INTERVENE-HF

Integrated Diagnostics Driven
Diuretic and Chronic Medication Management
for Heart Failure

Clinical Investigation Plan

Version 5.0

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Regional Sponsor and Contact
United States Medtronic, Inc. 8200 Coral Sea Street NE Mounds View, MN U.S.A. 55112 1-800-328-2518

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ADMINISTRATIVE INFORMATION

SPONSOR CONTACT INFORMATION

Medtronic contact information is provided below. Contact information for study management and monitoring personnel may be updated under separate cover during the course of the study. Current information is as follows:

Table 1: US Study sponsor contact information

	Medtronic **8200 Coral Sea Street NE** **Mounds View, MN U.S.A.** **55112** **1-800-328-2518**	
Contact	**Phone**	**E-mail**
Joe Hobbs *Clinical Research Specialist*	1-763-269-2994	*joe.hobbs@medtronic.com*
Taryn Randall *Clinical Monitoring Manager*	1-763-250-0785	*taryn.randall@medtronic.com*
Vinod Sharma *Sr. Principal Scientist*	1-763-526-0139	*vinod.sharma@medtronic.om*

CRO AND CORE LABS

Table 2: CRO and core lab information

Contact Information	Duties performed
Cognizant Technology Solutions 500 Frank W. Burr Blvd. Teaneck, NJ 07666 Direct Phone: (201) 801-0233 Direct Fax: (201) 801-0243	• Development of study electronic case report forms, edits checks, and study management reports. • Review of electronic case report forms, management of discrepancies, and coding of medications and deviations.

Any changes/additions to CRO or core labs may be distributed under separate cover.

1. INTRODUCTION

1.1 Study Purpose

Medtronic, Inc. is sponsoring Integrated Diagnostics Driven Diuretic and Chronic Medication Management for Heart Failure (INTERVENE-HF), a prospective, non-randomized, multi-center, feasibility study. The purpose of this clinical feasibility study is to gain experience with a research system that combines a device diagnostic based risk stratification algorithm with a guided work flow process managed by a centralized communication center. Findings from this feasibility study will be used to guide subsequent efforts to develop a heart failure patient management solution that may include integrated device diagnostics, a centralized communication center and medication intervention as key components.

1.2 Study Description

The INTERVENE-HF study is a prospective, non-randomized, multi-center (US only), investigational, feasibility study. Patients with heart failure that have an implanted commercially available Medtronic cardiac resynchronization therapy defibrillator (CRT-D) device will be enrolled in the study. The basic INTERVENE-HF research system is comprised of the pre-existing Medtronic, CRT-D device, investigational 2090 programmer software capable of turning ON/OFF the silent OptiVol® wireless CareAlert, and the INTERVENE Study Communication Center (ISCC). The ISCC will reside with the Care Management Service (formerly Cardiocom) business unit of Medtronic. The INTERVENE-HF study will have a dedicated team of licensed nurses at ISCC that will guide and monitor subjects through an individualized, physician prescribed medication intervention for diuretics and other acute volume management drugs after their silent OptiVol CareAlert has been transmitted and medication intervention is warranted.

The study is expected to be conducted at up to 20 centers located in the United States. Up to 400 subjects will be enrolled to yield up to 200 eligible subjects that meet screening criteria. This study will be conducted in subjects with an implanted, commercially available, Medtronic, CRT-D device. A detailed list of these devices and model numbers is provided in Table 4. To ensure a widespread distribution of data and minimize center bias in study results, the maximum number of subjects enrolled at a single center is 30 subjects. It is estimated that subject enrollment will take approximately 12 to 18 months. Each enrolled subject will be followed every 2 months from time of enrollment to end of the study. It is anticipated that subjects will participate in the study for a minimum duration of 12 months and up to approximately 30 months. The study will end after the last enrolled subject completes the 12-month follow-up. Because INTERVENE-HF is a feasibility study, it is not intended to show an outcome of improvement. Rather the objective is to test the operational feasibility and safety of device diagnostics *plus* an intervention system as set forth in the primary and secondary objectives. Interim analyses of these objectives will take place and if data are deemed to sufficiently characterize the study objectives by the sponsor at one of these analyses, enrollment and/or follow-up will be stopped.

2. BACKGROUND AND JUSTIFICATION

Assessment of risk to guide appropriate medical care has become a necessary tool in the management of cardiovascular disease. Published guidelines for managing cardiovascular disease are based in large part on identifying subjects at risk and then treating patients in a manner to reduce that risk.[1] The development of risk prediction models for cardiovascular diseases dates back to at least the 1960s.[2,3] Since that time, new and updated risk models have continued to be developed.[4-7] Risk prediction models also exist for specific cardiovascular diseases. For example, the Seattle Heart Failure Model was developed to predict survival in patients with congestive heart failure[8] and the CHADS2 score was developed to predict the risk of stroke in patients with atrial fibrillation.[9]

These risk models, while clinically useful, are generally static in nature and cannot necessarily respond to dynamic changes in the many factors that may impact patient risk. For example, these models can likely predict which patient is at higher risk of developing frequent HF worsening events, but when exactly such an event might occur temporally cannot be predicted. Because device diagnostics dynamically vary with patient status (see description of various device diagnostic parameters below), they have the potential to be a robust and dynamic cardiovascular risk assessment tool to help guide appropriate medical intervention.

CRT-D devices, such as those included in this study, collect valuable clinical diagnostics data. These diagnostic variables can be combined to generate patient risk status using a variety of methodologies. One methodology uses a Bayesian Belief Probabilistic model to categorize patients into three risk categories – Low, Medium and High. The details of the model have been discussed in a paper by Cowie et al.[10] Briefly, the model uses 5 distinct variables as input - thoracic impedance, activity, heart rate variability, heart rate, and a combination variable based on arrhythmia and shock related information collected by the device. All of these variables have a mechanistic link with worsening heart failure, and several of them have been shown to have a prognostic value for heart failure event in the literature. Below is a brief description of each of the device variables that are input into integrated diagnostics algorithm.

a. **Intrathoracic impedance (OptiVol**): As a patient's HF status worsens, it is generally associated with rise in atrial filling pressure and retention of fluid in the pulmonary circulation. If sustained over time, this can eventually lead to fluid infiltration into interstitial space, thus leading to worsening pulmonary congestion.[11] Since blood and interstitial fluid are highly conductive, their accumulation in the pulmonary system leads to a reduction in thoracic impedance. Thus, intrathoracic impedance appears to have mechanistic link with worsening HF.[11-13]

b. **Heart rate variability (HRV)**: HRV is a marker of autonomic tone and has been shown to provide prognostic information for mortality risk.[14] Research has demonstrated a correlation between the decrease in HRV and increased sympathetic tone. Cardiac resynchronization therapy, that has been shown to improve heart failure status, results in an increased HRV indicative of shift away from sympathetic

dominance.[15] Using HRV device diagnostic data, Adamson et al.[16] showed that patients with low HRV (<100 ms) are at a higher combined risk of death and hospitalization. The same study showed that patients with HRV < 50 ms were even at higher risk than those with HRV in the range of 50-100 ms.

c. **Heart Rate**: Similar to HRV, elevated heart rate is a marker of elevated sympathetic tone and has been shown to have prognostic value for worsening HF. Night Heart Rate (NHR) (measured between midnight and 4 AM) is a better metric than the day time heart rate, which can be confounded by varying activity level (e.g. rest and exercise). A study in implantable device patients demonstrated that patients with high NHR (75±25 bpm) were at higher risk of being hospitalized or dying than those who had low NHR (73±11 bpm).[16]

d. **Activity**: As patients retain fluid in the pulmonary circulation resulting in pulmonary congestion, they can easily develop dyspnea, thus limiting their functional capacity and activity level. In patients with a CRT device, patient activity declined from 188±109 min/day at baseline to 164±118 min/day at the time of hospitalization.[16] Thus, decline in patient activity is associated with worsening HF status and potentially has value for predicting HF hospitalization.

e. **Combination variable**: The final variable that is input into the integrated diagnostic algorithm combines pacing and arrhythmia related information. Specifically, one of the components of this variable is substantial decrease (>8%) in CRT pacing, which is associated with high HF events.[17] A decline in CRT pacing can occur because of rapid conduction during AF. Thus, mean ventricular rate $\geq$ 90 bpm and atrial fibrillation (AF) burden $\geq$ 6 hours/day and shocks delivered to Ventricular Fibrillation/Ventricular Tachycardia (VT/VF) are also components of this variable.

Each of the five variables input into the Heart Failure Risk Status - Integrated Diagnostics Algorithm (ID1.0 HFRS-ID) has a prognostic value for HF. Combining these variables into a single HF risk metric yields a prognostic indicator that is better than each of the individual components alone because these variables capture slightly orthogonal information (e.g. while decrease impedance is an indicator of elevated pulmonary pressure, HRV is an indicator of autonomic imbalance), and hence add to provide a better overall snapshot of patient status. Our model development data indicate that a patient with a risk score in the 'high' group were 10 times more likely to have an Heart Failure Hospitalization (HFH) in the next 30 days compared with 'low' risk patients.[10] A patient with 'medium' risk status is at 2x higher risk of hospitalization in the next 30 days. [10]

While a high performance diagnostic is necessary for effective HF patient management, previous clinical trials have shown that diagnostic information alone is not sufficient to improve patient management. For example, the COMPASS-HF[18] and REDUCE-HF[19] trials that provided clinically relevant estimated pulmonary artery (PA) pressure measurements to physicians for HF management did not show statistically significant difference in HF based outcomes between PA pressure management arm and control arm. This lack of outcome improvement was attributed to lack of clinical actions in response to changes in PA pressure.

In contrast, in the CHAMPION trial[20] using another version of a PA pressure measuring device, the treatment arm using PA pressures to manage patients yielded a significant decrease in HF events compared to the control arm (~30% reduction at 6 months and 40% reduction at 15 months in HF hospitalization). In addition, alert mechanism and workflow are also important as they can influence healthcare utilization.[21] The key attribute of the CHAMPION trial that presumably led to positive outcome results was that actions to control the PA pressure were in fact mandated as part of the trial. And in fact, CHAMPION reported significant medication changes from the baseline not only in the diuretic doses, but also in other medications such as beta-blockers, ACE inhibitors, Angiotensin receptor blockers and nitrates among other drugs.[18, 19]

Therefore, combining a prescribed medication regimen with a diagnostic variable seems to be a necessary condition to drive actions and improve patient outcomes. Thus, the goal of the INTERVENE-HF study is to test the feasibility of combining an integrated device diagnostics-based risk stratification algorithm with a guided work flow process managed by a centralized communication center. INTERVENE-HF is a feasibility study with a single-arm design and a limited number of subjects, and is not intended to show an outcome of improvement. Rather, the objective is to test the operational feasibility of diagnostics plus an intervention system, and quantification of the operation effectiveness and safety as set forth in the primary and secondary objectives.

3. SYSTEM DESCRIPTION AND INTENDED USE

The study will be conducted using the following components described in Figure 1 below. Additional CRT-D devices listed may be used during the course of the study as they become FDA approved. Instructions for use of the devices used in this study are provided in their respective manuals.

The INTERVENE-HF system consists of the following investigational and non-investigational components depicted in Figure 1 and listed in the tables below.

3.1 System Process & Component Overview

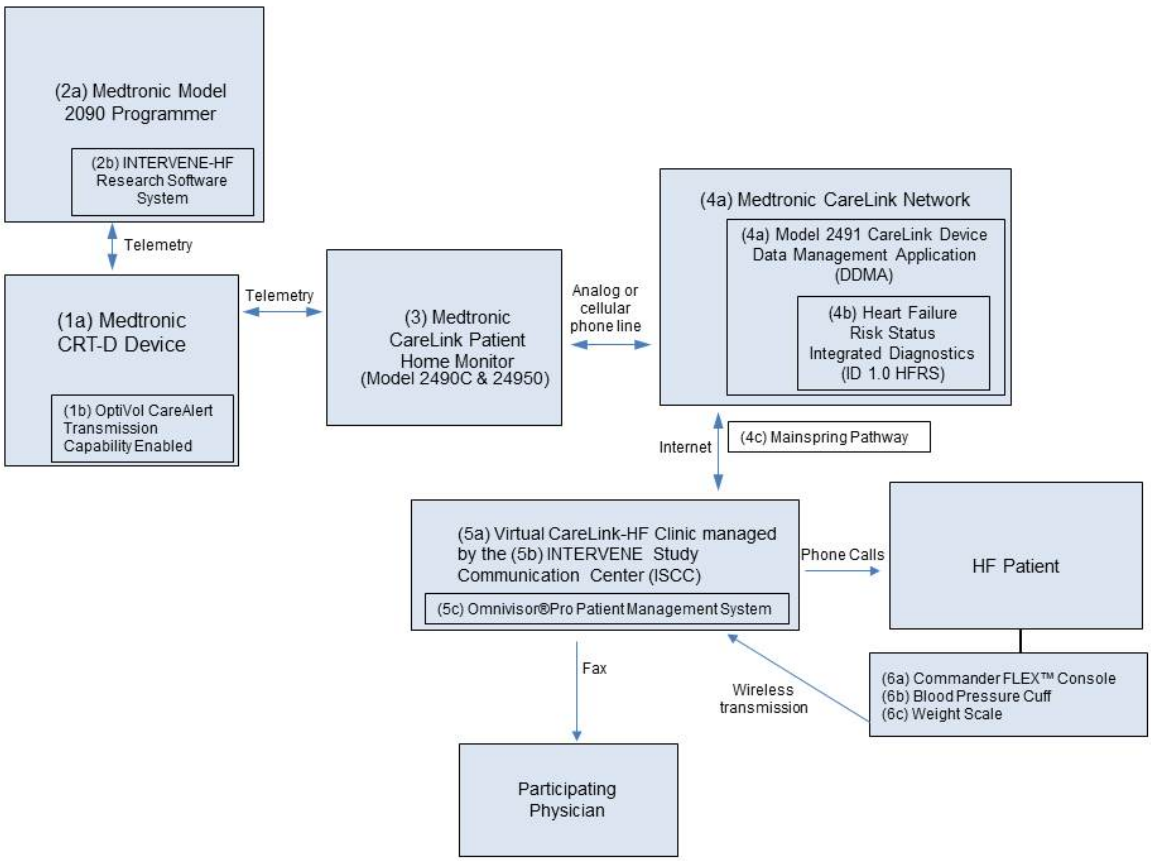


Figure 1: Schematic of the INTERVENE-HF System Components & the Clinical Process.

3.2 Component Details

Each research system component as it relates to the study is described below.

Table 3: System component #1 (CRT-D Device)

Figure 1 **Component #**	**Component**	**Description**	**Market-Released or Investigational?**
1 a/b	Medtronic CRT-D device with OptiVol CareAlert transmission Capability enabled	Medtronic CRT-D device with OptiVol CareAlert enabled that allows for transmission of device diagnostics data, including intrathoracic impedance fluid index, to CareLink when set OptiVol threshold is met.	Investigational

Medtronic implantable cardiac resynchronization therapy – defibrillator (CRT-D) devices (1a) currently have several diagnostic parameters, including the OptiVol Fluid Status Monitoring Feature. The OptiVol Fluid Status Monitoring Feature itself is not investigational; however the ability to perform CareAlert transmissions upon crossing of OptiVol Fluid threshold is investigational (1b). Therefore, an existing CRT-D device that has the OptiVol CareAlert capability turned ON is considered Investigational. No change will be made to therapy delivered by the CRT-D device. Any subsequent market released device with the OptiVol capability will be included in this study once the device is FDA approved.

Table 4: Model numbers of CRT-D devices used in the INTERVENE-HF study.

CRT-D Device Name	**Model Numbers**	**Market-Released or In Development**
Protecta XT CRT-D	D314TRM D314TRG	Market-Released
Viva Quad C CRT-D	DTBX1QQ	Market-Released
Viva Quad XT CRT-D	DTBA1QQ DTBA1Q1	
Viva XT CRT-D	DTBA1D1 DTBA1D4	
Viva Quad S CRT-D	DTBB1QQ DTBB1Q1	
Viva S CRT-D	DTBB1D4 DTBB1D1	
Consulta CRT-D	D204TRM D224TRK	Market-Released
Concerto II CRT-D	D274TRK	Market-Released

NOTE: Any subsequent market released device with the OptiVol capability will be included in this study once the device is FDA approved.

Table 5: System component #2 (Programmer with Research Software)

Figure 1 **Component #**	**Component**	**Description**	**Market Released or Investigational?**
2a/b	Medtronic Programmer Model 2090 with INTERVENE-HF Research Software Rev. 1.0	CRT-D programmer used to interrogate and program CRT-D devices with investigational INTERVENE HF application software to turn ON/OFF OptiVol CareAlert	Investigational

The INTERVENE-HF Research Software will be installed on Model 2090 programmers (2a). The research software provides a user interface that allows the user to turn ON the OptiVol CareAlert in the subject's CRT-D device (1b) and then later turn the OptiVol CareAlert OFF at the time of study termination/subject exit.

Since the INTERVENE-HF investigational software will be distributed electronically through the Medtronic Software Distribution Network (SDN), physical media labeling is not required (see Section 8 for software handling information).

The study center will need authorization from Medtronic in order for the software to be made available on the SDN as described in the User Manual. Only the 2090 programmer can be used for this study. Therefore, the site must have access to, or maintain, a 2090 programmer for the duration of the study.

When the investigational INTERVENE-HF Research Software is downloaded onto the Medtronic 2090 Programmer (2b),that programmer becomes investigational and will be labeled to indicate that it contains investigational software until the INTERVENE-HF software is removed.

Table 6: System component #3 (CareLink Monitor)

Figure 1 **Component #**	**Component**	**Description**	**Market Released or Investigational?**
3	Medtronic CareLink Patient Monitor Model 2490C or 24950	A home-based monitor used to transmit device data via the CareLink Network where the data is accessed by INTERVENE Study Communication Center (ISCC) and investigator.	Market-Released

The Medtronic CareLink Monitor Model 2490C or 24950 are indicated for use in the transfer of patient/subject data from some Medtronic implantable cardiac devices based on investigator instructions and as described in the product manual. OptiVol triggered transmission will occur automatically without patient/subject requiring any action. All study

subjects will be required to have a CareLink Monitor that is appropriately powered by plugging into wall and is capable of transmitting data via wired or wireless/cellular connection.

Table 7: System component #4 (CareLink Network)

Figure 1 **Component #**	**Component**	**Description**	**Market Released or Investigational?**
4a	Model 2491 CareLink Network Device Data Management Application (DDMA)	Converts device data in human readable form that can be stored to the network directly from the CareLink Monitor located at patient's home.	Market-Released
	Medtronic CareLink Network	A secure, web based application that allows the viewing of device data transmitted via the CareLink Monitor. Data is loaded to the network directly from the CareLink Monitor located at the subject's home.	Market-Released
4b	Heart Failure Risk Status Integrated Diagnostics Feature (ID1.0 HFRS)	A diagnostic feature based on an algorithm (referred to as HFRS-ID) that runs on the Medtronic CareLink Network and uses existing device diagnostic parameters (OptiVol Fluid Index, shocks, patient activity night heart rate, heart rate variability, atrial tachyarrhythmia, ventricular rate during AT/AF, ventricular arrhythmia and percent ventricular pacing) and adjudicated heart failure events from historical Medtronic clinical studies to produce a dynamically-updated individual patient risk (Low, Medium or High) of having a heart failure hospitalization in the next 30 days. The HFRS will be displayed on the Medtronic CareLink Network on the Heart Failure Management Report that will be received by the INTERVENE Study Communication Center for this study.	Investigational
4c	Mainspring Pathway	The CareLink Network pathway for relaying transmissions from the CareLink Network to the INTERVENE Study Communication Center.	Market-Released

The Medtronic CareLink Network (4a) is indicated for use in the transfer of patient data from some Medtronic implantable cardiac devices based on the investigator instructions and as described in the product manual. The Medtronic CareLink Network enables subjects to remotely transfer data from their device to the CareLink network via phone line or wireless

network. Clinic personnel can access the data, including the Cardiac Compass Report and/or Heart Failure Management Report, by logging onto the CareLink website via the Internet.

