parameters	Adhoc	Stored in Aptible (HIPPA, HITRUST & ISO27001)	No	if full DOB is provided this becomes PII
23	Patient ID	Contact information	Own Device	A unique ID used by the clinical site and Bodyport to identify a patient	Adhoc	Stored in Aptible (HIPPA, HITRUST & ISO27001)	No	If PII is shared with Bodyport
24	Bodyport ID	Contact information	Own Device	A unique ID used by Bodyport used to identify a patient	Adhoc	Stored in Aptible (HIPPA, HITRUST & ISO27001)	No	If PII is shared with Bodyport
25	Device ID	Device Information	Own Device	A unique ID assigned by Bodyport to a device	Adhoc	Stored in Aptible (HIPPA, HITRUST & ISO27001)	No	If PII is shared with Bodyport
26	Name (optional)	Contact information	Own Device	(optional) user identifier on device display and contact name for care services	Adhoc	Stored in Aptible (HIPPA, HITRUST & ISO27001)	Yes	If PII is shared with Bodyport
27	Phone Number (optional)	Contact information	Own Device	(optional depending on care services provided) Phone number for patient follow up	Adhoc	Stored in Aptible (HIPPA, HITRUST & ISO27001)	Yes	If PII is shared with Bodyport
28	Address (optional)	Shipping information	Own Device	(optional depending on enrollment pathway) Address of where to send device	Adhoc	Stored in Aptible (HIPPA, HITRUST & ISO27001)	Yes	If PII is shared with Bodyport
29	Communication History (optional)	Communications (patient/care team)	Own Device	(optional depending on care services provided) To manage care delivery	Adhoc	Stored in Aptible (HIPPA, HITRUST & ISO27001)	No	If PII is shared with Bodyport
30	Medical History (optional)	Health data of patient	Own Device	(optional depending on care services provided) To manage care delivery	Adhoc	Stored in Aptible (HIPPA, HITRUST & ISO27001)	No	If PII is shared with Bodyport

#	API description	API Type (SOAP (Simple Object Access Protocol), RPC (Remote Procedure Call), and REST (Representational State Transfer)	Data currently exchanged via this API	Is it PHI? (yes/no)	Additional Comments
1	**/groups/{group_id} Returns group information for a specific account**	REST	JSON - Group Name, Group ID, Bodyport ID	No	Used Internally & Externally
2	**/users/{user_id} Returns information about patients assigned to a group**	REST	JSON - Height, Date of Birth, Gender, Patient ID, Name, Bodyport ID	Yes (if PII is shared with Bodyport)	Used Internally & Externally
3	**/measures/{measurement_id} Returns measurements belonging to a patient or a group**	REST	No	Yes (if PII is shared with Bodyport)	Used Internally & Externally
4	**/devices/{device_id} Returns devices assigned to patients in a group**	REST	JSON - Temperature, Humidity, Battery Voltage, Signal Strength	No	Used Internally & Externally
5	**/device Used internally to support measurement uploads**	REST	Multi-part Binary File + JSON	No	Bodyport Internal Use Only
6	**/dashboard Returns data for populating Clinical Dashboard**	REST	JSON	Yes (if PII is shared with Bodyport)	Bodyport Internal Use Only
7	**/user_dashboard Returns data for populating Patient Dashboard**	REST	JSON	Yes (if PII is shared with Bodyport)	Bodyport Internal Use Only

Data to be used as triggers to notify providers when values reach specific thresholds may include the following, and are subject to change based on provider burden, utility, and frequency of alerts: weight, fluid index, heart rate, heart rate variability, impedance, electrocardiogram values, and systolic time intervals.

Coaching Based Interventions:

- Noom: A live, data-driven coaching application personalized to individuals for diet and weight management. Patients will be encouraged to use this application on a daily basis to track their activity and steps, their caloric intake, daily weights, blood pressure measurements, glucose measurements, and medication logs (i.e. patients can track when/if they take their daily medications). Educational modules and coaching support are also available through the application. While Noom does not have an information manual, they do have online support, FAQs, and instructions for individual portions of the application on their website: https://web.noom.com/support/. There are also several video tutorials that can be found here and will be given to the patient:
- Food Logging:
- iOS and Android : https://bit.ly/2D7Xanh
- Syncing Fitbit:
- iOS : https://bit.ly/2FtgRYn
- Android : https://bit.ly/2tfoomu
- Group Posts, Threads And Direct Messages (DM):
- iOS : https://bit.ly/2UOMoIK
- Android : https://bit.ly/2GxFSSH
- Meal Reminders:
- iOS : https://bit.ly/2VTmaGu
- Android : https://bit.ly/2SCEowR
- Syncing Apple Watch:
- iOS : https://bit.ly/2UpINB5
- Saving A Custom Dish:
- iOS : https://bit.ly/2H891pC
-
- Patients will be given a thorough orientation to the application and these materials during enrollment.

  The following data will be collected by Noom for use in our study and stored by Medullan in a HIPAA-compliant manner.