In this study, CRT-D device data will be utilized in an investigational Heart Failure Risk Status-Integrated Diagnostic (ID1.0 HFRS) feature (4b) to calculate a heart failure risk score (see Section 2 for HFRS-ID algorithm background). The risk score and CareLink reports will then be relayed to the INTERVENE Study Communication Center (ISCC) via the Mainspring pathway (4c). The HFRS with OptiVol is intended to be used by the ISCC nurse as a source of information to help identify which patients may require closer attention and therefore initiate medication intervention for fluid volume management.

The investigational ID 1.0 HFRS (4b) feature is based on an algorithm that runs on the Medtronic CareLink Network and uses existing device diagnostic data including OptiVol to produce a dynamically-updated individual patient/subject risk (Low, Medium or High) of having a heart failure hospitalization in the next 30 days. The HFRS will be displayed on the Medtronic CareLink Network on the Heart Failure Management Report.

Table 8: System component #5 (INTERVENE STUDY COMMUNICATION CENTER)

Figure 1 **Component #**	**Component**	**Description**	**Market Released or Investigational?**
5a	Virtual CareLink-HF Clinic managed by ISCC	A satellite heart failure clinic managed by INTERVENE Study Communication Center (ISCC) residing at Medtronic Care Management Services (formally known as Cardiocom).	NA
5b	INTERVENE Study Communication Center (ISCC)	ISCC is managed by dedicated licensed nurses who along with the physicians will use the device data (HFRS score and other health failure related information from CareLink) and in-home biometrics as an additional source of information to manage study subjects.	NA
5c	Omnivisor® Pro Patient Management System	A patient (subject) software management system used by the ISCC nurse along with a guided workflow process that standardizes subject care and provides efficient remote subject monitoring.	Market-Released

As part this study, the investigator/site will agree to transfer their patient into the virtual CareLink-HF clinic (5a) that will be managed by the INTERVENE Study Communication Center (ISCC) (5b) that will reside at the Medtronic Care Management Services. However, the CRT-D subject will still be maintained and managed for arrhythmia and device/lead related events through the CareLink EP clinic. The EP clinic will continue to have the

uninterrupted access to the subject's device and clinical information while enrolled in the study. The EP clinic will also receive device data initiated by OptiVol CareAlert transmission once the subject is enrolled into the study. However the EP clinic will be able to clearly see in their software that that their patient is an INTERVENE-HF study subject and will be trained to not take action on unscheduled transmissions related to the study.

Device information from CareLink and data from the CommanderFLEX™ are relayed to OmniVisor® Pro (5c) for use by the ISCC nurse(s). With that information, ISCC nurse(s) will implement a validated guided workflow process that the ISCC nurse will follow to standardize subject care and provide efficient remote subject monitoring.

Table 9: System component #6 (CommanderFLEX™ Biometric Equipment)

Figure 1 **Component #**	**Component**	**Description**	**Market Released or Investigational?**
6a	CommanderFLEX™	A Class II Medtronic (formally Cardiocom) device for collecting and wirelessly transmitting subject's biometric information to ISCC.	Market-Released
6b	Blood Pressure Cuff	In-home blood pressure cuff that is compatible with CommanderFLEX™ device.	Market-Released
6c	Weight Scale	Medtronic (formally Cardiocom) in-home scale with maximum weight of 500lbs.	Market-Released

The CommanderFLEX™ is a device for in-home use to collect and transmit "YES/NO" health symptom questions and patient/subject biometric information (blood pressure and weight) data from the subject to the ISCC. The device is similar to a simple personal computer with a built-in cellular modem that stores and transmits data wirelessly to remote locations.

It is recommended that the subject's health symptoms related answers, blood pressure, and weight be provided on a daily basis and the data will be automatically transmitted to and managed by ISCC nurses. The CommanderFLEX™ is cleared for use with the blood pressure cuff (6b) and weight scale (6c).

Figure 2: Top view of the CommanderFLEX™ device.

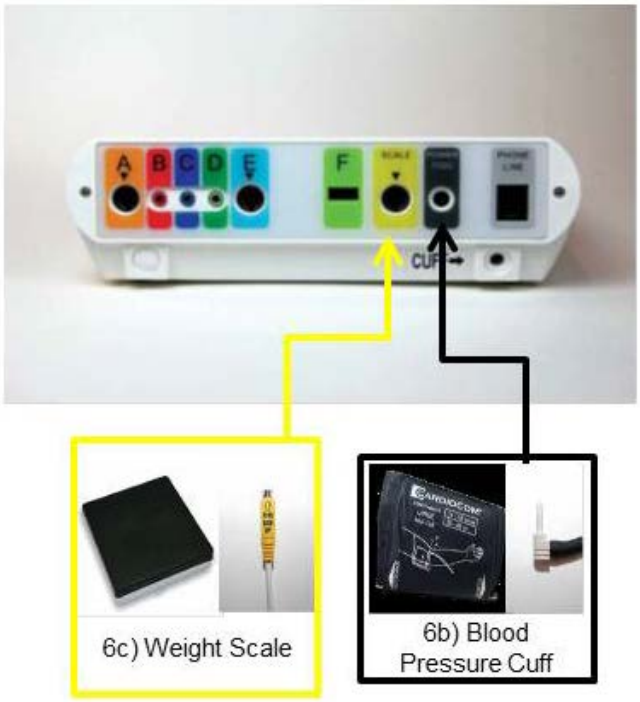


Figure 3: Back view of the CommanderFLEX™ device.

4. REGULATORY COMPLIANCE

This INTERVENE-HF study will be conducted in compliance with international ethical and scientific quality standards, known as good clinical practice (GCP). GCP includes review and approval by an independent IRB before initiating and obtaining and documenting the freely given informed consent of a subject before initiating the study.

The INTERVENE-HF study was designed to reflect the GCP principles outlined in ISO 14155:2011. These include the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the clinical investigation and the definition of responsibilities of the sponsor and investigators. In accordance with the ISO standard, the sponsor shall avoid improper influence on, or inducement of, the subject, monitor, any investigator(s) or other parties participating in, contributing to, the clinical investigation. All investigators shall avoid improper influence on or inducement of the subject, sponsor, monitor, other investigator(s) or other parties participating in or contributing to the clinical investigation.

The study will be conducted according to federal, national and local laws, regulations, standards, and requirements of the countries/geographies where the study is being conducted. The principles of the Declaration of Helsinki have been implemented through the patient informed consent (PIC) process, IRB approval, study training, clinical trial registration, preclinical testing, risk-benefit assessment and publication policy.

All investigators are required to complete financial disclosure, as outlined in 21 CFR Part 54 and all sites will need to comply with:

- 21 CFR Part 11
- 21 CFR Part 50
- 21 CFR Part 56
- 21 CFR Part 812

The study will be publicly registered on http://clinicaltrials.gov prior to first enrollment in accordance with the 2007 Food and Drug Administration Amendments Act (FDAAA) (PL 110-85, Section 801(a)) and the Declaration of Helsinki.

Approval of the CIP is required from the following groups prior to any study procedures at a study center:

- Medtronic
- An Institutional Review Board at each individual study center

Similarly, approval of subsequent revisions to the CIP is required at each study center from the above mentioned groups prior to implementation of the revised CIP at that center.

5. METHODOLOGY

5.1 Study objectives

INTERVENE-HF is a prospective, non-randomized, single-arm feasibility study to evaluate the system that combines integrated device diagnostics based risk stratification algorithm with a guided work flow process managed by a centralized communication center to manage HF patients. This system, for purposes of defining study objectives will be termed the "Integrated Diagnostics Medication Intervention Strategy". Details of this system are available in Section 3. Findings from this feasibility study will be used to guide subsequent planning of a pivotal study.

As a feasibility trial, the INTERVENE-HF study is not designed to be powered for specific endpoints. Therefore, it does not require justification on sample size. The following two primary objectives are proposed to determine effectiveness and safety of the Integrated Diagnostics Medication Intervention Strategy. No secondary objectives are proposed. Additionally, one ancillary objective characterizing the occurrence of HF events in the study population will be assessed.

Primary Objectives:

1. To characterize the effectiveness of the Integrated Diagnostics Medication Intervention Strategy in resolving the subject risk.

2. To characterize the safety of the Integrated Diagnostics Medication Intervention Strategy in resolving the subject risk.

Ancillary Objectives:

1. To characterize the occurrence of HF events in the study subjects.

NOTE: Intervention for heart failure decompensation (HF event) is defined as an event requiring invasive intervention (i.e. IV diuretics, ultrafiltration, or equivalent) or inpatient hospitalization.

5.2 Subject selection criteria

Patients must meet all of the inclusion and none of the exclusion criteria prior to being enrolled.

5.2.1 Inclusion criteria

- Subject (or subject's legally authorized representative) is willing and able to provide written informed consent
- Subject has been implanted with a CRT device for at least 9 months and has had a wireless Medtronic CRT-D device (see Table 4 for Applicable Model Numbers) for at least 34 days
- Subject has >1 year life expectancy
- Subject's CRT-D device has at least 18 months of device longevity left
- Subject has an eGFR> 25 ml/min/1.73 m^2
- Subject is NYHA Class II or III
- Subject has elevated BNP values (BNP>400 or NTpro BNP>800) within the last 3 months
  OR
  Subject has had at least one OptiVol threshold crossing in the last 9 months
  OR
  Subject has had a HF event within the last 9 months

  HF event is defined as meeting *<u>any one of the following two criteria</u>*:

  1. Subject was admitted to the hospital for worsening HF
     OR
  2. Subject has received Intravenous HF therapy (e.g. IV diuretics/vasodilators) or ultrafiltration at any settings including:
     - Emergency Department
     - Ambulance
     - Observation Unit
     - Urgent Care
     - HF/Cardiology Clinic
     - Patient's Home

- Subjects who are currently prescribed and taking medications for the management of heart failure and are able to tolerate transient increases in diuretic dosage
- Subject is willing and able to comply with the protocol, including screening, baseline and programming visit(s), remote care directions, follow-up visits, and exit visit.
- Subject can send device transmissions and daily biometric data with in-home patient devices.

5.2.2 *Exclusion criteria*

- Subject has systolic BP of < 90 mmHg at the time of enrollment
- Subject not responsive to diuretic therapy or is on chronic renal dialysis
- Subject unable to undergo one round of medication intervention (3 day up-titration of diuretic) without requiring safety check
- Subjects enrolled in a concurrent study that may confound the results of this study without documented pre-approval from a Medtronic study manager
- Subject weighs more than 500 pounds
- Subject is younger than 18 years of age
- Subject has hemodynamic monitoring device implanted

5.3 Minimization of Bias

Selection of subjects, treatment of subjects, and evaluation of study data are potential sources of bias. Methods incorporated in the study design to minimize potential bias include (but are not limited to):

- Subject demographics assessment information will be collected on possible differences that may affect outcome. Information gathered on subject will include gender, race, height, weight and medical background
- Data are collected using standardized electronic Case Report Forms (CRFs) to provide uniform data collection
- Site and sponsor study personnel will be trained using standardized training materials provided by Medtronic
- Subjects will be screened to confirm eligibility for enrollment with defined inclusion/exclusion criteria prior to enrollment
- The limitation on maximum subjects (30) a site can enroll
- Standardize data collection requirements and study procedures across sites.
- Training sites and MDT personnel of the study based on the protocol
- An independent clinical events committee (CEC) will be utilized to regularly review and adjudicate reported adverse events.

In summary, potential sources of bias that may be encountered in this clinical study have been considered and minimized by careful study design.

6. STUDY PROCESS OVERVIEW

The INTERVENE-HF study process is outlined in Figure 4 and is described below. Site related procedures are described in Section 7.

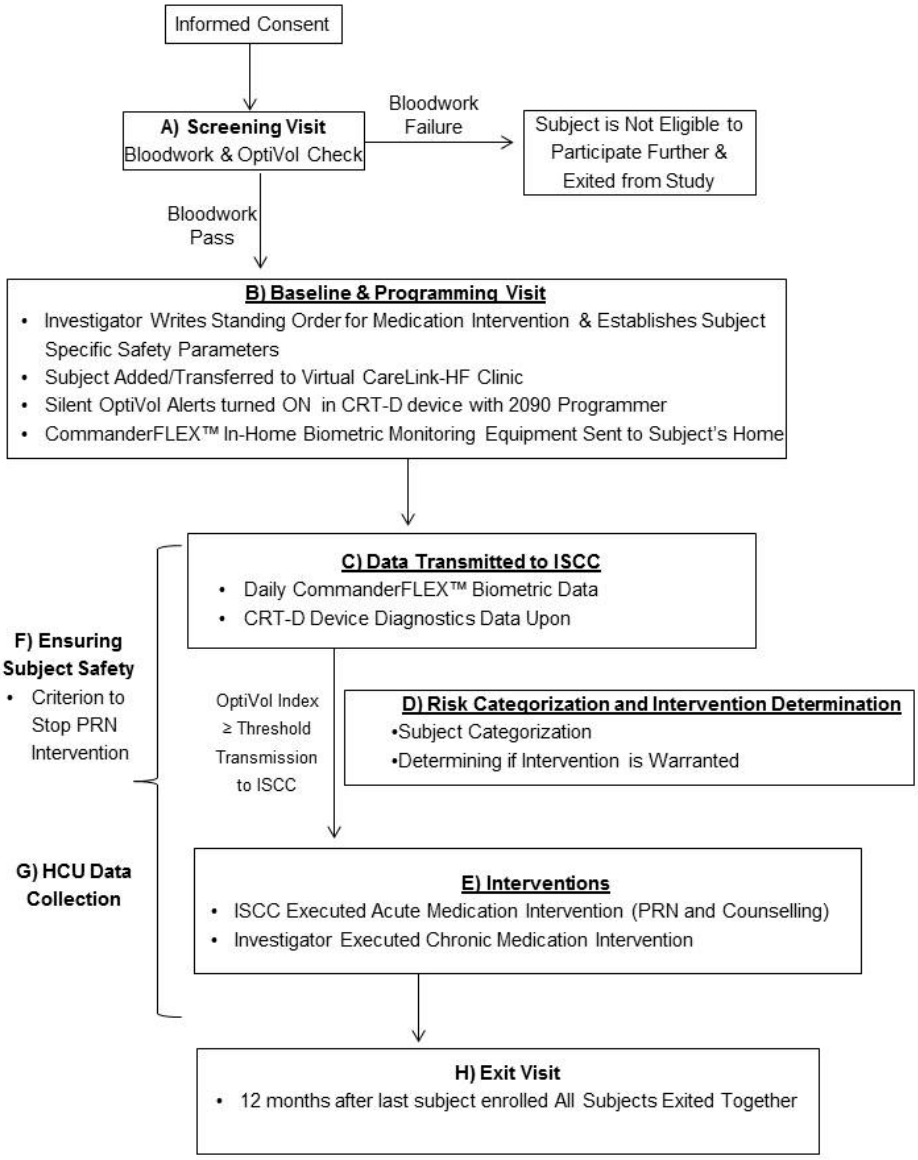


Figure 4: General study process for INTERVENE-HF.

6.1 A) Screening Visit

6.1.1 Patient Informed Consent & Screening

The consent and screening process will take place prior to the baseline & programming visit. Bloodwork and CRT-D device values will need to be verified for study eligibility. These values

and procedures are described in section 7.7. If the subject does not meet eligibility, the subject will be exited and documented as a screen failure.

6.2 B) Baseline & Programming Visit

6.2.1 Investigator Writes Standing Order for Medication Intervention and Establishes Subject Specific Safety Parameters

Once the subject has completed the consent and screening processes the subject's investigator will conduct the baseline visit. At this baseline visit the investigator will create an individualized medication intervention plan that is customized to the subject. This physician prescribed medication intervention plan is focused on the use of routine volume management medication, i.e. a transient elevation in diuretics or other volume management drugs (e.g. nitrates), and will include instructions for changes in the subject's diuretic dose for up to two rounds of medication intervention during a single episode. (One round = 3 days of taking medication that was prescribed at baseline. Two rounds = 6 days of taking baseline prescribed medication). This medication intervention of transient increase in volume management drugs is referred to as PRN (*pro re nata* or 'as needed') in the remaining text below.

Prescription(s) and adequate refills will be provided to the subject by the subject's primary care provider or investigator. The subject's individualized medication intervention plan will reside on file at the subject's participating clinic/hospital and also at the INTERVENE Study Communication Center (ISCC). The investigator (or responsible care team provider under the supervision of investigator) will be allowed to make changes to this prescription any time they deem necessary and will be required to notify ISCC with any changes within 24 hours with supplied forms.

In addition to the customized medication intervention plan, the investigator will collect information on the subject's chronic baseline medication and establish subject specific safety parameters for blood pressure changes and weight loss thresholds.

6.2.2 Subject Added/Transferred to Virtual CareLink-HF Clinic

For study purposes, a virtual CareLink-HF clinic will be created to host all study subjects. The virtual clinic will be managed by ISCC, and only designated ISCC nurses will have access to this virtual CareLink-HF clinic for scheduling and monitoring transmissions. Monitoring transmissions are needed to assess the effect of the PRN intervention(s). For the duration of the study, the investigator/site will agree to add the subject into the virtual ISCC CareLink-HF clinic. If the investigator/site currently utilizes a HF CareLink Clinic, the enrolled subject shall be transferred into the virtual CareLink-HF clinic for the duration of the study.

The CRT-D subject will still be maintained and managed for defibrillation events through the CareLink EP clinic. The EP will continue to have the uninterrupted access to the subject's device and clinical information while enrolled in the study. The EP will also receive any manual downloads and device data initiated by CareAlert transmission once the subject is enrolled into the study. However the EP will be able to clearly see in CareLink Network that

their patient is an INTERVENE-HF study subject. The EP will be trained to not take action on unscheduled transmissions related to the study.

6.2.3 Silent OptiVol CareAlert Turned ON in CRT-D device with 2090 Programmer

With the use of a Medtronic 2090 programmer installed with investigational programmer software, enrolled subjects will have their CRT-D devices programmed to allow for silent OptiVol CareAlert transmissions to take place when the OptiVol Fluid Index programmed threshold value is exceeded (see Table 5 in section 3 for information on the 2090 Programmer and Investigational Software). This threshold value will be programmed uniformly to 70 Ohm-Days for all study subjects. Physician adjustment of OptiVol threshold value will not be allowed during the course of the study. If necessary, the OptiVol threshold may be changed during the course of the study. However, this change will be applied uniformly to all study subjects.

At the study exit, each subject will have their OptiVol CareAlert turned OFF by the same investigational software used to turn it ON at the beginning of the study. Verification of OptiVol CareAlert enable (at baseline) and disable (at exit) will take place by printing the information report from the 2090 and placing it into the subject's file. This information will also be captured by electric Case Report Forms (eCRF). The investigational software on the 2090 programmer should not be removed from the programmer until all study subjects are exited.

6.2.4 CommanderFLEX™ In-Home Biometric Monitoring Equipment Sent to Subjects Home

This study will leverage Care Management Services (formerly Cardiocom) biometric monitoring equipment and nursing staff as part of the ISCC. Each enrolled subject will receive a CommanderFLEX™ device, including a weight scale, blood pressure cuff and console that will allow the subject to perform measurements of weight, blood pressure, and prompts the subject to answer Yes or No questions related to their HF symptoms (see Figure 2, Figure 3 and Table 9 in Section 3 for images and description and of the CommanderFLEX™ device and accessories). The CommanderFLEX™ kit will be provided at no cost, for use in their home during the length of the study. This kit will be be drop shipped to the subject's place of residence after the subject has completed the baseline and programmer visit. At the end of the study, the subject will be required to return the CommanderFLEX™ and accessories.

6.3 C) Data Transmitted to ISCC

6.2.1 Daily CommanderFLEX™ Biometric Data

The subjects will be asked to collect daily blood pressure, weight and HF symptom information via the in-home CommanderFLEX™ kit they received after the baseline and programming visit. These data will be transmitted directly to ISCC. The ISCC nurse will place

a call to the subject at 5 days and then 21 days after the baseline and programming visit if the subject has not set-up the CommanderFLEX™ and encourage data transmission by the subject.

6.2.2 CRT-D Device Diagnostics Data

Once the silent OptiVol CareAlert is turned ON, the subject will not hear or notice anything different from their previous experience with their implanted CRT-D device. They can return to normal routines and activities. The CRT-D device will now monitor the subject's OptiVol Fluid Index for any threshold crossings. When the OptiVol Fluid Index value crosses the programmed threshold, the device will perform an automatic wireless CareLink transmission of the device diagnostics data to ISCC. The ISCC nurse will then make arrangements for the CRT-D device to transmit data at set intervals within the next 28 days to continue assessment of the fluid index for either therapy initiations, recovery criteria to stop medication intervention, and/or an OptiVol reset when applicable.

6.3 D) Risk Categorization and Intervention Determination

6.3.1 Subject Risk Categorization

Transmissions sent to the ISCC virtual CareLink-HF clinic integrate all device diagnostics data and assign a numerical value that corresponds to a risk status (Low, Medium or High). This risk status is based on OptiVol Fluid Index and other device diagnostics data (i.e. intrathoracic impedance, heart rate variability, activity, night heart rate, and other variables) using the published algorithm as described by Cowie et al.[10] (Further information on this published algorithm is provided in the Section 2).

Upon receiving the transmission, the ISCC nurse will use the most recent value listed on the transmission record to categorize the numerical value provided by the algorithm to a corresponding risk status in the following way:

- Value is between 0 and less than 5.4 = Low
- Value is greater than or equal to 5.4 and less than 20 = Medium
- Value is greater than or equal to 20 = High

A transmission that is categorized as 'High' will result in an overall subject risk status of 'High' and the ISCC nurse will contact the subject for further assessment. When 'Medium' transmissions are received, the weight and HF symptom data from the previous 7-days are considered to determine if the overall subject risk status of the subject is 'High'.

For example, a transmission category of 'Medium' AND weight gain and/or symptom data indicating the presence of one or more HF symptoms from questions listed in Table 10, will assign the subject with an overall risk status of 'High' and the subject will be contacted by the ISCC nurse for further assessment. This will also be true for a subject that has a 'Medium' transmission AND the subject has weight gain of more than 2 pounds in one day or 5 pounds in 7 days.

Note: CareAlert transmission will arrive to the ISCC after 5 p.m. of the subject's time zone, therefore subject contact will be attempted the day following the receipt of transmission.

Table 10: Biometric HF Symptom Questions Collected by the CommanderFlex™

Questions in Table 10 will be asked of the subject by the CommanderFlex™ unit and collected/reviewed by the ISCC nurse when determining the overall risk status of a subject with a 'Medium' transmission.

Are you feeling more short of breath? If Yes then, Feel more short of breath with activity? If Yes then, Are you more short of breath at rest? If Yes then, Are you getting enough air?
Awaken during night short of breath? If Yes then, Feel more short of breath lying down? If Yes then, Did you need extra pillows last night? If Yes then, Did you sleep sitting up last night?
Are your ankles or feet more swollen?
Are you coughing more than usual? If Yes then, Is your cough different today? If Yes then, Does lying flat cause coughing?

If the biometric or symptom data are missing from the day of the CareAlert transmission, the day the CareAlert transmission is reviewed, or the subject has provided less than three days of biometric data in the 7 days prior to receiving the CareAlert transmission, the ISCC nurse will contact the subject to assess the presence of HF related symptoms from questions outlined in Table 10. If any of these symptoms are present, the subject will be assigned an overall risk status of 'High' and further evaluation will be performed to assess if medication intervention is warranted (see section 6.3.2 for information on determining warranted intervention). If no weight gain or symptoms are present and the transmission is categorized as 'Medium' the subject status will be monitored remotely by the ISCC after receiving the transmission.

6.3.2 Determining if Intervention is Warranted

To ensure that the intervention is warranted, the ISCC nurse will first determine that the subject is not hypotensive per the following criteria. (If the subject is hypotensive a notification in the form of a 'Interim Patient Report' is sent to the site and intervention will not proceed).

- The subject has no signs of hypotension. For the subject to be considered hypotensive, systolic BP < 85 mmHg or diastolic BP <40 mmHg.

The ISCC nurse will also ask the subject a series of questions to ensure the OptiVol crossing is HF related.

- Have you had a CRT-D device change or lead revision?
- Have you been discharged from a hospital within the last 2 days and did you receive intravenous fluids for 1 or more days while in the hospital?
- Are you experiencing chills/shivering, shaking or muscle aches?
- Have you recently been treated for a COPD exacerbation?
- Any changes in baseline diuretic medication in the past 3 weeks?

If the subject answers YES to any of the above questions, the OptiVol crossing is deemed to not be HF related and the intervention will not proceed. Once the nurse has ensured that the OptiVol crossing is HF-related, the nurse will initiate the prescribed PRN intervention on file that was created at the baseline visit by the subject's investigator.

6.4 E) Interventions

The medication intervention will have two components. The first component is the ISCC acute medication intervention for acute volume management executed by ISCC as per investigator's standing orders (left arm in Figure 5 below and Section 6.4.1). In addition, the ISCC nurse will perform dietary and medication counseling when applicable.

The second component of the medication intervention will be the responsibility of the investigator (right arm in Figure 5 below and Section 6.4.2). ISCC will provide notifications to the participating site to alert the investigator when a re-evaluation of the subject's chronic medication is requested (see Appendix B: ISCC Reports to Physician for an example of this report).

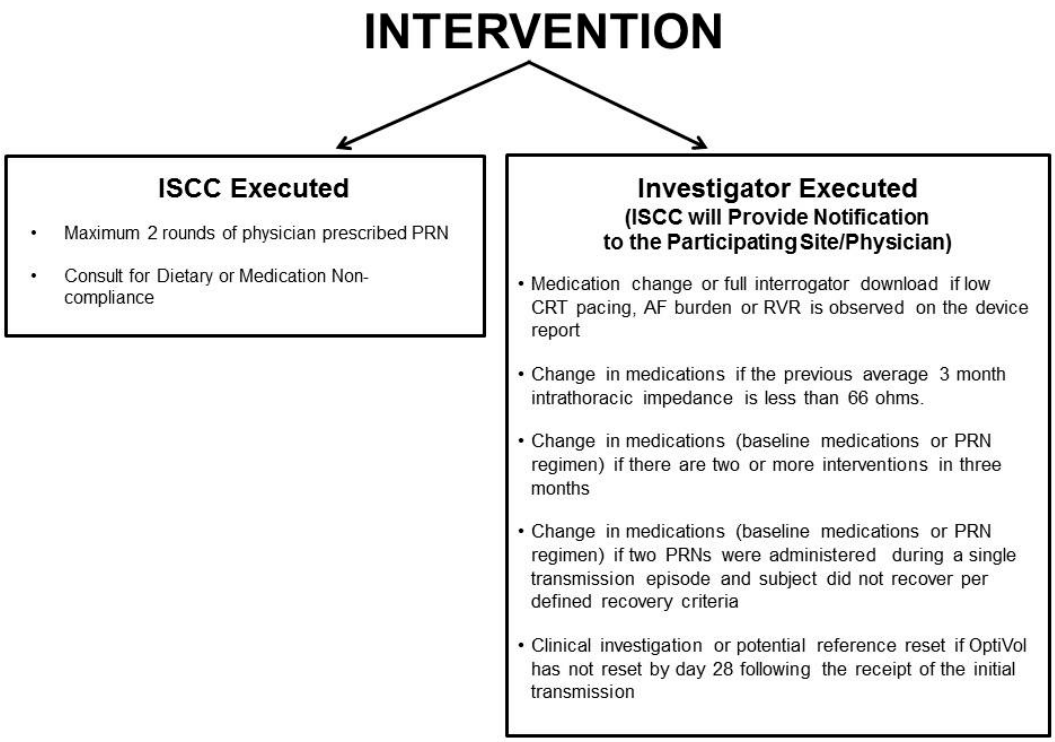


Figure 5: Intervention in INTERVENE-HF study.

The Intervention for this study has two components: ISCC executed intervention (left arm) and Investigator executed intervention (right arm).

6.4.1 ISCC Executed Acute Medication Intervention (PRN and Counseling)

The ISCC facilitated intervention component will consist of providing reinforcement and direction to the subject as to when they are to self-administer up to two rounds of investigator prescribed PRN to the subject per single transmission that warrants action. The investigator prescribed PRN is initiated after ISCC nurse has ensured that subject has been compliant with their baseline medication regimen including diuretic medications. Each round of PRN will be 3 days long. Thus, no more than 6 days of PRN medication will be administered to the subject.

The example scenario in Figure 6 below is an illustration of this ISCC executed intervention. Referring to Figure 6, the day of the transmission is considered Day 0. Since the OptiVol CareAlert transmission is initiated by the device at 5 PM, the nurse will attempt to contact the patient on the following day (includes weekends). Thus, the ISCC nurse will call the subject via phone on Day 1 (1 day post initial transmission), and upon subject contact, guide the subject to take their first round of investigator prescribed diuretic for 3 days if intervention is warranted (Section 6.3.2 above).

The ISCC nurse will notify the subject's investigator using a 'Interim Patient Report' indicating that the first round of PRN has been initiated (see Appendix B: ISCC Reports to Physician for an example of this report).

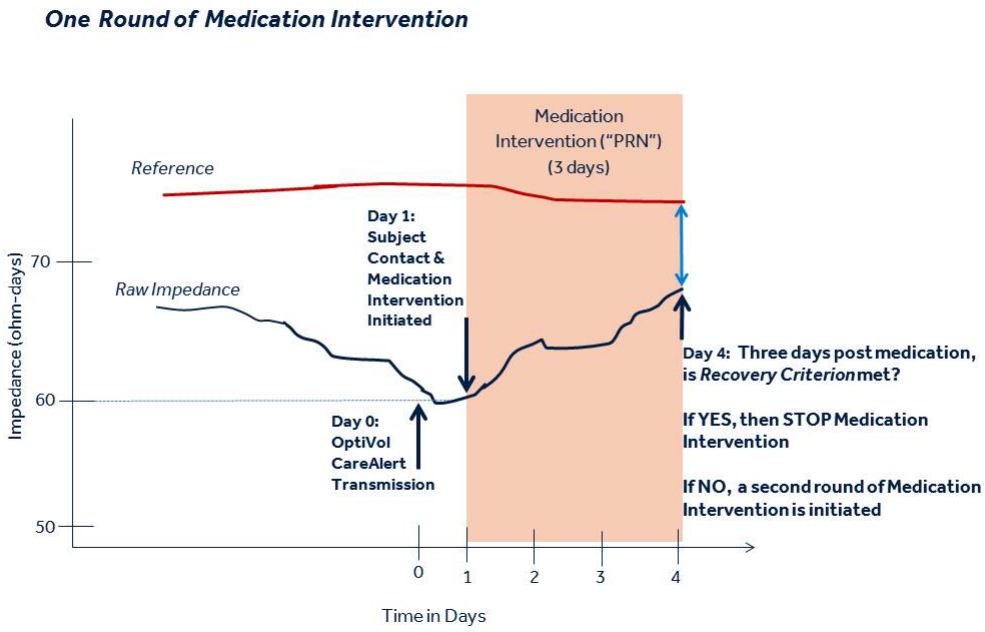


Figure 6: Example Scenario of One Round of Medication Intervention (PRN).

The efficacy of the PRN is evaluated using raw impedance based recovery criterion. (Refer to section 6.4.1.1 and Figure 8 for a detailed description of determining recover criterion.) Recovery criterion is evaluated on Day 4 (when possible) (4 days post initial transmission or 3 days post PRN initiation) and then again on day 8 (when possible) after first PRN. If the recovery criterion is not met on day 4, a second round of PRN is initiated. The ISCC nurse will notify the subject's investigator using a 'Interim Patient Report' indicating that the second round of PRN has been initiated. Figure 7 illustrates this example scenario of 2 rounds of successive PRNs.

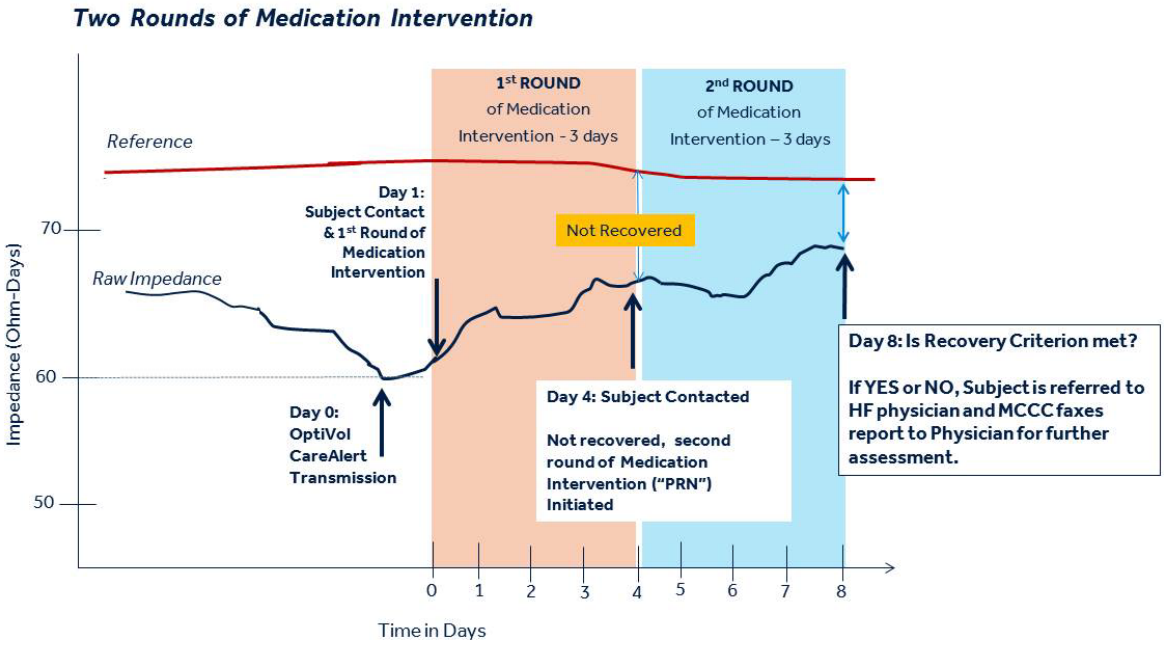


Figure 7: Example Scenario of Two Rounds of Medication Intervention (PRN).

The efficacy of the second round of PRN will be evaluated on Day 8 (when possible) (8 days post initial transmission or 7 days post first day of first round of PRN). If the recovery criterion is met, subject is deemed as recovered and no further action is taken. If the recovery criterion is not met after second round of PRN, an Interim Report and Baseline Medication Report is sent by the ISCC nurse to the investigator for review and asked to re-evaluate the subject's chronic baseline medications (Right Arm of Figure 5)

In the event that it has been determined on initial subject contact, that the subject has been non-compliant with baseline medications for one or more days prior to contact, the subject will be instructed to take baseline medications for three days. Recovery criterion will be evaluated for effectiveness of reinstituting baseline medications on day 4 and day 8 in the same fashion as described above. If recovery criterion is not met on either of these two evaluations, the first PRN will be initiated and the same schedule takes place and evaluation scheme thereafter is similar to as described above for a compliant subject except for a shift of at least 4 days.

If the subject has not been compliant with baseline medications but returning to baseline medications is not possible (e.g. unavailability of medications), subject will be instructed to contact their investigator immediately. An 'Interim Report' will be sent to the participating investigator (see Appendix B: ISCC Reports to Physician for an example of this report).

6.4.1.1 Criterion for Evaluating PRN Efficacy in ISCC Medication Intervention

A recovery criterion will be computed by the ISCC nurse to evaluate PRN efficacy using raw intrathoracic impedance since it responds dynamically to patient volume status. Computation of recovery criterion requires the difference between raw intrathoracic impedance and the reference impedance. Reference impedance is a component of market approved OptiVol feature in Medtronic devices. Daily values for both raw and reference impedance are included with all device diagnostic transmissions spanning duration of up to 14 months.

The difference between raw and reference impedances on four days is required to compute recovery criterion (RC) – the day CareAlert is received (x_0), and the three PRN intervention days prior to the day RC is evaluated (x_1, x_2 and x_3), Recovery criterion is then computed according to the following equation and as illustrated in the figure below:

$$\mathrm{RC} = 100 * \frac{(x_0 - x_1) + (x_0 - x_2) + (x_0 - x_3)}{x_0}$$

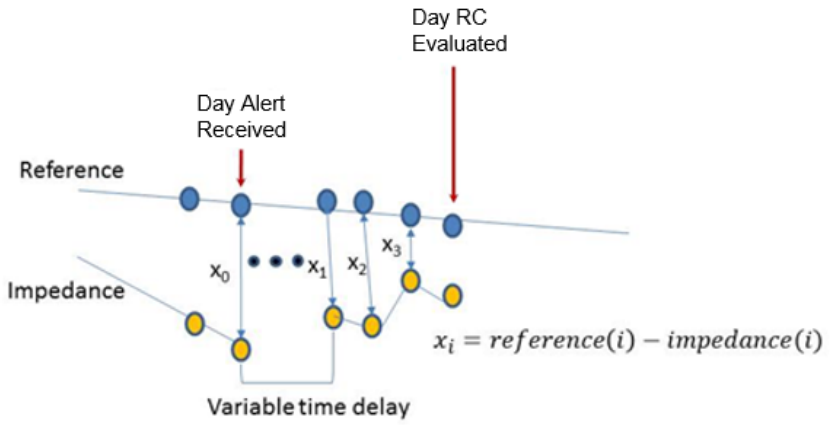


Figure 8: Recovery Criteria Illustration

If the value of RC is greater than a threshold value of 70 (i.e. cumulative impedance recovery over the last 3 days is 70% or more from Day 0 of receiving the initial transmission), the intervention is deemed to be successful. If the value of RC is less than or equal to 70, the intervention is deemed to be not a success and appropriate follow-up action (i.e. second PRN or notification to the investigator) is taken.

6.4.1.2 ISCCC Timeframe for Patient Contact to Initiate Intervention

If the ISCC nurse is unable to contact the patient during the first attempt for initiation of first or second rounds of PRN, the following schedule will be used to establish subject contact:

For initiating a first round of PRN: The ISCC nurse will make 1 attempt per day, for a total of 8 subsequent attempts to establish the contact (including weekends). If the ISCC nurse is unable to establish subject contact, a notification will be sent to the investigator. The day of successful subject contact will then be the first day of the medication intervention.