#	Source data	Data type	How Collected	Intended use	Collection Frequency	Data storage (specify where the data is stored and the compliance with HIPPA, ISO and or Hitrust)	Is it Protected Health Information (PHI)?	Additional Comments
1	Weight	Physical data	Both	Tracking/monitoring of weight, Calculation of caloric needs	Adhoc	Data is stored in the AWS cloud database. Noom is HIPAA compliant. AWS is SOC 1,2, &3 certified.	No	The patient (Noom user) can choose the data source - manual entry or connected device
2	Height	Physical data	Own Device	Calculation of caloric needs	Adhoc	Data is stored in the AWS cloud database. Noom is HIPAA compliant. AWS is SOC 1,2, &3 certified.	No	
3	Gender	Physical data	Own Device	Calculation of caloric needs	Adhoc	Data is stored in the AWS cloud database. Noom is HIPAA compliant. AWS is SOC 1,2, &3 certified.	No	
4	Age	Physical data	Own Device	Calculation of caloric needs	Adhoc	Data is stored in the AWS cloud database. Noom is HIPAA compliant. AWS is SOC 1,2, &3 certified.	No	
5	Username	Personal data	Own Device	Identification for coach and peers	Adhoc	Data is stored in the AWS cloud database. Noom is HIPAA compliant. AWS is SOC 1,2, &3 certified.	No	
6	Steps	Activity data	Both	Tracking of activity	Daily	Data is stored in the AWS cloud database. Noom is HIPAA compliant. AWS is SOC 1,2, &3 certified.	No	The patient (Noom user) can choose the data source - manual entry or connected device
7	Email address	Personal data	Own Device	Account creation	Adhoc	Data is stored in the AWS cloud database. Noom is HIPAA compliant. AWS is SOC 1,2, &3 certified.	Yes	
8	Exercise	Activity data	Both	Tracking of activity	Adhoc	Data is stored in the AWS cloud database. Noom is	No	The patient (Noom user) can choose the data source - manual entry or connected device

						HIPAA compliant. AWS is SOC 1,2, &3 certified.		
9	Food/Meal	Activity data	Own Device	Tracking of food & caloric intake	Daily	Data is stored in the AWS cloud database. Noom is HIPAA compliant. AWS is SOC 1,2, &3 certified.	No	
10	Blood pressure (systolic)	Biometric data	Both	Tracking/monitoring of blood pressure	Adhoc	Data is stored in the AWS cloud database. Noom is HIPAA compliant. AWS is SOC 1,2, &3 certified.	No	The patient (Noom user) can choose the data source - manual entry or connected device
11	Blood pressure (diastolic)	Biometric data	Both	Tracking/monitoring of blood pressure	Adhoc	Data is stored in the AWS cloud database. Noom is HIPAA compliant. AWS is SOC 1,2, &3 certified.	No	The patient (Noom user) can choose the data source - manual entry or connected device
12	Blood glucose	Biometric data	Both	Tracking/monitoring of blood glucose	Adhoc	Data is stored in the AWS cloud database. Noom is HIPAA compliant. AWS is SOC 1,2, &3 certified.	No	The patient (Noom user) can choose the data source - manual entry or connected device
13	User message	Personal data	Own Device	Communication with coach or peer group	Adhoc	Data is stored in the AWS cloud database. Noom is HIPAA compliant. AWS is SOC 1,2, &3 certified.	No	

#	**API description**	**API Type** (SOAP (Simple Object Access Protocol), RPC (Remote Procedure Call), and REST (Representational State Transfer)		**Data currently exchanged via this API**	**Collection Frequency**	**Data storage (specify where the data is stored and the compliance with HIPPA, ISO and or Hitrust)**	**Is it Protected Health Information (PHI)?**
1	Validic Device API	REST	3rd-Party Connected Device	Noom can receive the following data from connected devices via Validic API: weight, steps, exercise, blood pressure, blood glucose.	Adhoc	Data is accessed through HIPAA-compliant REST API. Data is stored in the AWS cloud database. Noom is HIPAA compliant. AWS is SOC 1,2, &3 certified.	No

Data to be used as triggers to notify providers when values reach specific thresholds may include the following and are subject to change based on provider burden, utility, and frequency of alerts: daily weights, number of daily steps, blood pressure, sodium intake, and self-reported medication adherence.

- Conversa: An automated conversational platform and coaching application designed to motivate patients to take more active and engaged roles in their healthcare using AI technology to create "clinically intelligent" conversations. Patients can interact with the application by participating in brief (approximately 5 minute) "conversations" about their health and current symptoms, with prompts to keep engaged in their disease management. Each conversation ends with an educational tutorial about some aspect of their condition. The device itself does not measure any new clinical data, but records clinical data based on patient input during these conversations. Conversa does not have a user manual, as conversations and instructions are customized based on the engagement of the patient. We have attached with this protocol an example of a user brochure used for similar programs with the application.

  The following data will be collected by Conversa for use in our study and stored by Medullan in a HIPAA-compliant manner. Data to be used as triggers based on patient conversations in the application may include the following, and are subject to change based on provider burden, utility, and frequency of alerts: patient complaints of increased swelling, increased weakness and fatigue, and/or increased shortness of breath.

#	**Source data**	**Data type**	**How Collected**	**Intended use**	**Collection Frequency**	**Data storage (specify where the data is stored and the compliance with HIPPA, ISO and or Hitrust)**	**Is it Protected Health Information (PHI)?**
1	Biometrics readings	Medical and fitness device data	3rd-Party Connected Device	Experience personalization	Adhoc	HIPAA compliant	No
2	EHR / Clinical	Patient clinical history		Experience personalization	Adhoc	HIPAA compliant	Yes
3	EHR / Medications	Patient medications history		Experience personalization	Adhoc	HIPAA compliant	Yes
4	EHR / Preferences	Patient communication preferences		Experience personalization / communication	Adhoc	HIPAA compliant	Yes

5	EHR / Care team	Patient care team (provider relationship)		Experience personalization	Adhoc	HIPAA compliant	Yes

#	API description	API Type (SOAP (Simple Object Access Protocol), RPC (Remote Procedure Call), and REST (Representational State Transfer)	Data currently exchanged via this API	Collection Frequency	Data storage (specify where the data is stored and the compliance with HIPPA, ISO and or Hitrust)	Is it Protected Health Information (PHI)?
1	Patient	REST	Patient entity per FHIR		http://hl7.org/fhir/STU3/patient.html	Yes
2	Conversation	REST	Transactional service for conversation support			No
3	Encounter	REST	Encounter entity per FHIR		http://hl7.org/fhir/STU3/encounter.html	No
4	Questionnaire Response	REST	QuestionnaireResponse per FHIR		http://hl7.org/fhir/STU3/questionnaireresponse.html	No

Patients will be thoroughly trained and oriented to their designated digital health product during their clinical visit by a study coordinator using on-site demo products (or over the phone if not consented in the clinic), and they will receive their product via mail. Each vendor will be responsible for the delivery, tracking, and distribution of their specific product.

Patients will be asked to actively engage with their product throughout the course of the study. If necessary, based on an eligibility questionnaire which assesses smart phone and data plan availability, patients will also be given a smart phone device that can be used with the product, such that no eligible patient is excluded on the basis of lack of access to a smart phone or internet connection.

Patients randomized to the control arm of the study will receive usual care only. Patients in the control group will attend their normal clinic visits throughout the first three months of the study as they normally would, however, they will not receive any of the four digital health technologies above and their healthcare team will receive no additional information from any of these products.

Patient Follow-Up and Data Collection

All subjects will be enrolled in the study for a period of 6 months. The first three months will involve active clinic management, and subjects will be seen every 2-3 weeks as clinically indicated for an in-person visit as they normally would outside the research paradigm. Between visits, data regarding device usage, withdrawal rates, and device-generated health data described above will be passively collected from patients in the intervention arms of the trial and stored on a secure HIPAA-compliant database created by Medullan. During clinic visits, patients will also have the opportunity to meet with a study coordinator, who will administer surveys assessing device usability and user satisfaction (for those patients in the intervention groups only), as well as the KCCQ, health literacy and technology questionnaires, and medication adherence surveys (for all patients in the study, regardless of randomization status) to assess changes from baseline.

Once patients have "graduated" from the clinic, they will be followed for the final three months of the study via monthly phone calls from the study team. During this time, passive data collection from devices will continue. At 6 months, subjects will be asked to complete the final surveys appropriate to their randomization group either electronically or via telephone with one of our study coordinators.

Overview and Timeline of the Patient Experience

Day 0

- Patients who have passed initial screening will be approached by site study coordinators at a clinic visit (or via phone call/text messaging) regarding their interest in study participation.
- Study coordinators will describe, in detail, the study protocol with all interested patients, and patients will be asked to provide e-consent via a hippa-compliant, secure website set up for the purpose of the study, after all questions have been adequately answered.
- Consented patients will be asked to fill out a series of surveys and questionnaires used to collect baseline data for the study, including:
    - Both a health and technology literacy survey, to gauge baseline status that will be tracked throughout the course of the study
    - A KCCQ questionnaire to assess baseline quality of life metrics that will be tracked throughout the course of the study as a measure of primary outcome
    - A medication adherence survey to assess and baseline medication adherence that will be tracked throughout the course of the study
- Patients will be randomized to one of four study arms. Those in one of the three intervention arms will receive the appropriate digital health product. A study coordinator will educate the patient on the product, demonstrating all available features and ensuring the patient understands how to use the product and its value. The digital health product will be mailed to the patient's home and the patient will be encouraged (but not required) to engage with it on a daily basis.

Days 1-89
- Ongoing data collection regarding usage statistics of all digital health products will occur.
- Patients (regardless of randomization status to intervention or usual care groups) will be seen once every 2-3 weeks at in-person clinic visits as they normally would outside of this study. Physicians will have an opportunity to engage with patients about that data collected from their digital health product and make any changes or recommendations to their plan of care.

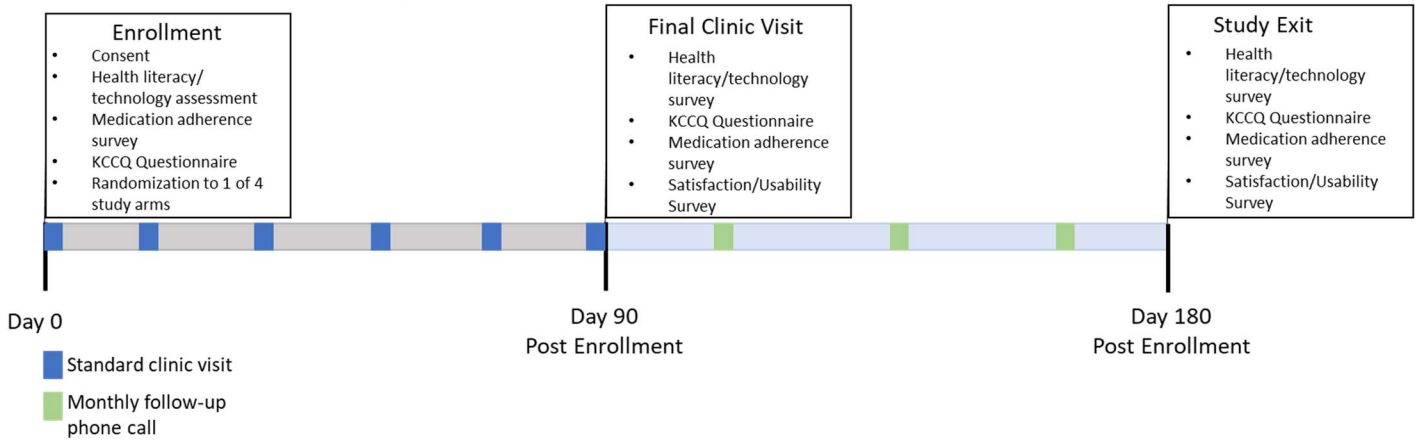
Day 90
- Patients will have their final in-person clinic visit. At this time, patients will meet with an on-site or virtual (via phone calls) study coordinator and be asked to complete a variety of study-related questionnaires and surveys electronically, including:
    - A health and technology literacy survey, to track progress over the course of the study
    - A KCCQ questionnaire to track any changes over the course of the study as a measure of the primary outcome
    - A medication adherence survey to track changes from baseline
    - A product satisfaction survey (intervention groups only), to determine a Net Promoter Score (NPS) that measures satisfaction with the digital health product
    - A usability survey (intervention groups only), which assesses user friendliness, frequency of use, product satisfaction, and perceived impact of the product.
- Patients will graduate from the clinic, but will be asked to continue using their products until study close-out.