For initiating the second round PRN (or for any medication surveillance on days 8, 12, and 16 post initiation of the first day of medication intervention): The ISCC nurse will make 1 attempt per day of any CareLink transmission to establish subject contact. If unable to establish contact, an 'Exception Report' will be sent to the investigator with continued monitoring per the protocol (see Appendix B: ISCC Reports to Physician for an example of this report).

6.4.2 Investigator Executed Chronic Medication Intervention

The investigator will be responsible for performing the re-evaluation of the subject's chronic medications or HF treatment. Any changes in baseline medications will need to be reported to the ISCC. If no changes were made, rationale as to why changes were not made will need to be provided. In absence of an investigator intervention or documented rationale, lack of intervention by the investigator will be considered a protocol deviation. To aid the investigator in making such changes, a summary of the subject's heart failure related medications at baseline along with guideline recommended doses for these medications will be provided to the investigator as part of the notification (see Appendix B: ISCC Reports to Physician for an example of this report).

6.5 F) Ensuring Subject Safety

6.5.1 Criterion for not initiating or continuing with a PRN Intervention

At the time of subject contact, (following the CareLink transmission and subject having been stratified as High risk), the ISCC nurse will make sure that the subject is not hypotensive based on the blood pressure measurement for the day of contact. If the subject has not yet transmitted the blood pressure measurement for the day of contact, the nurse will instruct the subject to obtain blood pressure measurement while on the phone. If the subject's systolic blood pressure is below 85 mmHG with associated hypotensive symptoms, the intervention will not be initiated. Additionally in the instance that the subject is unable or unwilling to provide a blood pressure measurement, the subject will be assessed for potential hypotensive symptoms – if positively reported, the medication intervention will not be initiated. ISCC will send an 'Interim Patient Report' to the subject's investigator noting the reason for not initiating PRN intervention. Subject's investigator will be required to further evaluate the subject, take necessary actions, and document them in eCRFs.

To ensure subject safety while a PRN intervention is underway, the subject's will be asked to provide a blood pressure and weight daily. If a predefined, physician specified, patient specific, safety threshold is crossed for either weight or blood pressure the subject will be

contacted by ISCC nurse. The nurse will telephonically evaluate the subject for symptoms known to suggest that intervention may not be safe (Table 11). If any one of the two symptoms is present, PRN will be stopped and the investigator will be sent an 'Exception Report' to assist with further subject follow-up (see Appendix B: ISCC Reports to Physician for an example of this report). The ISCC nurse will make one attempt to establish the contact with subject to evaluate subject symptoms to potentially stop PRN intervention. If the nurse is unable to establish the subject contact, a report will be sent to the investigator and/or phone call will be made to the site to notify that values were outside threshold(s).

Table 11: Safety Thresholds for Cessation of Medication Intervention (PRN)

<table>
<tr><td colspan="4"><u>PRN Cessation and Safety Threshold(s):</u>
Hold/Discontinue PRN Diuretic use if telephonically assessed to have met Weight <u>or</u> BP threshold <u>and</u> Symptom(s):</td></tr>
<tr><td>Weight Loss:</td><td>Weight < 150lbs:
3 lbs/2days
Weight 151-300lbs:
4 lbs/2 days
Weight > 301lbs:
5 lbs/2days</td><td>Or</td><td>_____lbs/ _____days
(Physician specified range)</td></tr>
<tr><td colspan="4">OR</td></tr>
<tr><td>Blood Pressure:</td><td>Systolic of < 85 mmHG or a diastolic of <40 mmHg</td><td>Or</td><td>< _____ /_____ mmHg
(Physician specified value)</td></tr>
<tr><td colspan="4">AND</td></tr>
<tr><td>Telephonically Assessed Symptom(s):</td><td colspan="3">New lightheadedness when moving from sitting to standing
or
Muscle cramping or Charlie horses</td></tr>
</table>

6.5.1.1 Criteria to Perform Blood work and Related Actions

Blood work will be performed by the site if PRN intervention is stopped anytime because of safety concern. Blood work will also be performed if 2 rounds PRNs are completed irrespective of whether the intervention is deemed success or failure after 2 PRNs. The participating site will be notified by ISCC via Interim Patient Report to notify site to perform blood work for the subject. Blood work and evaluation by the participating investigator will be required to be performed within 7 days of the notification and associated eCRF will need to be completed. Blood work, at a minimum, should include creatinine (needed to estimate eGFR) and electrolytes (K+ and Na+). Investigators will be required to record creatinine,

eGFR, K+ and Na+ in the eCFR. Any actions taken along with the rationale will also be recorded in the eCFR. If the action is updating of HF medications or PRN prescription, the updated medication and PRN forms will be sent to ISCC within 24 hours. Lack of completing this blood work eCFR in its entirety will be considered a deviation.

6.5.1.2 Safety Monitoring Using External Biometric Data

Outside of the PRN medication intervention window, subject's blood pressure will be monitored for hypotension per nominal safety threshold of a systolic blood pressure of <85 mmHG or a diastolic blood pressure <40 mm Hg or physician specified threshold, if different. If the hypotension criterion is met, subject will be contacted and assessed for presence of two hypotensive symptoms. These hypotensive symptoms will be assessed by asking the following two questions: Are they experiencing new lightheadedness when moving from sitting to standing? And, are they experiencing any cramping or Charlie horses? If any of the two symptoms or both symptoms are present, the subject will be asked to contact their physician. An 'Exception Report' will be sent to the investigator including a note about their patient's safety issue (see Appendix B: ISCC Reports to Physician for an example of this report). The Investigator will be required to review the report and determine if clinical actions are necessary. Actions along with rationale will be documented in the eCRF. If no actions are needed, rationale for that will also be recorded in the eCRF. If the action is updating of HF medications or PRN prescription, updated medication and PRN forms will be sent to ISCC within 24 hours. Lack of completing eCFR in its entirety will be considered a protocol deviation.

6.6 H) Exit Visit

Please refer to section 7.14 for details on exiting procedures.

7 SITE RELATED PROCEDURES

Prior to performing study related procedures, all sites must have IRB and associated regulatory authority approval (if applicable) as well as documentation from Medtronic of site readiness.

7.1 Investigator/Investigation site selection

All clinical investigators managing the subject's heart failure must be qualified practitioners and experienced in the diagnosis and treatment of subjects with heart failure.

The role of the investigator is to implement and manage the day-to-day conduct of the clinical investigation as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical investigation.

The investigator shall:

- Be qualified by education, training, and relevant experience appropriate to the use of the product and associated procedures as defined below:

- Diagnoses/Treats patients with HF

- Willing to partner with ancillary service provider hosted at Medtronic to guide medication intervention for acute HF volume management under physician standing order.

- Center is willing to coordinate with their CareLink Manager to transfer patient into the Virtual CareLink-HF clinic for the duration of the study. (The patient will still be part of the CareLink EP).

- Disclose potential conflicts of interest, including financial, that interfere with the conduct of the clinical investigation or interpretation of results

The investigator shall be able to demonstrate that the proposed investigational site has adequate resources, including, as applicable, facilities, laboratories, equipment, and a qualified trial site team. Center personnel training will be completed prior to participation in this clinical study.

The investigator shall have access to an adequate number of patients with the following:

- Center should have a pool of patients with implanted Medtronic CRT-D devices with wireless telemetry.

- Center should have a pool of patients with NYHA Class II and/or Class III Heart Failure.

7.2 Site activation

During the activation process (prior to subject enrollment), Medtronic will train site personnel on the clinical investigation plan, relevant standards and regulations, if needed, informed consent, and on data collection and reporting tools. If new members join the study center team, they will receive training on the applicable clinical study requirements relevant to their role before contributing to the clinical study.

Prior to performing study related activities, all local regulatory requirements shall be fulfilled, including, but not limited to the following:

- IRB approval of the current version of the CIP and Patient Informed Consent.
- Regulatory authority approval or notification (as required per local law)
- Fully executed Clinical Trial Agreement (CTA)
- Financial Disclosure
- Curriculum Vitae (CV) of investigators
- Documentation of delegated tasks

- Documentation of study training

Additional requirements imposed by the IRB and regulatory authority shall be followed, if appropriate.

In addition, all participating site staff must be trained on the current version of the CIP and must be delegated by the investigator to perform study related activities.

Medtronic will provide each study center with documentation of study center/investigator readiness; this letter must be received prior to subject enrollment.

7.3 Equipment requirements

The following equipment must be available at each center to support study activities:

- Fax machine (Or fax account)
- Medtronic Programmer Model Number 2090

7.4 Data Collection

Data collection requirements are summarized in Table 12 below.

Table 12: Data Collection Table

DATA COLLECTION	Screening	Baseline/Programming	ISCC Notification to Site							Scheduled call	Study Exit
			Intervention not initiated (OptiVol artifact/non-HF)	First PRN Initiated	Unable to contact subject	Safety Criteria met During PRN OR 2 PRNs given	One of Three Criteria met for chronic meds/PRN review	OptiVol not reset at 28 days	Safety criteria met outside PRN Window		
Patient Informed Consent	√										
Eligibility Verification	√										
Bloodwork/Labs	√					√					√
Demographic Information		√									
Individualized Medication Intervention Plan (PRN Regimen)		√									
Cardiovascular Medication Regimen Information		√								√	√
HF Event (6 mos. prior to enrollment)		√									
Safety Parameter Thresholds for PRN Cessation		√									
OptiVol Information Report from 2090 Programmer		√									√

DATA COLLECTION		Baseline/Programming	ISCC Notification to Site							Scheduled call	Study Exit
			Intervention not initiated (OptiVol artifact/non-HF)	First PRN Initiated	Unable to Contact Subject	Safety Criteria met During PRN OR 2 PRNs given	One of Three Criteria met for chronic meds/PRN	OptiVol not reset at 28 days	Safety criteria met outside PRN Window		
Symptoms, Compliance, HCU utilization & Actions						√				√	
OptiVol Artifact/Non-HF Related Event			√								
Device Diagnostics Review and Actions			√	√	√						
ISCC Unable to Contact Subject					√						
Chronic Meds/PRN Assessment						√					
OptiVol Review & Resetting							√	√			
Safety Review									√		
Device Data (Save-to-Disk)		√									√
CareLink Transfer Verification		√									√
Adverse Events	Upon Occurrence										
System modification											
Study Deviation											
Death											

7.5 Role of the sponsor representatives

Sponsor representatives may provide support as required for the study under supervision of the Investigator, including:

- Provide study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities
- Technical support study visits under the supervision of a study investigator, but no data entry, shall be performed by Medtronic personnel or their representatives at sites
- Monitoring and auditing activities

7.6 Patient informed consent process

Patient informed consent (PIC) is defined as a legally effective documented confirmation of a subject's voluntary agreement to participate in a particular clinical study after information has been given to the subject on all aspects of the clinical study that are relevant to the subject's decision to participate. This process includes obtaining a Patient Informed Consent Form that has been approved by the study center's IRB and an Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law which are signed and dated by the subject. A subject may only consent after information has been given to the subject on all aspects of the clinical investigation that are relevant to the subject's decision to participate.

Prior to enrolling subjects, each center's IRB Committee will be required to approve the PIC Form. The document(s) must be controlled (i.e. versioned and/or dated) to ensure it is clear which version(s) were approved by the IRB. Any adaptation of the sample Consent Form must be reviewed and approved by Medtronic and the IRB reviewing the application prior to enrolling subjects.

The investigator must notify the subject of any significant new findings about the study that become available during the course of the study which are pertinent to the safety and well-being of the subject, as this could impact a subject's willingness to participate in the study. If relevant, approval may be requested from subjects to confirm their continued participation.

The sample Patient Informed Consent Form(s) will be provided under separate cover.

Prior to initiation of any study-specific procedures, patient informed consent must be obtained from the subject. Likewise, privacy or health information protection regulation may require subjects to sign additional forms to authorize centers to submit subject information to the study sponsor. The informed consent process must be conducted by the investigator or an authorized designee, and the Patient Consent Form and Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law must be given to the subject in a language he/she is able to read and understand. The process of patient informed consent must be conducted without using coercion or undue improper influence on or inducement of the subject to participate by the investigator or other center personnel. The informed consent process shall not waive or appear to waive subject's

legal right. The language used shall be as non-technical as possible and must be understandable to the subject and the impartial witness, where applicable.

The subject must have ample time and opportunity to read and understand the informed consent form, to inquire about details of the study, and to decide whether or not to participate in the clinical study. All questions about the study should be answered to the satisfaction of the subject.

When the subject decides to participate in the clinical study, the PIC must be signed and personally dated by the subject and investigator or authorized designee, as required by the Patient Consent Form. If applicable, the witness shall also sign and personally date the consent form to attest that the information in the PIC was accurately explained and clearly understood by the subject, and that informed consent was freely given.

A copy of the Patient Consent Form and the Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language, signed and dated as required by law, must be provided to the subject.

If the PIC is obtained the same day the subject begins participating in study-related procedures, it must be documented in the subject's case history that consent was obtained prior to participation in any study-related procedures. It is best practice for the informed consent process to be documented in the subject's case history, regardless of circumstance.

In the event the subject cannot read and/or write, witnessed (impartial third party) patient informed consent will be allowed, provided detailed documentation of the process is recorded in the subject's case history and the witness signs and dates the patient informed consent. The subject should "make his mark" (sign or otherwise physically mark the document so as to indicate consent) on the ICF as well. The Consent Form should document the method used for communication with the prospective subject and the specific means by which the prospective subject communicated agreement to participate in the study.

The original of the signed Patient Consent Form must be filed in the hospital/clinical chart and/or with the subject's study documents.

The Patient Consent Form and Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law must be available for monitoring and auditing. Any Medtronic Field personnel who support the INTERVENE-HF study must be able to review the subject's signed and dated Consent Form and verify its completeness prior to proceeding with any study procedures. In the event the Medtronic Field personnel identify patient informed consent as being incomplete, the INTERVENE-HF study procedures will not be allowed to occur until the consent of the subject can be adequately and appropriately obtained.

When a patient and the principal investigator or authorized designee, as required have personally signed and dated the Consent Form, the patient is considered a subject enrolled in the study. The date the subject signed the Consent Form and data protection authorization must be documented in the subject's medical records.

7.7 Screening Visit

During the screening visit, the subject's OptiVol Fluid Index and bloodwork will be verified to confirm subject eligibility.

7.7.1 OptiVol Fluid Index Verification

The subject's OptiVol Fluid Index on the day of screening must be below prescribed threshold to be eligible.

If the subject's OptiVol Fluid Index is above threshold, then the subject can return at a later date for OptiVol reevaluation. If the subject does not return for a later OptiVol reading, they shall be exited and reported as a screen failure.

If at the time of screening the OptiVol Fluid Index is equal to or greater than threshold and is deemed to be an artifact by the investigator and the subject is otherwise stable and euvolemic, a reference reset can be performed at the time of the baseline visit and the patient shall stay in the study and proceed to the next step.

7.7.2 Bloodwork Eligibility

To be considered eligible for the baseline and programming visit, the subject's most current bloodwork results (within the past 6 months) must meet the values listed below. If no prior lab data is available, then new labs should be taken at the screening visit as long as OptiVol is below threshold.

- eGFR> 25 ml/min/1.73 m^2
- Hemoglobin value of ≥ 9.0 g/dl
- Potassium (K+) values in the range of 3.5 to 5.5 mmol/L
- Sodium (Na+) values ≥ 130 mmol/L

Once the Investigator has reviewed the lab values and verified they are within the ranges listed above, the site will contact all subject(s) to inform them of their eligibility to continue. Eligible subjects will be scheduled to return to the site within 30 days from the screening visit for the baseline and programming visit to occur. Non-eligible subjects (i.e. lab values are out of the ranges listed above) will be documented as screen failures and exited as described in section 7.14.

The following information is required to be collected at the screening visit:

- Patient Informed Consent
- Eligibility Verification (Inclusion/Exclusion Assessment)

- Confirmation of bloodwork eligibility (within 6 months)
- Confirmation of OptiVol eligibility
-

7.8 Baseline and Programming Visit

Upon successful screening per section 7.7, the subject will return to the site for the baseline and programming visit.

The following information is required to be collected at the baseline and programming visit:

- Demographic Information
- Individualized Medication Intervention Plan (PRN Regimen)
- Baseline Cardiovascular Medication Regimen Information
- HF Event History in the last 6 months
- Safety Parameters Thresholds for PRN Cessation
- OptiVol Information Report from 2090 Programmer
- Device Data (Save to Disk)
- CareLink Transfer Verification

If the threshold value is changed during the study by the sponsor, the subject will be notified and asked to return to the site for a reprogramming visit. Re-programming visits will be performed in the same manner as the initial programming visit.

For information regarding investigational software handling, storage and traceability, refer to section 8.

7.9 Scheduled follow-up phone calls

Data analyses include follow-up phone calls, regardless of whether the phone call occurs within the window. Therefore, should contact to the subject not be established within the pre-specified window, a late phone call is preferred over a missed phone call.

The participating investigator/study coordinator will attempt to reach the subject for this follow-up phone call for up to ±14 calendar days from target date listed in Table 13. Follow-up visit windows are based on the day post-OptiVol CareAlert was turned ON.

Note: Because the study is estimated to be completed in approximately 30 months (includes approximately 18 months of enrollment and 12 months of follow-up from the last enrolled subject) window dates are provided for 30 months. If follow up phone calls need to continue beyond 30 months, the windows will continue at 60 day intervals with ±14 day windows.

Table 13: Data collection and study procedure requirements at subject phone call

Study Follow-up Phone Call	Window (Based on Day OptiVol CareAlert was turned ON)		
	Window Start (days post-OptiVol CareAlert turned ON)	Target (days post-OptiVol CareAlert turned ON)	Window End (days post-OptiVol CareAlert turned ON)
2-Month	46	60	74
4-Month	106	120	134
6-Month	166	180	194
8-Month	226	240	254
10-Month	286	300	314
12-Month	346	360	374
14-Month	406	420	434
16-Month	466	480	494
18-Month	526	540	554
20-Month	586	600	614
22-Month	646	660	674
24-Month	706	720	734
26-Month	766	780	794
28-Month	826	840	854
30-Month	886	900	914

The following information is required to be collected at the follow-up phone call:

- Current Medications or changes in medication
- Document any reportable AEs (refer to section 10 for Adverse Events and Device Deficiencies)
- Record any changes to the CRT-D implanted system
- Worsening HF symptoms
- Recent hospitalizations or surgeries
- Change in co- morbidities

7.10 ISCC Communication & Notifications to Site

Throughout the duration of the study, notifications from ISCC to the Site will be sent to the sites when the following events occur:

- Intervention not initiated (OptiVol artifact/non-HF)
- First PRN Initiated
- Unable to contact subject for 1st PRN
- Unable to Contact Subject for 2nd PRN or After Safety Issue
- Safety Criteria met During PRN OR 2 PRNs given
- One of Three Criteria met for chronic meds/PRN review
- OptiVol not reset at 28 days
- Safety criteria met outside PRN Window
- Adverse Event

Upon receiving the notifications from ISCC, the site will be directed in the notification to complete the appropriate forms. These forms include:

- Bloodwork/Labs Form
- Symptoms, Compliance, HCU utilization and Actions Form
- OptiVol Artifact/Non-HF Related Event Form
- Device Diagnostics Review and Actions Form
- ISCC Unable to Contact Subject Form
- Chronic Meds/PRN Assessment Form
- OptiVol Review and Resetting Form
- Safety Review Form
- Device Data (Save-to-Disk)
- CareLink Transfer Verification Form
- Adverse Event Notification Form

Additionally, if any of the following circumstances occur, a notification will be sent to the investigator to prompt for Chronic Medication Evaluation in the subject:

- Mean 90 day impedance less than 66 ohms
- Subject does not recover after 2 consecutive rounds of medication intervention
- Two or more medication interventions were performed in the last 3 months

7.11 Unscheduled follow-up visits

An unscheduled visit is defined as any non-standard of care visit to the study site for reasons related to the INTERVENE-HF system including any device alerts. The following procedures are required at each unscheduled visit:

- Document any reportable AEs (refer to section 10 Adverse Events and Device Deficiencies)

7.12 Healthcare Utilization

In this study, Health Care Utilization information will be collected at specified study events as listed in Table 12 above.