Days 90-179
- Ongoing data collection regarding usage statistics of all digital health products will continue.
- Patients will receive monthly calls from the clinic, regardless of randomization status, to track progress, assess engagement with products, and answer any questions.

Day 180

- Patients will be asked to complete a final electronic visit with study coordinators for study close-out. They will also be mailed a return-labeled envelope to return the digital health product. During this visit, patients will work with study coordinators and be asked to fill out final assessments electronically, including:
    - A health and technology literacy survey, to track progress over the course of the study
    - A KCCQ questionnaire to track any changes over the course of the study as a measure of the primary outcome
    - A medication adherence survey to track changes from baseline
    - A product satisfaction survey (intervention groups only), to determine a Net Promoter Score (NPS) that measures satisfaction with the digital health product
    - A usability survey (intervention groups only), which assesses user friendliness, frequency of use, product satisfaction, and perceived impact of the product.
- Study coordinators will collect any final data needed and answer any remaining questions, and patients will complete their participation in the study.

The study timeline for an enrolled patient is as follows:



Clinician Data Collection

An important aspect of our study is to determine whether the digital health products enhance clinical efficiency and reduces physician burden. At the end of the study, we will ask participating clinicians to complete an anonymous survey that assesses physician satisfaction with the products, ease of use, effect on workload and efficiency, and contribution to clinical-decision making.

Outcomes

Our primary outcome is the rate of improved quality of life of enrolled patients after 90 days as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ), which will be given to patients prior to enrollment, at the 90 day mark, and after study completion (day 180). The KCCQ is a standardized 23- question instrument that combines aspects of physical functions, symptoms (frequency, severity, and recent changes), social function, self-efficacy, and quality of life into a single summary score on a scale of 0 to 100, giving a sensitive and specific measure of quality of life for heart failure patients.

The following pre-specified secondary outcomes will be measured to determine the effect of the various technologies on patient outcomes, quality of patient care, clinical efficiency, and both patient and provider satisfaction with the products.

Patient Outcomes			
	Outcome	**Measure**	**Data Storage**
Adverse Events	Hospital Admissions	Epic, Ping	RedCap (Yale)
	Guideline directed medical therapy	Rates of prescribing and dosing of beta blockers, ACEi/ARBs, spironolactone (via Surescripts)	RedCap (Yale)
	ED visits	Hospital records	RedCap (Yale)
	Mortality	Hospital records	RedCap (Yale)
	Clinic no show rates	Medical records	RedCap (Yale)
	AKI/AKD Development	Medical records	RedCap (Yale)
Usability	Satisfaction with device/technology	NPS score via post-study survey	HIPAA-compliant dashboard (Medullan)
	Frequency of use (overall and feature level)	Post-study survey	HIPAA-compliant dashboard (Medullan)
	Content rating	Post-study survey	HIPAA-compliant dashboard (Medullan)
	Perceived impact	Post-study survey	HIPAA-compliant dashboard (Medullan)
Clinician Outcomes			
	Outcome	**Measure**	**Data Storage**
Clinical Efficiency	Amount of intravisit contact	Telephone logs in medical record	RedCap (Yale)
	Number of clinic visits	Medical records	
	Time devoted to patient care	Number of chart openings per patient	
	Provider assessment of global disease severity	Post-study survey	
Satisfaction	Effect on workload and efficiency	Post-study survey	
Usage Analytics of Digital Health Products			
	Outcome	**Measure**	**Data Storage**
Completion of subject enrollment	Number of enrolled patients	Continuous data collection via product databases	HIPAA-compliant dashboard (Medullan)
	Number of incomplete enrollments		
Completion rate of baseline assessments	Number of complete and incomplete aseessments		
	Time to complete initial assessments		
Completion of digital health product set-up	Number of complete and incomplete product set-ups		
	Number of products that completed initial data sync		
Subject drop-off rates	Percent of patients with last screen assessed in session		
Device usage (Descriptive statistics)	Number of active (>1 login per week) patients per week		
	Average number of logins per week		
	Number of patients without logins per week		
	Statistic for each session (time of day, day of week, number of page views, origin of login (direct, email))		
	Average number of interactions		
	Average number of daily check-ins		
	Number of patients not using product per week		
	Time of day of product usage		
	Completeness of data provided per question in session		
User engagement	Dwell time per feature		

We will also perform prespecified secondary analyses to determine the above primary and secondary outcomes at day 180, to determine if outcomes improve once clinic visits end.

An additional secondary analysis will assess the heterogeneity of the effect of each product across clinics.

5. Genetic Testing N/A ☒

6. **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.
   This study will enroll adult patients attending one of the nine clinics located within YNHHS specializing in the treatment of heart failure, for management of congestive heart failure. See inclusion and exclusion criteria below.

7. **Subject classification:** Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☐Children	☐ Healthy	☐Fetal material, placenta, or dead fetus
☐Non-English Speaking	☐ Prisoners	☐Economically disadvantaged persons
☐Decisionally Impaired	☐ Employees	☐Pregnant women and/or fetuses
☐Yale Students	☐ Females of childbearing potential	

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects?
Yes ☐ No ☒

8. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?
   Inclusion Criteria:
   1. Adults ≥ 18 years and < 80 years of age
   2. Enrolled in a YNHHS clinic specializing in heart failure treatment
   3. Diagnosed with congestive heart failure (CHF) (preserved ejection fraction (HFpEF) or reduced ejection fraction (HFrEF)) with or without diabetes
   4. Within one month of a clinic visit

   Exclusion Criteria:
   1. Class IV heart failure
   2. Stage 4 or end stage renal disease (eGFR < 30)
   3. Recipient of a heart transplant or ventricular assist device
   4. Under hospice care
   5. Dementia
   6. Incarceration
   7. Pregnancy
   8. Currently homeless or residing in an unstable living situation (i.e., transitional housing, rehab facility, etc.)
   9. Inability to consent
   10. Currently enrolled in a study investigating a digital health product or technology
   11. Life expectancy of less than 6 months as determined by the clinical judgement of the patient's primary physician
   12. Weight greater than 400 pounds

13. Unable to stand up straight for thirty seconds without assistance, such as from a cane or walker
14. Non -english speaking

Note regarding pacemakers, and other implantable electronic devices:
While Bodyport has statements in their user manuals that their products are not to be used in patients with pacemakers and other electronic implanted devices, we have received statement from the vendor that the device is safe to use in this patient population.

Bodyport has stated that "With respect to the Bodyport product, there are no known safety issues related to the use of the device with patients with pacemakers or ICDs. However, we have not specifically tested the device in this population, and cannot make claims about its performance in these patients." We have included in the application an informational sheet on the theory of operation behind the Bodyport scale, which outlines the possible affect that a pacemaker or other device may have on the ability of the scale to perform accurate ECG readings, which is the reason that the warning statement regarding use in this patient population was included in the manual.

The BodyPort scale has been previously used in studies that do not exclude patients with pacemakers. Given that there are no safety concerns regarding the use of this device, we plan to enroll patients with pacemakers and other implantable devices, as excluding this population would be highly restrictive to the study.

9. How will **eligibility** be determined, and by whom?
   Eligibility will be assessed by on site and central study coordinators who will prospectively review our patient dashboard and further consult the electronic medical record for inclusion and exclusion criteria of patients currently enrolled in the clinics. Criteria will be further confirmed during the patient's in clinic visit or via a telephone call with a study coordinator prior to consent. Digital and technology literacy is not considered an eligibility requirement, as one main goal of the study is to assess whether these digital health products would be efficacious and applicable for this patient demographic. Once a patient has consented to participate in the study and has been enrolled, he/she will be asked to take a digital literacy survey as a means for baseline assessment and to track improvement of this metric over the course of the study.

10. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.
    General study risks:
    - Loss of confidentiality: We will be collecting patient information and data, which is subject to loss of confidentiality in any clinical trial.
    - Physician burden: Physicians will be receiving additional information about their patients via the study devices, which may increase workload via additional time spent on patient care, reviewing medical record data, and/or ordering additional tests and reviewing subsequent results.
    - Overtreatment: It is possible that patients in the intervention group may be at risk for more aggressive therapies or treatments and increased medical costs as a consequence of closer monitoring.

    Bodyport-specific risks and restrictions:
    - The Bodyport scale cannot be exposed to extreme temperatures or submerged in liquid.
    - The scale should not be used if the glass surface is cracked or chipped, as this could result in personal injury.
    - The scale should not be used of the surface is wet, as this could cause a slippery surface that could result in personal injury.

11. Minimizing Risks: Describe the manner in which the above-mentioned risks will be minimized.
    - Risk of loss of confidentiality: Data collected both from patient visits/assessments/surveys and abstracted from the medical record will be de-identified and stored on RedCap and on a secure HIPAA-compliant central server within the Program of Applied Translational Research. The server is only accessible from within the Yale intranet (or via VPN remotely) and additionally requires separate logon username and password. No PHI will be included in analysis or publication. All analyses will proceed on this server alone.

      We will maintain a linking file in a separate location that will allow for future linking of de-identified data to protected health information (PHI) for the purpose of potential future studies. Studies that require the use of PHI (for example, linking patient info to national outcomes databases) will require approval of both the manuscript and executive committees and a separate IRB approval.

      We plan to share non-aggregate de-identified data with Medullan under with the appropriate data sharing agreements. We will provide periodic transfer of this data via encrypted secure file transfer.

    - Risk of physician burden: We have strived to create a study in which physician burden is minimized. Additional clinic visits outside of usual care are minimized, and physicians are expected to manage patient care at their own discretion. The study devices were designed to increase clinical efficiency rather than hamper it, and one of our secondary outcomes is to assess provider satisfaction with the products and usability so that we can better understand how these technologies have helped or hindered their provision of care. Additionally, this risk will be mitigated in part as there will be a technical support hotline (independent of physician involvement) maintained by Medullan, inc to address technical issues with the device or software interventions. Support staff working for Medullan are trained to escalate issues that prove to be medical to the supervising physician.

    - Risk of overtreatment: The technologies in this study are designed to relay additional information to providers that can be used *in conjunction* with all other medical information available to them to aid in the clinical decision-making process. Any additional tests or treatments should be prescribed using their own clinical judgement based on all available information sources regarding the patient's condition. We will appropriately educate providers about the nature of the study devices and the information that each provides so that physicians can understand how to best incorporate this information into their decision-making.

    - Device-specific risks for Bodyport: We will discuss the above risks with the patient before and during the consent process to ensure the patient understand the risks and proper use of the device. The patient will be shown product manuals and informational materials for the scale and will be given the opportunity to answer any questions. Once enrolled into the study and assigned to a treatment group, patients will be given manuals and instructions for the device they receive, and will receive a thorough orientation to the product by a study coordinator who will emphasize any risks involved.

12. Data and Safety Monitoring Plan: Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.)

a. What is the investigator's assessment of the overall risk level for subjects participating in this study? This protocol presents minimal risk to all subjects.

b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? N/A

c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://your.yale.edu/policies-procedures/forms/420-fr-01-data-and-safety-monitoring-plans-templates for

   i. Minimal risk
   ii. Greater than minimal

Assessing the Efficacy of Digital Health Technology in the Management of Congestive Heart Failure: An Evaluation of Four Novel Digital Health Products
420 FR.1
PI: F. Perry Wilson, MD MSCE

The principal investigator is responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews bi-monthly. During the review process the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment.