7.13 System Modification

The subject will be exited if a device or lead replacement takes place or if the device is taken out of service (e.g. repositioned, explanted or capped). The subject must be exited from the study after all system and/or procedure related AEs have been resolved or remain unresolved with no further action planned. All explanted product (device, leads, etc.) should be returned to Medtronic for analysis when permissible by local laws and regulations (see section 8.2 for final product disposition details).

A system modification will be reported in the event the device and/or leads require invasive modification (e.g., generator or lead explant, generator or lead replacement, lead repositioning).

For a system modification the following activities are required:

- Participating investigative site shall notify the INTERVENE Study Communication Center of any system modifications within 24 hours with the appropriate eCRF.

7.14 Study Exit

At study exit, an eCRF is required for all subjects except in the case of death. Prior to exiting a subject from the study, it is recommended to follow the subject until all ongoing system and/or procedure related AEs are resolved or unresolved with no further actions planned. Following exit, subjects will continue to receive standard medical care with their primary/enrolling physician. Upon exiting from the study, no further study data will be collected and no further study visits will occur for the subject. All data available through the time of the subject's exit will be used for analysis.

Subjects are urged to remain in the study as long as possible but may be exited from the study for any of the following situations:

- Subject has completed follow-up
- Subject lost to follow-up
- Subject death
- Subject has an explant without the intent to re-implant
- Subject did not meet inclusion/exclusion criteria
- Subject did not provide consent or data use protection authorization
- Subject chooses to withdraw (e.g., consent withdrawal, relocation to another geographic location)
- Investigator deems withdrawal necessary (e.g., medically justified, inclusion/exclusion criteria not met, failure of subject to maintain adequate study compliance)
- Lead or generator replacement

If subject is not lost to follow up, the OptiVol alert will be turned off at study exit and the following information is required to be collected:

- Reason for exit (eCRF)
- AE
- Blood work: Includes but not limited to Potassium and Sodium (K+ and Na+), eGFR, and Hemoglobin.
- OptiVol Information Report from 2090 Programmer: Print AFTER using the software to disable the OptiVol alert. See User Manual for instructions on how to access the software and how to turn off the OptiVol alert.

Note that an in-person visit will be required to turn OFF the OptiVol alert in the CRT-D device by use of a Medtronic 2090 programmer. See User Manual for instructions on how to access the software and how to turn off the OptiVol alert.

In the case that the subject is determined to be lost to follow-up, details of a minimum of two attempts and the method of attempt (e.g., one letter and one phone record or two letters) to contact the subject must be recorded. In addition, follow the regulations set forth by the governing IRB.

If discontinuation is because of safety or lack of effectiveness, the subject shall be asked to be followed for collecting safety data outside the clinical investigation.

Additionally, the CommanderFlex™ unit and accessories will need to be returned upon study exit.

7.15 Medications

Record the use of all Cardio vascular medications (including HF medications), anti-platelet, anticoagulant, antibiotics, corticosteroids, insulin, or oral diabetic agents at baseline with the appropriate eCRF and send to the INTERVENE Study Communication Center at baseline visit and any time changes are made to the subject's medications.

8 INVESTIGATIONAL DEVICE/SOFTWARE STORAGE, HANDLING AND TRACEABILITY

8.1 Investigational Device/Software Storage, Handling and Traceability

The CRT-D devices used in this study are commercially available, however once the INTERVENE-HF research software that was downloaded onto the 2090 programmer is used to turn ON the OptiVol CareAlert feature, the CRT-D device will be considered an investigational product.

When the INTERVENE-HF investigational software is downloaded on the 2090 programmer, the programmer becomes investigation as well and should only be used in the clinical study according to the CIP. When the INTERVENE-HF software is downloaded or removed from the 2090 programmer, the programmer/software distribution log must be updated. The investigational device will be tracked via Investigational Product Distribution logs. Programmers or study devices that have the INTERVENE-HF software removed will no longer be considered investigational after the time of removal.

The INTERVENE-HF software will be distributed to a center only when Medtronic has received all required documentation and has notified the center of center readiness. Distribution of the INTERVENE-HF software to study centers during the clinical study will be managed by Medtronic. The INTERVENE-HF software will be distributed via Medtronic's Secure Download Network (SDN). Software distributed via the SDN will be downloaded onto study 2090 programmers over a secure internet connection.

It is the responsibility of the investigator to correctly handle, store and track the investigational products (2090 programmers with the INTERVENE-HF software installed and devices with the OptiVol CareAlert feature turned ON).

Investigational Product Disposition records must be maintained for each center to track investigational product information. Investigational Product Disposition records consist of:

- Software/Programmer Disposition Log (eCRF)
- CRT-D Device Disposition Log (eCRF)

8.2 Final Product Disposition

At the end of the study, the OptiVol CareAlert feature will need to be turned to OFF and the investigational software on all study programmers must be removed. The software/programmer disposition log and CRT-D device disposition Log must be updated at

that time. In the case that software cannot be manually removed, the 2090 programmer must be returned to Medtronic for removal of the software.

In the event of a CRT-D explant, all explanted devices (devices or leads) should be returned to Medtronic for analysis when permissible by local laws and regulations. If the products are explanted but not returned, a justification will be reported on the appropriate case report forms or disposition logs. The Investigational Device Distribution Log must be updated for explanted devices. To receive a Returned Product Mailer Kit, please contact your local Medtronic field personnel. The Investigational Product Disposition Log must be updated with the final device disposition of investigational product.

9 STUDY DEVIATIONS

A study deviation is defined as an event within a study that did not occur according to the Clinical Investigation Plan or the Clinical Trial Agreement.

Prior approval by Medtronic is expected in situations where the investigator anticipates, contemplates, or makes a conscious decision to deviate. Prior approval is not required when a deviation is necessary to protect the safety, rights or well-being of a subject in an emergency or in unforeseen situations beyond the investigator's control (e.g. subject failure to attend scheduled follow-up visits, inadvertent loss of data due to computer malfunction, inability to perform required procedures due to subject illness).

For medically justifiable conditions which preempt a subject's ability to complete a study-required procedure, it may be permitted to report only one deviation which will apply to all visits going forward. This may also apply for other unforeseen situations (e.g. the subject permanently refuses to complete a study required procedure and the data will not contribute to the primary end point analysis). However, prior approval from Medtronic is required for such situations.

All study deviations must be reported on the Case Report Form regardless of whether medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the subject in an emergency. The deviation must be recorded with an explanation. Multiple deviations of the same type at the same visit may be reported on one case report form if they occur at the same date/visit and they have the same root cause.

In the event the deviation involves a failure to obtain a subject's consent, or is made to protect the life or physical well-being of a subject in an emergency, the deviation must be reported to the Institutional Review Board (IRB) as well as Medtronic within five (5) working days. Reporting of all other study deviations should comply with IRB policies and/or local laws and must be reported to Medtronic as soon as possible upon the center becoming aware of the deviation. Reporting of deviations must comply with IRB policies, local laws, and/or regulatory agency requirements.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the Clinical Investigation Plan, conduct additional training, and terminate the investigation). Repetitive or serious investigator compliance issues may result in initiation of a corrective action plan with the investigator and site, and in some cases, necessitate suspending enrollment until the problem is resolved or ultimately terminating the investigator's participation in the study. Medtronic will provide center-specific reports to investigators summarizing information on deviations that occurred at the investigational site on a periodic basis.

10 ADVERSE EVENTS AND DEVICE DEFICIENCIES

Timely, accurate, and complete reporting and analysis of safety information for clinical studies are crucial for the protection of subjects. Reporting and analysis of safety data are mandated by regulatory authorities worldwide. Medtronic has established procedures in conformity with worldwide regulatory requirements to ensure appropriate reporting of safety information. This study is conducted in accordance with these procedures and regulations.

Since the safety reporting requirements and classification systems vary for each regulatory agency, requirements from all geographies are taken into account for the collection and reporting of safety information.

10.1Adverse Event and Device Deficiency definitions

Where the definition indicates “device”, it refers to any device used in the study. This might be the device under investigation, or any market released component of the system.

Table 14: Adverse Event definitions

General	
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device NOTE 1: This definition includes events related to the investigational medical device or the comparator. NOTE 2: This definition includes events related to the procedures involved. NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices. (ISO 14155:2011, 3.2) NOTE 4: The initiation of an PRN by the ISCC nurse will not be considered an AE
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from an error use or from intentional misuse of the investigational medical device. (ISO 14155:2011, 3.1)
Device Deficiency (DD)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. NOTE: Device deficiencies include malfunctions, use errors and inadequate labeling (ISO 14155:2011, 3.15) NOTE 2: CareLink connectivity related DD will not be collected on an eCRF
Relatedness	

System Related	An adverse event that results from the presence or performance (intended or otherwise) of the system component. • Device Related: An adverse event that results from the presence or performance (intended or otherwise) of the CRT-D device • RA Lead Related: An adverse event that results from the presence or performance (intended or otherwise) of the right atrial lead • RV Lead Related: An adverse event that results from the presence or performance (intended or otherwise) of the right ventricular lead • LV Lead Related: An adverse event that results from the presence or performance (intended or otherwise) of the left ventricular lead • Other system component related: An adverse event that results from the presence or performance (intended or otherwise) of another system component
Cardiovascular Related	An adverse event related to the heart and blood vessels or the circulation.
Heart Failure Related	An AE related to the hearts inability to meet the metabolic demands of the body. A heart failure adverse event would include worsening heart failure signs and symptoms such as hypervolemic and hypovolemic status requiring the administration, alteration, adjustment or augmentation of HF therapy (diuretics, inotropes and/or vasodilators etc.) or the utilization of certain treatment devices.
PRN Treatment Related:	An AE related to the utilization of PRN Medication Intervention as defined in Section 6.
Seriousness	

Serious Adverse Event (SAE)	Adverse event that a) led to death, b) led to serious deterioration in the health of the subject, that either resulted in 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to fetal distress, fetal death or a congenital abnormality or birth defect (ISO 14155:2011, 3.37) NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) ISO 14155:2011	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. (ISO 14155:2011, 3.36)
Unanticipated Adverse Device Effect (UADE) *21 CFR 812*	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death, was not previously identified in a nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. (21 CFR 812.3(s))
Timing	
Pre-PRN initiation	An adverse event that occurs on the day of PRN treatment initiation, but before the subject implemented the medication adjustment.
Post-PRN initiation	An adverse event that occurs on the day of PRN treatment initiation, but after the subject implemented the medication adjustment.

10.2Adverse Event and Device Deficiency Assessment

10.2.1 Adverse Events

All system related events, all cardiovascular-related events, all events that may be associated with the PRN intervention and all SAEs will be collected throughout the study duration, starting at the time of signing the consent form.

An exception to this subset of collected events mentioned above, would be the protocol-initiated PRN intervention, which will not be collected on the Adverse Event form (AE CRF).

When the protocol initiated PRN intervention occurs, it will be collected on the ISCC Notification form.

Reporting of these events to Medtronic will occur on an Adverse Event (AE) Form, including a description of AE, date of onset of AE, date of awareness of site, treatment, resolution, assessment of both the seriousness and the relatedness to the investigational device. Each AE must be recorded on a separate AE Form. Subject deaths are also required to be reported. Refer to section 10.5 for Subject Death collection and reporting requirements.

Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened. Adverse events impacting users or other persons are also reportable during the course of the study.

For AEs that require immediate reporting, initial reporting may be done by phone, secure file transfer system, or on the eCRF completing as much information as possible. The AE eCRF must be completed as soon as possible. Refer to the study contact list provided in the center's study documents binder/investigator site file or refer to the contact information provided on the title page.

10.2.2 Device Deficiencies

Device deficiency information will be collected throughout the study and reported to Medtronic. Note that device deficiencies that result in an adverse device effect (ADE) to the subject should be captured as an Adverse Event only.

Device related issues that involve the subject's Carelink monitor will not be collected on the Device Deficiency form,

10.2.3 Processing Updates and Resolution

For any changes in status of a previously reported adverse event (i.e. change in actions taken, change in outcome, change in relatedness), an update to the original AE must be completed. All adverse events must be followed until the adverse event has been resolved, is unresolved with no further actions planned, the subject exits the study or until study closure, whichever occurs first.

In the event that a subject is exited from the study prior to study closure, all efforts should be made to continue following the subject until all unresolved or system related adverse events, as classified by the investigator, are resolved or they are unresolved with no further actions planned.

At the time of study exit, all adverse events with an outcome of "Unresolved, further actions or treatment planned" must be reviewed and an update to the original AE must be reported. At a minimum, if there are no changes to the description, relatedness, test and procedures or actions taken, the outcome must be updated to reflect "Unresolved at time of study closure."

10.3 Events Classification and Reporting

Upon receipt of adverse events at Medtronic, a Medtronic representative will review the adverse event/device deficiency for completeness and accuracy and when necessary will request clarification and/or additional information from the Investigator. AEs will be classified by the investigator for relatedness and seriousness, according to the definitions provided.

Medtronic will utilize MedDRA, the Medical Dictionary for Regulatory Activities, to assign a MedDRA term for each adverse event based on the information provided by the investigator.

Regulatory reporting of events will be completed according to local regulatory requirements. Refer Table 16 for a list of required investigator and Medtronic reporting requirements and timeframes. It is the responsibility of the investigator to abide by any additional AE reporting requirements stipulated by the IRB responsible for oversight of the study.

Foreseeable adverse event information associated with the market released system components are provided in the device labeling that is included with each system component. Additionally, information related to possible risks associated with the utilization of the system components and software can be found in Table 17.

For emergency contact regarding a UADE, SAE and/or SADE, contact a clinical study representative immediately. Refer to the study contact list provided in the center's study documents binder/investigator site file or refer to the contact information provided on the title page.

Adverse Events and Deaths will be classified according to the standard definitions as outlined below:

Table 15: Adverse Event classification responsibilities

What is classified?	Who classifies?	Classification Parameters
Timing of the Event	Investigator	Pre-PRN initiation, Post PRN initiation
Relatedness	Investigator	System Related
	Sponsor	HF Related, PRN Related[1]
Seriousness	Investigator	SAE, UADE
	Sponsor	SAE, UADE
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Sponsor	MedDRA term assigned based on the data provided by Investigator
Death Classification	Investigator	Sudden Cardiac, Non-sudden Cardiac, Non-Cardiac, Unknown[2]

[1] The CEC will adjudicate all AEs for system relatedness, HF, and PRN relatedness
[2] CEC will adjudicate deaths to relatedness and death classification. All other adjudication information for deaths will be taken from the corresponding AE with the outcome of death.

10.4 Adverse Event and Device Deficiency Reporting Requirements

Regulatory reporting of AEs/DDs will be completed according to local regulatory requirements. Refer to Table 16 for a list of required investigator reporting requirements and timeframes, and of required Medtronic reporting requirements and timeframes.

It is the responsibility of the investigator to abide by any additional AE/DD reporting requirements stipulated by the IRB responsible for oversight of the study.

For AEs/DDs that require immediate reporting, initial reporting may be done by contacting the study sponsor per the sponsor contact information provided in this document.

Table 16: Reporting requirements

Serious Adverse Events (SAEs)	
Investigator submit to:	
Medtronic	**US:** Submit in a timely manner after the investigator first learns of the event
IRB	**US:** Submit per local IRB requirement.
Serious Adverse Device Effects (SADEs)	
Investigator submit to:	
Medtronic	**US:** Submit in a timely manner after the investigator first learns of the event.
IRB	**US:** Submit per local IRB requirement.
Unanticipated Adverse Device Effects (UADEs)	
Investigator submit to:	
Medtronic	**US:** Submit as soon as possible, but no later than within 10 working days after the investigator first receives notice of the effect. (21 CFR 812.150(a)(1))
IRB	**US:** Submit as soon as possible, but no later than within 10 working days after the investigator first receives notice of the effect. (21 CFR 812.150(a)(1))
Sponsor submit to:	
Investigator	**US:** Notification as soon as possible, but no later than 10 working days after the sponsor first learns of the effect. (21 CFR 812.150(b)(1))
Regulatory authorities	**US:** Notification as soon as possible to FDA, but no later than 10 working days after the sponsor first receives notice of the effect. (21 CFR 812.150(b)(1))
IRB	**US:** Notification as soon as possible, but no later than 10 working days after the sponsor first learns of the effect. (21 CFR 812.150(b)(1))
All other reportable Adverse Events (system, cardiovascular-related, and PRN related)	
Investigator submit to:	
Medtronic	**US:** Submit in a timely manner after the investigator first learns of the event.
Regulatory Authorities	**US:** Submit or report as required per local reporting requirement.
IRB	**US:** Submit per local IRB requirement.
All other Device Deficiencies	
Investigator submit to:	
Medtronic	**US:** Submit in a timely manner after the investigator first learns of the event.

Regulatory Authorities	**US:** Submit or report as required per local reporting requirement.
IRB	**US:** Submit per local IRB requirement.

10.5Subject Death

10.5.1 Death data collection

All subject deaths must be reported by the investigator to Medtronic on a Subject Death form as soon as possible after the investigator first learns of the death. Document the Adverse Event that led to the subject death on an Adverse Event form.

In the event of a subject's death, the implanted system should be explanted and returned to Medtronic for analysis whenever possible. Local laws and procedures must be followed where applicable. For the CRT-D devices used in this study, the VT and VF detection capabilities must be disabled to avoid inadvertent shocks.

System Interrogation Data Recommendations:

- After the subject has died but prior to explant, the system shall be interrogated and a full summary interrogation (Interrogate All) performed when possible.
- Make the interrogation file before any programming to prevent overwriting information in the CRT-D device's memory and/or distinguishing between events detected during versus before the explant procedure
- Recommend obtaining the exact date and time of death as lower temperatures after death can cause ERI and other "event flags" to be stored in the CRT-D device memory

If the system is not interrogated, an explanation must be entered on the Subject Death form. If any system component is returned to Medtronic, internal return product reporting systems may be used to gather additional information about the returned device/component.

A copy of the death certificate, if available and allowed by state/local law, should be sent to the Medtronic clinical study team. When a death occurs in a hospital, a copy of the death summary report and all relevant hospital records should be sent to the Medtronic clinical study team, if available. If an autopsy is conducted, the autopsy report should also be sent to the Medtronic clinical study team if available and allowed by state/local law. When the death occurs at a remote site, it is the investigative center's responsibility to attempt retrieval of information about the death. Additionally, device disposition information should be updated. In summary, the following data will be collected:

- Date of death
- Detailed description of death

- Cause of death
- Relatedness
- Device interrogation (if available)
- Device disposition information
- Death summary/hospital records (if available and allowed by state/local law)
- Autopsy report (if available and allowed by state/local law)
- Death certificate (if available and/or allowed by state/local law)

10.5.2 Death classification and reporting

Sufficient information will be required in order to properly classify the subject's death. The Investigator shall classify each subject death per the following definitions:

Cardiac Death: A death directly related to the electrical or mechanical dysfunction of the heart.

Sudden Cardiac Death (SCD): Natural death due to cardiac causes, indicated by abrupt loss of consciousness within one hour of the onset of acute symptoms; preexisting heart disease may have been known to be present, but the time and mode of death are unexpected. If time of onset cannot be determined, SCD will alternatively be defined as any unexpected cardiac death occurring out of the hospital or in the emergency room as dead on arrival.

Non-sudden Cardiac Death: All cardiac deaths that are not classified as sudden deaths, including all cardiac deaths of hospitalized subjects on inotropic support.

Non-cardiac Death: A death not classified as a cardiac death.

Unknown Classification: A death in which there is no clinical evidence to support. Unknown death classification is intended for use only when there is insufficient or inadequate information to classify the death

The CEC will review deaths and provide a final adjudication of the primary cause of death, relatedness, and death classification.

Regulatory reporting of Subject Deaths will be completed according to local regulatory requirements. Refer to Table 16 for a list of required investigator and sponsor reporting requirements and timeframes.

10.6Clinical Events Committee (CEC) review

At regular intervals, an independent CEC will review and adjudicate at a minimum, all end-point related AEs and deaths for subjects participating in the study.

The CEC will consist of a minimum of three (3) non-Medtronic employed physicians that are not participating investigators for the study, including a CEC chairperson. At least two out of three CEC members must adjudicate, at a minimum, all deaths. All other AEs may be adjudicated by at least one physician member of the CEC.

Medtronic personnel may facilitate and participate in a CEC meeting but will be non-voting members.

For adverse events and deaths reviewed by the CEC, Medtronic will provide the CEC with the Investigator's description and classification. The CEC is responsible for reviewing the Investigator's assessment and supportive documentation (when available), reviewing applicable definitions, and determining final classifications for all adjudication parameters. Additionally, the CEC will provide an adjudication of the death and relatedness.

If the CEC disagrees with the investigator's classification of the event, the rationale will be provided to the investigator. If the investigator agrees with the CEC's adjudication, the case report form documenting the AE will be updated accordingly by the site.

If the investigator does not agree with the CEC's adjudication classification, both determinations will be provided within the final report; however the CEC's adjudication will be used for data analysis. The disagreement will also be included in reporting to ethic committees and regulatory authorities, if required.

10.7 Product Complaint Reporting

In geographies where devices are market-released, product complaint reporting is applicable. This includes when an AE is related to a market-released device during the study. The reporting of product complaints is not part of the clinical study and should be done in addition to the Adverse Event reporting requirements. Refer to local regulations for reporting requirements.

Product Complaint: Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a medical device that has been placed on the market.

It is the responsibility of the investigator to report all product complaint(s) associated with a medical device distributed by Medtronic, regardless whether they are related to intended use, misuse or abuse of the product. Reporting must be done immediately and via the regular channels for market-released products.

Medtronic will notify the regulatory authorities (e.g. Competent Authority) as applicable for the following incidents immediately upon learning of them:

- Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or instructions for use which led or might have led to the death or serious deterioration in the state of health of a patient, user, or other person.
- Any technical or medical reason resulting in withdrawal of a device from the market by the manufacturer.
- A serious deterioration in the state of heath includes:

- Life-threatening illness or injury
- Permanent impairment of a body function or permanent damage to a body structure
- A condition necessitating medical or surgical intervention to prevent permanent

11 RISK ANALYSIS

Medtronic follows rigorous Quality Assurance and Control procedures throughout the development and clinical study of a research system. The formal Hazard/ Risk Analysis for the INTERVENE-HF research system is completed according to ISO 14971 (Medical Device Risk Management), and will be used to ensure that the level of risk is acceptable prior to starting the INTERVENE-HF clinical study.

The INTERVENE-HF system includes commercially available systems and investigational software. The investigational software is on the programmer and it enables and disables the OptiVol wireless alert in selected CRT devices. Software design and interfaces between system components are assessed as part of the Hazard Analysis to ensure any potential risk is minimized. Assessment for acceptable end-to-end system connectivity, as well as system design verification and validation activities also form part of the Risk Management process followed for the INTERVENE-HF study.

The INTERVENE-HF study risks have been analyzed, evaluated, and controls are put in place to address all identified risks. During the course of the study, risks will be continuously monitored, assessed and documented by the investigators.

The risks are reduced as much as possible, with residual risk being documented within the Risk Management Report and disclosed in the Patient Informed Consent (PIC) forms provided to subjects.

A list of potential risks and risk reduction strategies associated with the INTERVENE- HF study is summarized in the table below. The comprehensive Research System Hazard Analysis is documented in DSN018588, INTERVENE Research Study Risk Management Report.

11.1 Risk Minimization

The potential risks associated with the INTERVENE-HF study were identified and have been successfully mitigated. Any potential risks associated with this study are further minimized by

selecting qualified investigators and training study personnel on the Clinical Investigation Plan.

Medtronic has further minimized the possibility of risks by performing pre-clinical testing prior to the INTERVENE-HF clinical study, implementing quality control measures into software development processes, providing guidelines for subject selection and evaluation, and providing adequate training instructions and labeling.

Subjects in the INTERVENE-HF clinical study will be followed remotely and at regular intervals to monitor the condition of their heart failure. At each protocol required in person follow-up, the investigator will interrogate the patient's CRT device to verify appropriate functionality and to assess any adverse events.

Table 17: Potential risks and risk minimization

Risks and Risk Reduction Strategy	
Risk	**Mitigations/ Risk Controls**
Improper/ unauthorized access to research system via the programmer	• Access code controls for appropriate access to the investigational programing software
Improper investigational software install and uninstall	• Software verification and validation testing • Data integrity checks and distribution of software via secure Medtronic Software Distribution Network • Install/ uninstall instructions are provided via the User Manual • Investigational software identification/ labeling provided in the Programmer software
Improper enabling of the OptiVol CareAlert on CRT-D devices	• System design with preconditions for enabling, and disabling of the OptiVol CareAlert functionality for only selected CRT models (which have the HF Risk Score)
Delay, missing, misleading or misinformation leading to inappropriate medical intervention	• System end-to-end (CRT device to HF Clinic) data connectivity assessment • Software design verification and validation testing • Patient selection and exclusion criteria to exclude more vulnerable patients or those who may be prone to impedance data inaccuracies • Investigational software identification/ labeling provided in the Programmer software • Pre-clinical integrated diagnostics algorithm for accuracy • Remote patient monitoring, and review of subject data and symptoms by licensed ISCC nurse

Risks and Risk Reduction Strategy	
	Note: Patients lost to follow-up may not have their OptiVol alert disabled. This may cause minor confusion in review of their device data outside of the study for geographies where the OptiVol feature is not approved, including the United States.
Premature System Revision	• Limited longevity impact to the implanted device based on minimal current drain impact from low expected number of OptiVol crossings and associated transmissions during the INTERVENE-HF study - For 1-4 crossings per year, longevity impact could be up to approximately 2 weeks in one year and 5 weeks for the 30 month study duration. - For 10 crossings per year, longevity impact could be approximately 5 weeks in one year, and 3 months for the entire 30 month study duration. •
• Procedural risks associated with coordinating care between two teams (two teams = site personnel and ISCC nurse), which results in missed or duplicated efforts, orders, or medications	• Study and site training for personnel, and subject training will address study protocols and the care that is provided by each health care team involved. • Risk disclosure: Patient Informed Consent discloses risks associated with coordinating care between two teams, (two teams = site personnel and ISCC nurse), which could include missed or duplicated efforts, orders or medications.

11.2 Potential Benefits

The INTERVENE-HF study may offer no benefit. Potential benefits of participating in the INTERVENE-HF study include having the OptiVol alert turned on and monitored remotely. This remote intrathoracic impedance monitoring, partnered with the external diagnostic information for risk stratification, may provide more individualized medication intervention that could lead to improved Heart Failure management.

The information gained from this study could result in the improved management of other Heart Failure study specific information. Additionally, information collected from this study may assist in the design of new product(s)/therapy(ies) and/or instructions for use.

11.3 Additional Considerations

The INTERVENE-HF study does not require exclusion of any aspects of standard of care in managing heart failure (HF) patients. Thus, physicians and nurses at a participating center can continue to manage their patients as per their clinic's standard of care practices. The INTERVENE-HF study provides additional opportunity for care interventions including use of PRN medications as per physician's standing orders (required) and reminders for assessment and adjustment to baseline medications (medication change or rationale for not changing medication required). These differences (between the standard of care for the subject as compared to the care provided to the subject when participating in the study) are described in further detail in the Patient Informed Consent (PIC) Template.

12 PLANNED STUDY CLOSURE, EARLY TERMINATION OF STUDY OR STUDY SUSPENSION

12.1 Planned study closure

Study Closure is a process initiated by distribution of a study closure letter. Study closure is defined as closure of a clinical study that occurs when Medtronic and/or regulatory requirements have been satisfied per the Clinical Investigation Plan and/or by a decision by Medtronic or regulatory authority), whichever occurs first. The study closure process is complete upon distribution of the Final Report or after final payments, whichever occurs last. Ongoing IRB oversight is required until the overall study closure process is complete. Refer to section 7.14 for additional information regarding study exit procedures.

12.2 Early termination or suspension

Early Termination of the Study is the closure of a clinical study that occurs prior to meeting defined endpoints. This is possible for the whole study or a single center. Study Suspension is a temporary postponement of study activities related to enrollment and distribution of the product. This is possible for the whole study or a single center.

12.2.1 Study-wide termination or suspension

Possible reasons for considering study suspension or termination of the study include but are not limited to:

- Adverse events associated with the system or product under investigation which might endanger the safety or welfare of the subject
- Observed/suspected performance different from the product's design intent
- Decision by Medtronic or regulatory body (where the study is operating under regulatory body authority)
- Technical issues during the manufacturing process

12.2.2 Investigator/center termination or suspension

Possible reasons for clinical investigator or center termination or suspension include but are not limited to:

- Failure to obtain initial IRB approval or annual renewal of the study
- Persistent non-compliance to the clinical investigation (e.g. failure to adhere to inclusion/exclusion criteria, failure to follow subjects per scheduled follow-ups)
- Lack of enrollment
- Noncompliance to regulations and the terms of the Clinical Trial Agreement (e.g. failure to submit data in a timely manner, failure to follow-up on data queries and monitoring findings in a timely manner, etc.)
- IRB suspension of the center
- Fraud or fraudulent misconduct is discovered (as defined by local law and regulations)
- Investigator request (e.g. no longer able to support the study)

12.3 Procedures for termination or suspension

12.3.1 Medtronic-initiated and regulatory authority-initiated

- Medtronic will promptly inform the clinical investigators of the termination or suspension and the reasons and inform the regulatory authority(ies) where required
- In the case of study termination or suspension for reasons other than a temporary IRB approval lapse, the investigator will promptly inform the IRB
- In the case of study termination, the investigator must inform the subjects and may inform the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subject enrollment must stop until the suspension is lifted by Medtronic
- In the case of a study suspension, enrolled subjects should continue to be followed out of consideration of their safety, rights and welfare

12.3.2 Investigator-initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension
- The investigator will promptly inform the institution (where required per regulatory requirements)
- The investigator will promptly inform the IRB
- The investigator will promptly inform the subjects and/or the personal physician of the subjects to ensure appropriate care and follow-up is provided

- In the case of a study suspension, subjects enrolled should continue to be followed out of consideration of their safety, rights and welfare

12.3.3 IRB-initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension within 5 business days
- Subject enrollment must stop until the suspension is lifted
- Subjects already enrolled should continue to be followed in accordance with IRB policy or its determination that an overriding safety concern or ethical issue is involved
- The investigator will inform his/her institution (where required per local requirements)
- The investigator will promptly inform the subjects, or legally-authorized designees or guardians and/or the personal physician of the subjects, with the rationale for the study termination or suspension

13 STATISTICAL METHODS AND DATA ANALYSIS

13.1 Sample size determination

INTERVENE-HF is a feasibility study to evaluate the system that combines integrated device diagnostics based risk stratification algorithm with a guided work flow process managed by a centralized communication center to manage HF patients. This system, for purposes of defining study objectives, will be termed the “Integrated Diagnostics Medication Intervention Strategy.” Findings from this feasibility study will be used to guide subsequent planning of a pivotal study.

As a feasibility trial, the INTERVENE-HF study is not designed to be powered for specific endpoints. However, the sample size for this study was chosen with the goal of gaining a first time experience with the Integrated Diagnostic Medication Intervention Strategy in a broad number of patients to understand the safety, effectiveness and potential patient benefit of the strategy.

The study plans to enroll up to 400 subjects to yield up to 200 eligible subjects that meet screening criteria from 20 centers in the US with follow up for at least 12 months. The study is estimated to be completed in approximately 30 months including 18 months of enrollment and 12 months of follow-up from the last enrolled subject. The objectives of the study focus on the effectiveness and safety of the Integrated Diagnostics Medication Intervention Strategy. Interim analyses of these objectives will take place and if data are deemed to sufficiently characterize the study objectives by the sponsor at one of these analyses, enrollment and/or follow-up will be stopped. In addition, in order to have an early check on the subjects’ safety, a preliminary safety interim data analysis will take place after 10 PRN interventions have been implemented and the last PRN intervention has been followed up for 14 days.

The unpublished data of a Medtronic sponsored study (OptiLink HF) shows that among the subjects who had had CRT-D implanted for at least nine months and had NYHA class II or III nine months post implantation, 58% had at least one OptiVol crossing within the next 12 months of follow-up (of which 39%, 28%, 19%, 9% and 5% had one, two, three, four and more than four OptiVol crossings, respectively). Furthermore, about two-thirds of the subjects in that study had OptiVol version 1 and the rest had OptiVol version 2 and it is known that OptiVol version 2 generates fewer alerts. Therefore, we assume in the INTERVENE-HF study that:

(1) 55% of the enrolled subjects who meet screening criteria and complete the baseline and programming visit will have at least one OptiVol crossing within the 12 months of follow-up; and

(2) The distribution for those experiencing OptiVol crossings during the 12 months of follow up is the same as the results from the unpublished data.

As shown in Table 18, this leads to approximately 233 OptiVol crossings in 110 subjects (55% of 200 subjects) to be observed in the INTERVENE-HF study. Furthermore, literature

has indicated that 45% of OptiVol crossings are HF related[20]. This means about 105 out of the 233 OptiVol crossings would require PRN implementation in this study.

Table 18: Number of OptiVol crossings expected from 110 (55% of 200) subjects

Assumption		Estimation	
Crossing(s)	% of subjects having the crossing(s)	Expected # of subjects having the crossings	Expected # of crossings
1	39%	43	43*1=43
2	28%	31	31*2=62
3	19%	21	21*3=63
4	9%	10	10*4=40
>4	5%	5	5*5=25
Total		**110**	**233**

13.2 General considerations

Medtronic employees or designees will perform all statistical analyses.

A separate Statistical Analysis Plan (SAP) will be created and will include a comprehensive description of the statistical methods and analyses to be included in reports that include analysis of endpoints. Any change to the data analysis methods described in the CIP will require an amendment only if it changes a principal feature of the CIP. Any other change to the data analysis methods described in the CIP, and the justification for making the change, will be described in the clinical study report.

In addition, the SAP will further describe pre-specified data handling rules. Additional exploratory analyses of the data may be conducted as deemed appropriate.

All objectives will be analyzed once the last enrolled subject has completed the 12-month follow-up visit and/or during interim analyses (interim analyses performed after 100 and 150 subjects are enrolled and have completed the baseline and programming visit). The primary analysis for each objective will not account for missing data. If missing data is an issue, a sensitivity analysis will be performed accordingly. The analysis results will be included in the study report(s).

13.3 Primary Objective #1

To characterize the effectiveness of the Integrated Diagnostic Medication Intervention Strategy in resolving subject risk.

13.3.1 Hypothesis

There is no statistical hypothesis for this objective

13.3.2 Endpoint Definition

Once initiated, the Integrated Diagnostic Medication Intervention Strategy will be regarded as being effective if all the following criteria are met:

- The intrathoracic impedance of a subject recovers per defined criterion after completion of the Integrated Diagnostic Medication Intervention;
- The subject has no HF-related event (as adjudicated by the CEC) during or in the next 14 days after completion of the Integrated Diagnostic Medication Intervention;

  NOTE: Intervention for heart failure decompensation (HF event) is defined as an event requiring invasive intervention (i.e. IV diuretics, ultrafiltration, or equivalent) or inpatient hospitalization.

- The subject has not experienced any adverse events that are related to the Integrated Diagnostic Medication Intervention per CEC adjudication and require medical care.

13.3.3 Performance Requirements

There are no performance requirements for this objective.

13.3.4 Rationale for Performance Criteria

Rational for performance criteria is not applicable for this objective.

13.3.5 Analysis Methods

For each episode that requires intervention as determined by this protocol, the effectiveness of Integrated Diagnostic Medication Intervention Strategy will be evaluated as a binary outcome variable, where 1 = effective and 0 = not effective. During the course of the study, a subject could experience more than one intervention. Therefore, a generalized linear model with the generalized estimating equation (GEE) method will be used to analyze this correlated binary data. The effectiveness rate and its 95% confidence interval (CI) will be calculated based on the log of odds estimated using the GEE.

13.3.6 Determination of Patients/Data for Analysis

All subjects who have received the Integrated Diagnostic Medication Intervention per protocol.

13.3.7 Sample Size

As the above-mentioned, based on the experience from previous studies we expect to observe about 233 OptiVol crossings from 110 enrolled subjects in this trial and of them 105 OptiVol crossings would require Integrated Diagnostic Medication Intervention. There are no data to help us predict the percentage of OptiVol crossings receiving Integrated Diagnostic Medication Intervention or the effectiveness rate of Integrated Diagnostic Medication Intervention Strategy. We consider different scenarios in Table 19 and Figure 9 to estimate the precision on measuring the effectiveness rate of Integrated Diagnostic Medication Intervention Strategy.

The width of 95% CI for the effectiveness rate represents the measurement precision. Using the first row in Table 19 as an example, a total of 70 independent episodes with Integrated Diagnostic Medication Intervention produces a two-sided 95% CI with an actual width of 0.225 when the observed proportion of having effective treatment among those episodes is 0.7. This is based on the exact Clopper-Pearson confidence interval for one proportion assuming independent effectiveness status of Integrated Diagnostic Medication Intervention. Note that each episode is an OptiVol crossing that lead to the initiation of an Integrated Diagnostic Medication Intervention. Note also that for each scenario, we expect a narrower width (i.e. better precision) of 95% CI for the effectiveness rate in the framework of generalized linear model with GEE method. This is because GEE method takes the correlation among the effectiveness status of multiple episodes from the same subject into account, thus presumably results in a smaller standard error of the effectiveness rate.

Figure 9 is a visual illustration of Table 19.