The principal investigator or the Institutional Review Board (IRB) have the authority to stop or suspend the study or require modifications. We will conduct an internal interim analysis at 50% recruitment to assess for efficacy, as described below.

This protocol presents minimal risks to the subjects and Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs), including adverse events, are not anticipated. In the unlikely event that such events occur, Reportable Events (which are events that are serious or life-threatening and unanticipated (or anticipated but occurring with a greater frequency than expected) and possibly, probably, or definitely related) or Unanticipated Problems Involving Risks to Subjects or Others that may require a temporary or permanent interruption of study activities will be reported immediately (if possible), followed by a written report within 5 calendar days of the Principal Investigator becoming aware of the event to the IRB (using the appropriate forms from the website) and any appropriate funding and regulatory agencies. The investigator will apprise fellow investigators and study personnel of all UPIRSOs and adverse events that occur during the conduct of this research project through regular study meetings and/or via email as they are reviewed by the principal investigator. The protocol's research monitors, including study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies will be informed of all adverse events within 5 days of the event becoming known to the principal investigator.

d. For multi-site studies for which the Yale PI serves as the lead investigator: N/A

13. **Statistical Considerations:** Describe the statistical analyses that support the study design.

Baseline comparisons across the study arms will be conducted with chi-square tests for categorical variables, applying the Maentel-Haenszel correction for stratification by clinic site. Continuous variables will be compared using the Van-Elteren test for continuous, non-parametric variables and stratified t-tests for normally distributed variables.

The study was designed to provide adequate power to detect a clinically significant change in the primary outcome measure, the score on the Kansas City Cardiomyopathy Questionnaire.[8]

The 23-item questionnaire has been validated in multiple heart failure populations, and quantified the physical limitations, symptoms, self-efficacy, social interference, and quality of life associated with living with heart failure. The KCCQ composite score can theoretically range from 0 – 100 (with 100 being the best possible score) and a change of 10 points has been determined to be the minimum clinically important difference. Within a given patient, the score is quite stable in the absence of clinical changes, with a within-patient standard of deviation of 11.8 for patients with no change in clinical status.[9]

In order to detect the minimum clinically important difference of a 10-point improvement in the KCCQ, we would need to enroll 40 patients in each arm of the trial across all centers to provide 90% power at an alpha threshold of 0.017. This gives a total of enrollment of 160. Given uncertainties around the intraclass correlation coefficient (assumed to be 0.10 here and reflecting the overall efficacy of each individual clinic) we will inflate the target sample size to 200, or 50 per arm of the trial. The lower alpha threshold represents a bonferonni correction that provides statistical power to test multiple comparisons – each of the 3 digital health interventions against the control intervention. We will attempt to balance recruitment across the centers with a per-center target of 5 individuals per trial arm.

An interim analysis will be completed at 50% enrollment. We will stop the trial for efficacy for a p value threshold of < 0.0006. Given the interim analysis, the threshold p-value for statistical significance at the end of the trial will be 0.016.

The primary analysis will be a mixed effects model comparing change in KCCQ over time in the intervention group versus the control, without accounting for a center-by-treatment interaction. In secondary analyses, we will model that interaction to determine if certain interventions are uniquely effective in certain centers.

Secondary and exploratory analyses will examine the outcomes listed above using the same procedure applied to baseline variables for outcomes assessed at one time point, and using mixed-effects models for continuous outcomes assessed at multiple timepoints.

SECTION II: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, check off N/A and delete the rest of the section.

A. RADIOTRACERS ☒N/A

B. DRUGS/BIOLOGICS ☒N/A

B. DEVICES ☐N/A

1. Are there any investigational devices used or investigational procedures performed at Yale-New Haven Hospital (YNHH) (e.g., in the YNHH Operating Room or YNHH Heart and Vascular Center)? ☐Yes ☒No

If Yes, please be aware of the following requirements:

A YNHH New Product/Trial Request Form must be completed via EPIC: **Pull down the Tools tab in the EPIC Banner, Click on Lawson, Click on "Add new" under the New Technology Request Summary and fill out the forms requested including the "Initial Request Form," "Clinical Evidence Summary", and attach any other pertinent documents. Then select "save and submit" to submit your request**; AND

Your request must be reviewed and approved **in writing** by the appropriate YNHH committee before patients/subjects may be scheduled to receive the investigational device or investigational procedure.

2. **Background Information:** Provide a description of previous human use, known risks, and any other factors that might influence risks. If this is the first time this device is being used in humans, include relevant data on animal models.

   Digital health devices or experiences:

   BodyPort: A novel data-driven smart scale that provides advanced cardiac monitoring and risk assessment data that feed directly to an analytics platform visible to providers. The scale also provides limited patient instruction and educational materials.

   BodyPort has not yet received clearance by the FDA and is not exempt from IDE regulations in this study, however, we assess this use representing a non-significant risk (NSR) investigational device (in an NSR study). We have included in our application both the instruction manuals for BodyPort as well as a review of previous clinical studies and their results.

   Noom: A live, data-driven coaching application personalized to individuals for diet and weight management. Noom is not an approved application and is not exempt from IDE regulations, however, we assess its use representing a non-significant risk (NSR) investigational device (in an NSR study).

   Conversa: An automated conversational platform and coaching application designed to motivate patients to take more active and engaged roles in their healthcare using AI technology to create "clinically intelligent" conversations. Conversa is not an approved platform and is not exempt from IDE regulations, however, we assess its use representing a non-significant risk (NSR) investigational device (in an NSR study).