Table 19: Table of the 95% Confidence Interval for 70-100 independent episodes

Confidence Level	Size (N)	Actual Width	Sample Proportion (P)	Lower Limit	Upper Limit
0.950	70	0.225	0.700	0.579	0.804
0.950	70	0.199	0.800	0.687	0.886
0.950	70	0.154	0.900	0.805	0.959
0.950	80	0.210	0.700	0.587	0.797
0.950	80	0.186	0.800	0.696	0.881
0.950	80	0.143	0.900	0.812	0.956
0.950	90	0.198	0.700	0.594	0.792
0.950	90	0.174	0.800	0.702	0.877
0.950	90	0.135	0.900	0.819	0.953
0.950	100	0.187	0.700	0.600	0.788
0.950	100	0.165	0.800	0.708	0.873
0.950	100	0.127	0.900	0.824	0.951

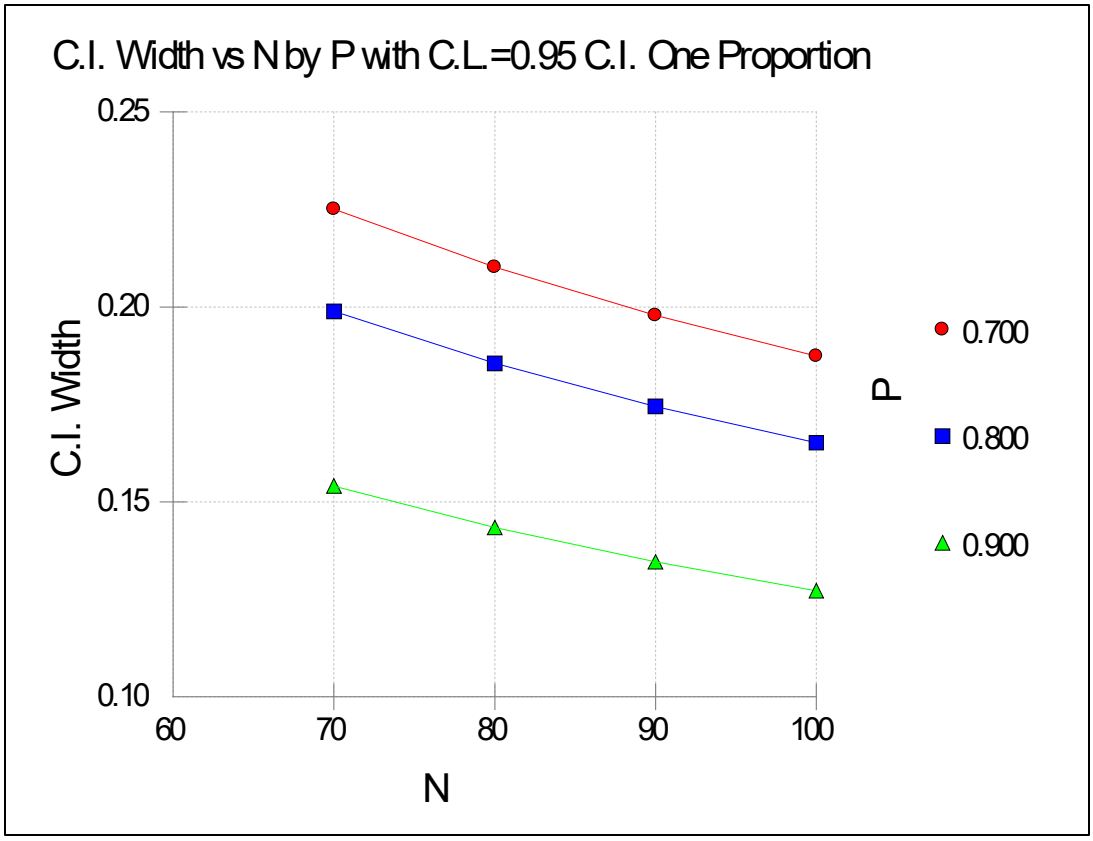


Figure 9: Graph of the 95% Confidence Interval for 70 to 100 independent episodes

13.4 Primary Objective #2

To characterize the safety of the Integrated Diagnostic Medication Intervention Strategy in resolving the subject risk.

13.4.1 Hypothesis

There is no statistical hypothesis for this objective.

13.4.2 Endpoint Definition

Once initiated, the Integrated Diagnostic Medication Intervention Strategy will be regarded as being safe if all the following criteria are met:

- The Integrated Diagnostic Medication Intervention applied to an episode is not terminated due to safety issues;

  NOTE: Safety issues include hypotension with/without patient contact and weight loss with patient contact.

- And, the Integrated Diagnostic Medication Intervention applied to an episode has not caused treatment-related adverse events (as adjudicated by the CEC).

13.4.3 Performance Requirements

There are no performance requirements for this objective

13.4.4 Rationale for Performance Criteria

Rationale for performance criteria is not applicable for this objective.

13.4.5 Analysis Methods

Similar to the effectiveness endpoint of Integrated Diagnostic Medication Intervention Strategy, the safety endpoint of Integrated Diagnostic Medication Intervention Strategy is a correlated binary outcome with 1=safe and 0=not safe. It will be analyzed using a generalized linear model with GEE method. The safety rate and its 95% CI will be calculated based on the log of odds estimated using GEE.

13.4.6 Determination of Patients/Data for Analysis

All subjects who have received the Integrated Diagnostic Medication Intervention.

13.4.7 Sample Size

The same estimates on the precision of measuring effectiveness rate of Integrated Diagnostic Medication Intervention Strategy under different scenarios illustrated in Table 19 and Figure 9 above are applicable to the safety rate as well. Again, using the first row in Table 19 as an example, a total of 70 independent episodes with Integrated Diagnostic Medication Intervention produces a two-sided 95% CI with an actual width of 0.225 when the observed proportion of having safe treatment among those episodes is 0.7.

13.5 Ancillary Objective

To characterize the occurrence of Heart Failure (HF) events in the study subjects.

13.5.1 Hypothesis

There is no statistical hypothesis for this objective

13.5.2 Endpoint Definition

The endpoint of this objective is the number of HF events per subject, as adjudicated by CEC.

13.5.3 Analysis Methods

The number of HF events will be summarized using frequency and percentage, and stratified by the implementation status of Integrated Diagnostic Medication Intervention (1=have ever received the intervention, 0=have never received the intervention). A Poisson regression model will be used to analyze the number of HF events, adjusting for the implementation of

Integrated Diagnostic Medication Intervention. The fit of the Poisson regression model will be checked. If over dispersion is a concern, a negative binomial model may be considered. It is important to note, that those who have received the Integrated Diagnostic Medication Intervention might be sicker when compared to subjects who have never received the Integrated Diagnostic Medication Intervention, and therefore, are more likely to have HF events. Thus, the number of HF events before and after the intervention will be summarized using descriptive statistics for the subjects who have received such intervention.

13.5.4 Determination of Patients/Data for Analysis

All the enrolled subjects who have completed the baseline and programming visit will be included.

13.6 Preliminary Safety Interim Data Analysis

To summarize preliminary safety of PRN intervention.

13.6.1 Hypothesis

There is no statistical hypothesis for this analysis.

13.6.2 Endpoint Definition

The endpoint of this analysis includes any adverse event reported per protocol.

13.6.3 Analysis Methods

The analysis will occur when 10 PRN interventions have been implemented and the last PRN intervention has been followed up for 14 days. Descriptive statistics such as count and percentage will be used. The seriousness and relatedness of adverse events will be based on the CEC adjudication. If an adverse event has not been adjudicated by the CEC by the time of the analysis, study investigators' assessment (if available) will be considered. The primary interest in the relatedness of adverse events includes but is not limited to safety issues leading to termination of PRN interventions, treatment-related adverse events after implementation of PRN interventions, and HF events occurring within 14 days after completion of PRN intervention. Adverse events occurring before and after PRN interventions will be summarized separately.

13.6.4 Determination of Patients/Data for Analysis

All the subjects who have completed the baseline and programming visit by the time of the analysis.

14 DATA AND QUALITY MANAGEMENT

Data will be collected using an electronic data management system for clinical studies. eCRF data will be stored in a secure, password-protected database which will be backed up nightly. Data will be reviewed using programmed and manual data checks. Data queries will be made available to centers for resolution. Study management reports may be generated to

monitor data quality and study progress. At the end of the study, the data will be frozen and will be retained indefinitely by Medtronic.

All records and other information about subjects participating in this study will be treated as confidential. Data will be transferred and processed by Medtronic or a third party designated by Medtronic in a key coded form, unless it's impossible to make it anonymous, for instance, where the patient's name cannot be removed from the data carrier, such as fluoroscopy images.

Procedures in the CIP require source documentation. Source documentation will be maintained at the site. Source documents, which may include, but not limited to, worksheets, patient medical records, lab results, ECGs, programmer printouts, and interrogation files, must be created and maintained by the investigational site team. In some cases, the data reported in the eCRFs may be considered source, as long as there is evidence of it in the subject's record. The eCRF may serve has the primary source for the following data points but is not limited to the list below (refer to the study-specific monitoring plan for complete listing).

The data reported on the eCRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing. If applicable, the eCRF may be considered source for the following data collection elements but not limited to:

- Enrollment Notification
    - Site assigned patient reference
- Baseline
    - Administrative Information
    - Cardiac Disease Classification
- Adverse Event eCRF
    - Date study center became aware of event
    - Relatedness of adverse event
- Device Deficiency eCRF
    - Date study became aware of event
- Subject Death
    - Date study became aware of death
    - Relatedness of death
    - System Explant Information
- System Modification
    - Justification for explanted product not being returned to Medtronic

- Deviations

Device data from transmissions will be uploaded to secure servers. Save-to-disk data collected at office visits will be sent to Medtronic. Upon receipt, device data will be maintained with databases and retrieved for analysis and reporting.

The sponsor or a regulatory authority may audit or inspect the study center to evaluate the conduct of the study. The clinical investigator(s)/institution(s) shall allow study related monitoring, audits, IRB review and regulatory inspection by providing direct access to source data/documents.

It has been determined that a data monitoring committee (DMC) would not be appropriate for this feasibility study.

15 WARRANTY/INSURANCE

Warranty information is provided in the product packaging for the commercially released CRT-D device and additional copies are available upon request.

Medtronic maintains appropriate Clinical Trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the IRB.

16 MONITORING

It is the responsibility of Medtronic to ensure proper monitoring of this clinical study. Trained Medtronic personnel or delegates appointed by Medtronic may perform study monitoring at the study center in order to ensure that the study is conducted in accordance with the CIP, the Clinical Trial Agreement, and applicable regulatory and local requirements. Medtronic, or delegates, must therefore be allowed access to the subjects' case histories (clinic and hospital records, and other source data/documentation) upon request as per the Subject Informed Consent, Research Authorization (where applicable) and Clinical Trial Agreement. The investigator should also be available during monitoring visits.

16.1 Monitoring Visits

Frequency of monitoring visits may be based upon subject enrollment, duration of the study, study compliance, number of adverse events, number of deviations, findings from previous monitoring visits and any suspected inconsistency in data that requires investigation. Regulatory documents may be reviewed at each study center. Monitoring for the study, including site qualification visits, site initiation visits, interim monitoring visits, and closeout visits, will be done in accordance to the study-specific monitoring plan.

Monitoring visits may be conducted periodically to assess site study progress, the investigator's adherence to the CIP, regulatory compliance including but not limited to

IRB/IRB approval and review of the study, maintenance of records and reports, and review of source documents against subject eCRFs. Monitors review site regulatory and study compliance by identifying findings of non-compliance and communicating those findings along with recommendations for preventative/corrective actions to site personnel. Monitors may work with study personnel to determine appropriate corrective action recommendations and to identify trends within the study or at a particular center.

17 REQUIRED RECORDS AND REPORTS

17.1 Investigator records

The investigator is responsible for the preparation and retention of the records cited below. All of the below records, with the exception of case history records and case report forms, should be kept in the Investigator Site File (i.e., the study binder provided to the investigator) or Subject Study Binder. Electronic CRFs must be maintained and signed electronically within the electronic data capture system during the study. The following records are subject to inspection and must be retained for a period of two years (or longer as local law or hospital administration requires) after product approval or the date on which the investigation is terminated.

- All correspondence between the IRB, sponsor, monitors, FDA or other regulatory agencies, including required reports that pertain to this study
- Subject's case history records, including:
    - Signed and dated informed consent form signed by subject.
    - Observations of adverse events/adverse device effects/device deficiencies
    - Medical history
    - Implant and follow-up data (if applicable)
    - Documentation of the dates and rationale for any deviation from the protocol
- List of investigation sites
- Financial disclosure
- Normal value(s)/range(s) for subject and clinical laboratory test
- Lab certificate (if applicable)
- Disposition Logs including, but not limited to, record of receipt, use, or disposition of investigational software, device serial number, subject ID, date of turning ON and OFF OptiVol Care Alerts
- All approved versions of the CIP and PIC
- Signed and dated Clinical Trial Agreement
- Current curriculum vitae of principal investigators
- Documentation of delegated tasks
- IRB approval documentation. Written information that the investigator or other study staff, when member of the IRB, did not participate in the approval process. Approval documentation must include the IRB composition, where required per local law.

- Regulatory authority notification, correspondence and approval, where required per local law
- Study training records for site staff
- Any other records that FDA and local regulatory agencies require to be maintained (e.g. financial disclosure)
- Final Study Report including the statistical analysis

17.2 Investigator reports

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all case report forms, adverse events and adverse device effects (reported per the country-specific collection requirements), device deficiencies, deaths, and any deviations from the clinical investigation plan; other reports are listed in Table 12. If any action is taken by an IRB with respect to this clinical study, copies of all pertinent documentation must be forwarded to Medtronic in a timely manner. Reports are subject to inspection and to the retention requirements as described above for investigator records.

Safety data investigator reporting requirements are listed in section 10 of the Adverse Event section. The investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in this section.

Medtronic records and reports will be maintained in a password-protected document management system, and paper documents (where applicable) will be stored in stored in secured file cabinets at Medtronic during the course of this study.

After closure of the study Medtronic will archive records and reports indefinitely.

Table 20: Investigator reports applicable for all geographies per Medtronic requirements

Report	Submit to	Description/Constraints
Withdrawal of IRB approval	Sponsor and Relevant Authorities	The investigator must report a withdrawal of approval by the reviewing IRB of the investigator's part of the investigation within 5 working days.
Study Deviations	Sponsor and IRB	Any deviation from the clinical investigational plan shall be recorded together with the explanation of the deviation. Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Except in such emergency, prior approval is required for changes in the plan or deviations.
Final Report	IRBs and Relevant Authorities	This report must be submitted within 3 months of study completion or termination.

Table 21: Additional Investigator reports applicable to the United States per FDA regulations

Report	Submit to	Description/Constraints
Withdrawal of IRB approval (either suspension or termination)	Sponsor	The investigator must report a withdrawal of approval by the reviewing IRB of the investigator's part of the investigation within 5 working days. *(21 CFR 812.150(a)(2))*
Progress report	Sponsor and IRB	The investigator must submit this report to the sponsor and IRB at regular intervals, but in no event less than yearly. *(21 CFR 812.150 (a)(3))*.
Study deviations	Sponsor and IRB	Notice of deviations from the CIP to protect the life or physical wellbeing of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Except in such emergency, prior approval is required for changes in the plan or deviations. If the deviation may affect the scientific soundness of the plan or the rights, safety and welfare of the subjects, the deviation must be approved by Medtronic, the IRB, and the FDA/applicable regulatory authorities. If the deviation does not affect these issues then only Medtronic must approve it. *(21 CFR 812.150(a)(4))*
Failure to obtain informed consent prior to investigational device use	Sponsor and IRBs	If an investigator uses a device without obtaining informed consent, the investigator shall report such use within 5 working days after device use. *(21 CFR 812.150(a)(5))*
Final report	Sponsor IRBs Relevant Authorities	This report must be submitted within 3 months of study completion or termination of the investigation or the investigator's part of the investigation. *(21 CFR 812.150(a)(6))*
Other	IRB and FDA	An investigator shall, upon request by a reviewing IRB, FDA or any other regulatory agency, provide accurate, complete, and current information about any aspect of the investigation. *(21 CFR 812.150(a)(7))*

Table 22: Sponsor reports for the United States

Report	Submit to	Description/Constraints
Withdrawal of IRB approval	Investigators, IRB, FDA, and relevant authorities	Notification within five working days. *(21 CFR 812.150(b)(2))*
Withdrawal of FDA approval	Investigators, IRB, and relevant authorities	Notification within five working days. *(21 CFR 812.150(b)(3))*
Investigator List	FDA	Submit at 6-month intervals, a current list of the names and addresses of all investigators participating in the investigation. *(21 CFR 812.150(b)(4))*
Progress Reports	IRB and FDA	Progress reports will be submitted at least annually. *(21 CFR 812.150(b)(5), 812.36(f)*

Report	Submit to	Description/Constraints
Recall and device disposition	Investigators, Head of Institution, IRB, relevant authorities, and FDA	Notification within 30 working days and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices. *(21 CFR 812.150(b)(6))*
Failure to obtain informed consent	FDA	Investigator's report will be submitted to FDA within five working days of notification. *(21 CFR 812.150(b)(8))*
Final report	Investigators, IRB, Regulatory authorities upon request, and FDA	Medtronic will notify FDA within 30 working days of the completion or termination of the investigation. A final report will be submitted to the FDA, investigators, and IRBs within six months after completion or termination of this study. *(21 CFR 812.150(b)(7))*
Study deviation	Investigators	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation. Site specific study deviations will be submitted to investigators periodically.
Other	IRB, FDA	Accurate, complete, and current information about any aspect of the investigation. *(21 CFR 812.150(b)(10))*

APPENDIX A: DRAFT DATA COLLECTION ELEMENTS (CASE REPORT FORMS)

Draft Case Report Forms for the INTERVENE-HF study will be provided under separate cover. Final eCRFs will be provided to sites via the electronic data management system after the site has fulfilled all requirements for database access.

APPENDIX B: ISCC REPORTS TO PHYSICIAN

Below are sample reports that will be sent to the participating physician by ISCC at defined moments during the study. Each form has an area for customized text, so the form can be updated with notes and/or other information pertinent to the subject.

The investigator will be contacted by ISCC with the following reports in the following circumstances:

1) Medication Evaluation Report:

Medical evaluation report if any of three chronic med/PRN med evaluation criterion met.

- Mean 90 day impedance less than 66 Ω
- Not recovered after 2 PRNs were initiated in the same treatment protocol
- Two or more PRN diuretic titrations in the last 3 months

2) Interim Patient Report:

- Initiation of PRN 1
- Initiation of PRN 2
- If unable to contact the patient within 8 days of intervention trigger
- If unable to contact the patient within 4 days of PRN 2 start date
- If patient is contacted and OptiVol is found to non-HF related
- Safety criteria met during Integrated Diagnostic Medication Intervention Strategy

3) Exception Report:

- Alert criterion based on external diagnostics met outside PRN execution window
- Cessation of PRN intervention due to meeting safety criteria during PRN

Medical Evaluation Report Sample

CARDIOCOM
EXPERTS IN TELEHEALTH

7/15/2015 - 8/4/2015

MULTIDISEASE, BARBARA

Chart ID 12003 **DOB** 2/20/1948 Physician Dr. Shareen
Phone 555-555-5555

Medication	*This List May Not Be Complete And Must Be Verified*					**Provider Comments**
Carvedilol	6.25 mg	bid	CARVEDILOL TARGET DOSE:	25 mg	bid	
Hydralazine	37.5 mg	qid	HYDRALAZINE TARGET DOSE:	75 mg	qid	
Lasix Baseline Dose	20 mg	bid	Lasix PRN:	20 mg	QD x 3 Days	
Lisinopril	5 mg	daily	LISINOPRIL TARGET DOSE:	20 mg	daily	

Notes
Please evaluate need for baseline medication change due to 2 or more PRN diuretic titrations in the past 3 months.