3. **Source:**
   a) Identify the source of the device to be used. Device vendors
   b) Is the device provided free of charge to subjects? ☒Yes ☐No

4. **Investigational device accountability**: State how the PI, or named designee, ensures that an investigational device is used only in accordance with the research protocol approved by the HIC, and maintains control of the investigational device as follows:

   a) Maintains appropriate records, including receipt of shipment, inventory at the site, dispensation or use by each participant, and final disposition and/or the return of the investigational device (or other

disposal if applicable): Vendors will be responsible for shipment and tracking of their respective devices, including maintaining inventory and appropriate records of each product, and for the distribution to subjects. Vendors will also be responsible for collecting the devices back from patients at study close-out.

b) Documents pertinent information assigned to the investigational device (e.g., date, quantity, batch or serial number, expiration date if applicable, and unique code number): Vendors will be responsible for documenting all relevant device information for their respective product.

c) Stores the investigational device according to the manufacturer's recommendations with respect to temperature, humidity, lighting, and other environmental considerations: Vendors will be responsible for the proper storage of their product. Study coordinators will also be trained on the proper storage environment for each device.

d) Ensures that the device is stored in a secure area with limited access in accordance with applicable regulatory requirements: Both vendors and study coordinators at each clinic will be responsible for the storage and access to study devices.

e) Distributes the investigational device to subjects enrolled in the IRB-approved protocol: Vendors will be responsible for the distribution of each study device to subjects. Study coordinators will be responsible for the training of subjects on the use of the device via in-clinic demos or in depth instructions during over the phone enrollment.

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. **Targeted Enrollment: Give the number of subjects:** 200
   a. Targeted for enrollment at Yale for this protocol: 200
   b. If this is a multi-site study, give the total number of subjects targeted across all sites: 200

2. **Indicate recruitment methods below.** Attach copies of any recruitment materials that will be used.

☒ Flyers	☒ Internet/web postings	☐ Radio
☒ Posters	☐ Mass email solicitation	☒ Telephone
☐ Letter	☒ Departmental/Center website	☐ Television
☒ Medical record review*	☐ Departmental/Center research boards	☐ Newspaper
☐ Departmental/Center newsletters	☐ Web-based clinical trial registries	☒ Clinicaltrails.gov
☐ YCCI Recruitment database	☐ Social Media (Twitter/Facebook):	
☒ Other: Informational screen advertisement in clinic waiting areas		

*** Requests for medical records should be made through JDAT as described at**
http://medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx

3. **Recruitment Procedures:**
   a. Describe how potential subjects will be identified.
   Subjects will be identified by on-site and central study coordinators through prospective daily review of the study dashboard and review of the electronic medical record for inclusion and exclusion criteria.
   b. Describe how potential subjects are contacted.

Potential subjects will be approached for e- consent by on- site study coordinators during any normal clinic visit.. Patients will have the opportunity to complete eligibility assessments and the consent form on a study tablet provided by a coordinator. Eligible patients who were not seen by an on-site coordinator will be contacted by a study coordinator via phone call and/or text messaging and/or MyChart messaging (as described above) for enrollment and consent. In this case, a link will be emailed to the patient allowing for access to the required eligibility assessments and consent form.

c. Who is recruiting potential subjects?
Specially-trained on-site and central study coordinators.

4. Assessment of Current Health Provider Relationship for HIPAA Consideration:
Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?
☐Yes, all subjects
☒Yes, some of the subjects
☐No

If yes, describe the nature of this relationship.
Doctors Soucier, Ahmad, and Desai are cardiologists who may encounter potential study participants in the course of their clinical care.

5. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)
Choose one:
☐ For entire study
☒ For recruitment/screening purposes only
☐ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website at hipaa.yale.edu.

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data:
Each clinic sees, on average, 80 patients per day. As screening would be required before patients are initially seen in the clinic, consenting each patient would be time consuming, impractical, and unnecessary for the majority of patients who will not enroll into the study. Eligibility assessments present no more than minimal risk, with the primary risk being loss of confidentiality, however, extensive safeguards are in place to prevent such loss and any data collected on patients who are not enrolled into the study will be immediately deleted.

ii. If requesting a waiver of signed authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data: *Write here*

The investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

6. Process of Consent/Assent: Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.
   An eligible patient will be approached for consent during his or her normal clinic visit by a trained on-site study coordinator. Patients will be given informational materials and ample time to review the information and have any questions or concerns addressed before making their decision. Should a study coordinator not be present for consenting at the time of the patient's clinic visit, the patient will be called at a later time by a coordinator for the purposes of consent. If agreeable, a link will be sent via email to the patient and the coordinator will be available to walk the patient through eligibility assessment and consent via phone.
7. Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent: Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.
   The study coordinator will decide whether the subject has expressed an accurate understanding of the study, its risk, and its benefits.
8. Non-English Speaking Subjects: Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.
   N/A

As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment? YES ☐ NO ☒

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are available on the HRPP website (yale.edu/hrpp) and translated HIPAA Research Authorization Forms are available on the HIPAA website (hipaa.yale.edu). If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via modification prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

9. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☐Not Requesting any consent waivers

☐Requesting a waiver of signed consent:

☐ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*
☐ Entire Study (Note that an information sheet may be required.)

For a waiver of signed consent, address the following:

- Would the signed consent form be the only record linking the subject and the research? YES ☐ NO ☐
- Does a breach of confidentiality constitute the principal risk to subjects? YES ☐ NO ☐

OR

- Does the research pose greater than minimal risk? YES ☐ NO☐
- Does the research include any activities that would require signed consent in a non-research context? YES ☐ NO ☐

☒ Requesting a waiver of consent:

☒ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*
☐ Entire Study

For a full waiver of consent, please address all of the following:

- Does the research pose greater than minimal risk to subjects?
  ☐ Yes *If you answered yes, stop. A waiver cannot be granted.*
  ☒ No
- Will the waiver adversely affect subjects' rights and welfare? YES ☐ NO☒
- Why would the research be impracticable to conduct without the waiver? It would be impracticable to conduct the research without the waiver as each patient would need to be engaged to determine eligibility with most being ineligible.
- Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date? Via fully informed consent.