8/4/2015 2:16 PM Page 1 Of 1

Interim Patient Report Sample

CARDIOCOM®
EXPERTS IN TELEHEALTH℠

Phone: 1-888-555-1212
Fax: 1-888-555-1212
Email: test@test.com

Interim Patient Report

Time Zone: Eastern
Report ID: 7386

Patient Name:	Maggie Welbersch
Patient ID:	
DOB:	12/19/1932
Gender:	Female
Address	1010 Bronson St
	Palatka , FL 32177
Patient Phone:	555-555-5555
Diagnosis Code:	
Chart ID:	30201

Physican Name:	Mariajosefina Rivera
Institution Name:	
Address	
Physican Phone:	386-325-8002
Physican Fax:	

Device:	CRT_D
Period	Jul 05, 2015 - Aug 04, 2015

Provider Considerations

High Risk CareAlert Received – 1st Round PRN diuretic initiated

60 ohm fluid threshold crossed

- Fluid Index crossing >60 ohm (corresponding to a significant reduction in intrathoracic impedance) is associated with increased risk of HF events. The etiology and severity can only be assessed by reviewing other device diagnostics and clinical assessment.

Patient activity averages < 1 hour/week or trending below baseline

- Decreased activity may be an indicator of progression of HF symptoms or reduction in functional capacity

Experienced new or worsening shortness of breath in the past week

Has been awakened by new or worsening shortness of breath or sensations of smothering in the past week

Clinical Status

Weight Change: gain 2.4lbs / 1 day
Today's Weight: 156.9
BP: 122/61
HR: 62

OptiVol CareAlert received. Contacted patient and instructed to take 1st round PRN diuretic per MD order of 40 mg of Lasix for 3 days.

Provider Care Plan

(Cardiocom is unable to accept nor act upon provider orders)

Small, R.; Rathman, L. (2008, April). Clinicians Practical Guide for Using OptiVol and Other Trends for Managing Heart Failure Patients. Retrieved from http://optivol.medtronic.com/wcm/groups/mdtcom_sg/@mdt/documents/documents/clinicanguideoptivolhfv2

Exception Report Sample Page 1 of 3

CARDIOCOM
EXPERTS IN TELEHEALTH

7/15/2015 - 8/4/2015

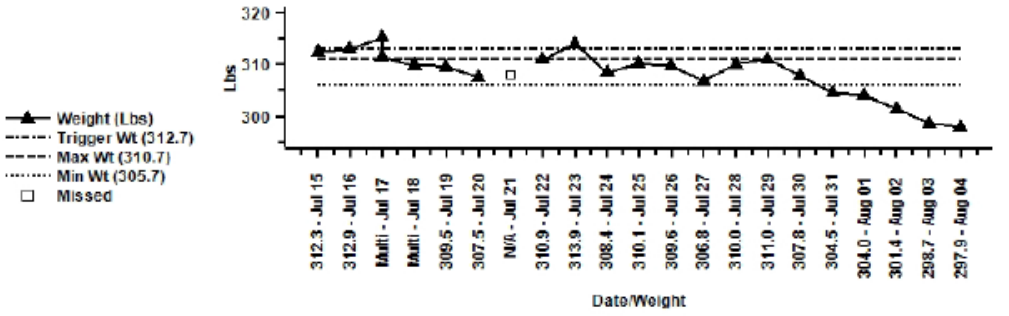
Avery, Rose

Chart ID 32502 **DOB** 1/31/1968 **Physician** Dr. Mondello

Phone 555-555-5555

Weight Graph

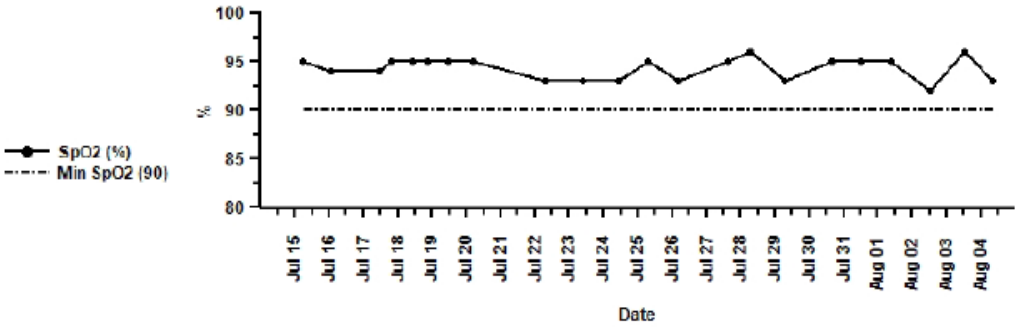
Highest Wt: 315.0 Lbs Lowest Wt: 297.9 Lbs Average Wt: 308.3 Lbs



NA - Missed Day H - Hospital A - Away From Home NH - Nursing Home ER - Emergency Room

Pulse Oximeter Graph

Highest SPO2: 96% Lowest SPO2: 92% Average SPO2: 94%



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Exception Report Sample Page 2 of 3

CARDIOCOM
EXPERTS IN TELEHEALTH

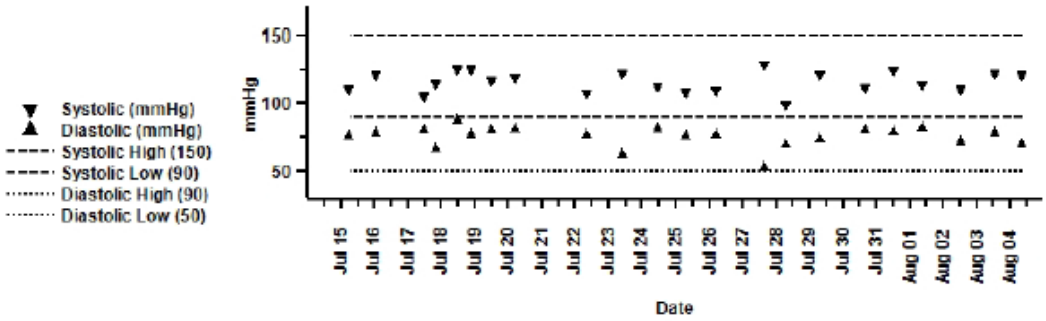
Exception Report

7/15/2015 - 8/4/2015

Avery, Rose

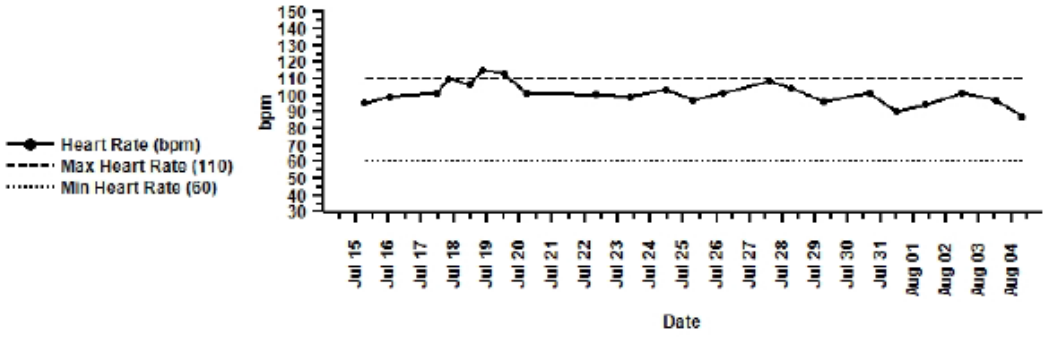
Blood Pressure Graph

Highest SBP: 128 mm/hg Lowest SBP: 99 mm/hg Average SBP: 116 mm/hg
Highest DBP: 87 mm/hg Lowest DBP: 53 mm/hg Average DBP: 75 mm/hg



Heart Rate Graph

Highest HR: 115 bpm Lowest HR: 87 bpm Average HR: 101 bpm



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Exception Report Sample Page 3 of 3

CARDIOCOM
EXPERTS IN TELEHEALTH

Exception Report

7/15/2015 - 8/4/2015

Avery, Rose

Medication *This List May Not Be Complete And Must Be Verified*						Provider Comments
Abilify			Advair Diskus			
Ambien			Amitriptyline			
Aspirin			BuSpar			
Carvedilol	25 mg		Clonazepam			
Cyclobenzaprine			Digoxin	.125 mg	daily	
Fenofibrate			Fish Oil			
Humulin	ss		Isosorbide	30 mg	daily	
Lasix	80 mg	bid	Lipitor			
Lomotil			Losartan			
Lyrica			Metformin			
Metoprolol	50 mg		Niacin			
Nitroglycerin			Nystatin			
Oxycodone			Oxygen	4L		
Potassium Chloride	10 mEq	bid	Prednisone			
Promethazine			Propranolol	60 mg		
Quetiapine			Singulair			
Spironolactone	25 mg	daily	Theophylline			
Valium			Venlafaxine			

Symptom Detail *Markers Indicate Symptomatic Response*	Jul 15	Jul 16	Jul 17	Jul 18	Jul 19	Jul 20	Jul 21	Jul 22	Jul 23	Jul 24	Jul 25	Jul 26	Jul 27	Jul 28	Jul 29	Jul 30	Jul 31	Aug 01	Aug 02	Aug 03	Aug 04
More tired or fatigued than usual																					●
Harder time doing normal activities today												●									
Problems with coughing last night																	●				
Woke up suddenly from sleep last night SOB				●																	
Stomach more swollen or bloated		●	●	●	●	●		●	●	●	●	●	●	●	●	●	●	●	●	●	●
Cough was worse when lying down																	●				

Last Note

8/4/2015 - 2:21 PM - Patient alerted for weight loss, down ~12 pounds in the last 6 days status post round 2 PRN diuretic initiation 2 days ago. BP noted to be stable, averaging 116/75, despite steady BP - patient does note increased lightheadedness, increased lightheadedness with position changes. Reviewed safety precautions with position changes, instructed to D/C PRN diuretic at this time - understanding expressed. Patient states she has lab follow up on Thursday per diuretic protocol. Will continue to monitor.

APPENDIX C: INFORMED CONSENT TEMPLATES

The Patient Informed Consent template for INTERVENE-HF will be provided under separate cover.

APPENDIX D: PARTICIPATING INVESTIGATORS AND INSTITUTIONS

At the time of INTERVENE-HF Clinical Investigation Plan Version 1.0 completion, center confirmation was not finalized. A complete list of participating investigators and institutions where study activities will be conducted will be distributed under a separate cover when available.

APPENDIX E: COMMITTEES

A complete list of committees used for this study (including steering committee) will be provided, distributed and updated under separate cover.

APPENDIX F: IRB

At the time of INTERVENE-HF Clinical Investigation Plan Version 1.0 completion, center confirmation was not finalized. Therefore, a complete list of participating IRBs and the Chairperson(s) will be distributed under a separate cover when available.

APPENDIX G: LABELING

Since the INTERVENE-HF software will be distributed electronically through the Software Distribution Network (SDN), physical media labeling is not required. INTERVENE-HF Research System set-up instructions will be included in the User Manual.

Investigational labeling requirements for the software INTERVENE-HF User Manual will include the following statement:

“CAUTION-Investigational device. Limited by Federal Law (USA) to Investigational use.”

APPENDIX H: BIBLIOGRAPHY

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APPENDIX I: PRELIMINARY PUBLICATION PLAN

If findings from this study are to be published, the following plan will be handled according to Cardiac Rhythm Disease Management Standard Operating Procedures and as indicated in the Clinical Trial Agreement.

Publication Committee

Medtronic may form the INTERVENE-HF Publication Committee from study investigators. Medtronic personnel may serve as members of the committee. This committee will manage study publications with the goal of publishing findings from the data. The Publication Committee will develop the final Publication Plan as a separate document.

The Publication Committee's role is to: 1) manage elements addressed in the publication plan as outlined in this appendix, 2) develop the final Publication Plan under separate cover, 3) execute the Publication Plan, 4) oversee the publication of primary, secondary and ancillary study results, 5) review and prioritize publication proposals, 6) provide input on publication content, and 7) determine authorship. In addition, the committee will apply and reinforce the authorship guidelines set forth in the Publication Plan.

Membership in the Publication Committee does not guarantee authorship. The committee will meet at as needed.

Management of Primary, Secondary and Ancillary Publications

The Publication Committee reviews, prioritizes, and manages all publications including primary, secondary and ancillary publications. Primary and secondary publications are those that address analyses of any or all primary objectives or secondary objectives, respectively, as specified in the Clinical Investigation Plan.
An ancillary publication is any publication that does not address the study objectives identified in the Clinical Investigation Plan. They include publications proposed and developed by other Medtronic departments or entities, clinicians participating in this clinical study, and clinicians not participating in this clinical study. The committee will work with Medtronic to ensure that requests do not present conflicts with other proposals, are not duplicative, and to determine which ancillary publication proposals, if any, will be supported. The committee may decide that no publications, including abstracts, will be published prior to the end of the study or with individual center data. Requests for publications on study objectives utilizing subset data (e.g., regional) will be evaluated for scientific validity and the ability of Medtronic to provide resources.

Criteria for Determining Authorship

Publications will adhere to authorship criteria defined by the International Committee of Medical Journal Editors (ICMJE, Uniform requirements for manuscripts submitted to biomedical journals, www.icmje.org). Individual authorship criteria defined by the target journal or conference will be followed when it differs from ICMJE criteria.

Authors, including Medtronic personnel, must at a minimum meet all of the conditions below:

- Substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data
- Drafting the article or revising it critically for important intellectual content
- Final approval of the version to be published

Decisions regarding authorship and contributor-ship will be made by the committee. The selected authors will be responsible for drafting the publication. All selected authors must fulfill the authorship conditions stated above to be listed as authors, and all contributors who fulfill the conditions must be listed as authors.
All investigators not listed as co-authors will be acknowledged as the “Medtronic INTERVENE-HF Clinical Study Investigators” and will be individually listed according to the guidelines of the applicable scientific journal when possible and affiliation. Any other contributors will be acknowledged by name with their specific contribution indicated.

Transparency

Transparency of study results will be maintained by the following means:

- a final report, describing the results of all objectives and analysis, will be distributed to all investigators, IRBs and Competent Authorities of participating countries when required by local law
- registering and posting the study results on ClinicalTrials.gov based on the posting rules stipulated
- submitting for publication the primary study results after the study ends
- disclosing conflicts of interest (e.g., financial) of the co-authors of publications according to the policies set forth by the corresponding journals and conferences
- making an individual centers study data accessible to the corresponding investigator after the completion of the study, if requested

APPENDIX J: ABBREVIATIONS

AE	Adverse Event
ADE	Adverse Device Effect
AF	Atrial Fibrillation
BPM	Beats Per Minute
CEC	Clinical Events Committee
CIP	Clinical Investigation Plan
CRT	Cardiac Resynchronization Therapy
CRT-D	Cardiac Resynchronization Therapy device with defibrillation capabilities
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
DMC	Data Management Committee
DTL	Delegated Task Log
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EP	Electrophysiology
FDA	Food and Drug Administration
GEE	Generalized Estimating Equation
HCU	Health Care Utilization
HF	Heart Failure
HFH	Heart Failure Hospitalization
HFRS	Heart Failure Risk Status
HIPAA	Health Insurance Portability and Accountability Act
HRV	Heart Rate Variability
ID	Integrated Diagnostics
IDE	Investigational Device Exemption
INTERVENE	Integrated Diagnostics Driven Diuretic and Chronic Medication Management
IRB	Institutional Review Board
ISCC	INTERVENE Study Communication Center
NHR	Night Heart Rate
PA	Pulmonary Artery
PIC	Patient Informed Consent
PRN	*Pro re nata*, used as abbreviation for the medication intervention
S2D	Save-to-Disk
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SAV	Sensed Atrioventricular
SCD	Sudden Cardiac Death
SDN	Software Distribution Network
SOP	Standard Operating Procedure
UADE	Unanticipated Adverse Device Effect
US	United States
USADE	Unanticipated Serious Adverse Device Effect
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia

APPENDIX K: MODIFICATIONS TO THE CLINICAL INVESTIGATION PLAN

This table will be used to summarize modifications made from current version 1.0 of the Clinical Investigation Protocol (CIP).

Table 23: Change history

Version	Applicable Sections	Change	Rationale
1.0	Initial Document	NA	NA
2.0	Cover Page	Added final IDE#	IDE# was not assigned at the time of CIP approval.
2.0	Risk Analysis Section 11	Added additional information regarding proposed care management plan vs. standard of care, risks associated with proposed care management, and battery life impact.	FDA conditional approval requirement
2.0	Statistical Section 13	Updated to include plan for a preliminary safety data analysis report.	FDA conditional approval requirement
3.0	Exclusion Criteria Section 5.2.2 & Bloodwork Eligibility Section 7.7.2	Corrected units on hemoglobin levels from mg/dl to g/dl	Clerical error

4.0	Table 1, 3.2, Inclusion Criteria 5.2.1, Exclusion Criteria 5.2.2, Screening Visit 7.7, 13, Throughout	• Table 1: updated trial lead name to Joe Hobbs • 3.2: added recommended for daily transmissions • 5.2.1 Revised Subject inclusion criteria to clarify that patient needs >9 of CRT therapy and not 9 months with current device, removed Medtronic only leads, added OptiVol crossing in the last nine months as an additional OR for inclusion, removed renal testing • 5.2.2 removed renal test from exclusion criteria • 6.4.2: deleted word daily • 7.7 Screening visit removed test after passing OptiVol crossing • Changed language to only include patients that have passed screening in analysis • Throughout: removed the word Fax(ed)	• Clerical • 3.2 revised to clarify daily commander flex transmissions are not required but requested • Inclusion was revised to expand the patient pool, internal analysis showed subjects that have had an OptiVol crossing in the last 9 months are likely to have another in the next year, streamlining testing to allow for standard of care for renal testing on file • Exclusion was revised to allow for streamlining when enrolling and adhere to sites standard of care • revised to clarify daily commander flex transmissions are not required but requested • removed word daily to clarify that transmissions are requested not required • Renal testing was expanded to allow for values on file with in six months to allow for smoother screening and follow sites standard of care • Clarified analysis to include only patients that passed screening

Version	Applicable Sections	Change	Rationale
			• Fax(ed) was removed to allow for additional secure file transfer systems.
5.0	6.2.2	Changed: make arrangements for ~~schedule~~	Allows for manual downloads when a follow up download cannot be scheduled on the correct day
	Figure 6	Added: (when possible)	Same as above
	Figure 7	Added: (when possible)	Same as above
	6.4.1.2	Changed: a total of 8 subsequent attempts ~~up to 8 days; scheduled download~~CareLink transmission	Same as above
	6.5.1	Added: will be asked to provide	To clarify that daily commander flex transmissions are not required but requested
	6.6	Deleted: all of section 6.6	HCU information is collected within the AE eCRF and not in a standalone form
	7.4 (Table 12)	Changed header to: scheduled call	Same as above
	7.14	HCU removed from exit section	Same as above

Version	Applicable Sections	Change	Rationale
	10.1	Added: The initiation of an PRN by the ISCC nurse will not be considered an AE and CareLink connectivity related DD will not be collected on an eCRF	Initiation of a PRN is collected on the ISCC notification form and does not need to be collected as an AE, CareLink connectivity issues are reported via complaint handling by our ISCC nurses and do not need to be collected on the device deficiency eCRF
	10.2.1	Added: Added: An exception to this subset of collected events mentioned above, would be the protocol-initiated PRN intervention, which will not be collected on the Adverse Event form (AE CRF). When the protocol initiated PRN intervention occurs, it will be collected on the ISCC Notification form.	Same as change in 10.1
	10.2.2	Added: Device related issues that involve the subject's Carelink monitor will not be collected on the Device Deficiency form.	Same as change in 10.1
	Figure 8	Adjusted recovery calculation window	Adjusted days used in recovery calculation to reflect what is actually used