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

1. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research? Name, SSN, zip code, DOB, medical record number, laboratory values, provider notes, medical procedures, medical history, medication lists, imaging/radiology results, hospital admission dates/discharges/records.

2. How will the research data be collected, recorded and stored?
   All data collected from study coordinators from the EHR and through clinic visits and assessments/surveys will be will be entered and stored in Red Cap, Yale's HIPAA-compliant and secure data collection platform. The primary dataset will contain no PHI. We will maintain a separate "linking file" that contains all PHI and will be stored on a separate secure HIPAA-compliant central server within the Program of Applied Translational

Research to limit the risk of accidental disclosure. The server is only accessible from within the Yale intranet (or via VPN remotely) and additionally requires separate logon username and password. No PHI will be included in analysis or publication. All analyses will proceed on this server alone. The linking file is being maintained for potential future linking to national databases of death and dialysis.

Medullan will collect data from the devices regarding frequency of use, user engagement and any health-related data and store on the secure HIPAA-compliant storage databases described in the methods above.

Information regarding the collection of the Participant data by the Vendor from the Participant and the storage of this collected data in the Vendor's solution is outlined below:

Bodyport: The following information is stored on the Bodyport scale: Bodyport device ID, Bodyport user ID, display name, year of birth, gender, and height. This profile information is retrieved and reset each time the device is power cycled (i.e. the batteries are inserted). Bodyport also stores measurement data on the scale so that uploads to the server can be re-attempted in the event of an upload failure. Up to 30 measurements are stored at any time. Once a data point is uploaded, it is flagged for deletion, with the oldest measurements deleted first. Once the scale is returned by the participant, it is scanned and the pairing between the device ID and user ID is deleted, resetting it to its factory state. Once a device is unpaired from a user or reassigned a new user ID, all existing measurements and profile information is erased from the device. Anonymized measurement data will be maintained by Bodyport on the server in perpetuity.

Noom: Data will be available within the application on their mobile device. Once participation is over, the account with all associated data will be deleted.

Conversa: All data is stored on the platform for 7 years, unless a specific request to redact the data is received by the participant.

3. How will the digital data be stored? ☐CD ☐DVD ☐Flash Drive ☐Portable Hard Drive ☒Secured Server ☐Laptop Computer ☐Desktop Computer ☐Other

4. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?
   All data will be stored on an encrypted, HIPAA-Compliant server with 2-factor authentication. Data will not be stored on personal computing devices of any kind. The server will only be accessible from within the Yale firewall or via VPN. No portable devices will be used to store study data at any time.

All portable devices must contain encryption software, per University Policy 5100. If there is a technical reason a device cannot be encrypted please submit an exception request to the Information Security, Policy and Compliance Office by clicking on url http://its.yale.edu/egrc or email it.compliance@yale.edu

5. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.
   PHI will be deleted by study personnel within one year of closing of the study.

6. If appropriate, has a Certificate of Confidentiality been obtained? *N/A*

SECTION V: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)
Subjects in the intervention arms of this study may benefit from the use of their device through the receipt of more optimal and individualized care. This benefit may be derived as a consequence of additional health coaching, access to more educational materials, closer physician monitoring, and more thorough disease management.

The results of this study will be used to refine how these technologies can provide better disease management of CHF. If successful, further refinement, testing, and broad adoption of these tools may overall lead to enhanced clinical efficiency and better quality of care for patients living with CHF, which may result in lower rates of CHF complications and a lower societal burden on the healthcare system.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?
   Usual care
2. **Payments for Participation (Economic Considerations):** Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.
   Participants will be compensated for their completion of assessments and surveys at study enrollment, the 90 day time point, and at study close out. Patients will be given up to a total of one hour to complete all study related surveys and will be compensated $60 for this time, for a total of $180 paid to the patient by study completion. This payment will take the form of a $60 prepaid Bank of America card sent to the patient after completion of each set of surveys (baseline, 90 day and 180 day).
   Costs for Participation (Economic Considerations): Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.
   N/A
3. **In Case of Injury:** This section is required for any research involving more than minimal risk, and for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws).
   N/A
   a. Will medical treatment be available if research-related injury occurs? *Write here*
   b. Where and from whom may treatment be obtained? *Write here*
   c. Are there any limits to the treatment being provided? *Write here*
   d. Who will pay for this treatment? *Write here*
   e. How will the medical treatment be accessed by subjects? *Write here*

IMPORTANT REMINDERS

Will this study have a billable service? Yes ☐ No☒

A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes ☐ No ☒

If Yes, please answer questions a through c and note instructions below.

a. Does your YNHH privilege delineation currently include the specific procedure that you will perform? Yes ☐ No ☐

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? Yes ☐ No ☐

c. Will a novel approach using existing equipment be applied? Yes ☐ No ☐

If you answered "no" to question 4a, or "yes" to question 4b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. By submitting this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH.

References:

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3. Murthy VH, Krumholz HM, Gross CP. Participation in cancer clinical trials: race-, sex-, and age-based disparities. *JAMA.* 2004;291(22):2720-2726.
4. Chang LL, DeVore AD, Granger BB, Eapen ZJ, Ariely D, Hernandez AF. Leveraging Behavioral Economics to Improve Heart Failure Care and Outcomes. *Circulation.* 2017;136(8):765-772.
5. McConnell MV, Turakhia MP, Harrington RA, King AC, Ashley EA. Mobile Health Advances in Physical Activity, Fitness, and Atrial Fibrillation: Moving Hearts. *J Am Coll Cardiol.* 2018;71(23):2691-2701.
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7. Perez MV, Mahaffey KW, Hedlin H, et al. Large-Scale Assessment of a Smartwatch to Identify Atrial Fibrillation. *N Engl J Med.* 2019;381(20):1909-1917.
8. Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. *J Am Coll Cardiol.* 2000;35(5):1245-1255.
9. The Kansas City Cardiomyopathy Questionnaire (KCCQ). 2004.