OptiLink HF Supplement

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This Supplement contains the following items:

1. **Original protocol, final protocol, summary of changes.**

2. Original statistical analysis plan, final statistical analysis plan, summary of changes

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Medtronic OptiLink HF Study
Clinical Investigation Plan

Version 3.0
October 12, 2008

Medtronic GmbH
Cardiac Rhythm Disease Management Clinical Cooperation

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Germany

Confidential

This clinical investigation plan was subject to critical review and has been approved by the following:

Principal Investigators

I agree that this clinical investigation plan contains all the information required to conduct this study.

By my signature below, I hereby certify that I have read, understood and agree to abide by all conditions, instructions and restrictions contained in this clinical investigation plan.

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1 SYNOPSIS

TITLE	OptiLink HF Study (Optimization of Heart Failure Management using Medtronic **Opti**Vol® Fluid Status Monitoring and Medtronic Care**Link**® Network)
AIM OF THE STUDY	The objective of the study is to establish whether the use of event-triggered HF-disease management through Medtronic's OptiVol® fluid status monitoring with an automatically generated wireless CareAlert® notification of the clinician via the Medtronic CareLink® Network can reduce cardiovascular related hospitalizations and the number of deaths in a subject population with HF and ICD / CRT-D treatment as compared to standard clinical assessment. As a measure for the reduction of hospitalizations and deaths the rate of all-cause deaths or cardiovascular related hospitalizations will be determined.
INDICATION	ICD / CRT-D indication for subjects with chronic heart failure
STUDY DESIGN	Prospective, multi-center, unblinded, 1:1 randomized, controlled study
STUDY DEVICES	Medtronic Inc., market approved, single- or dual-chamber ICD or CRT-D devices used within approved indication: 1) Access arm: Medtronic Virtuoso™ ICD or Concerto™ CRT-D system or subsequently market released devices providing at least the same functionality with fluid status monitoring OptiVol® and with CareLink® access (OptiVol® "ON" and CareAlert® "ON"), 2) Control arm: Medtronic Virtuoso™ ICD or Concerto™ CRT-D system or subsequent market released devices providing at least the same functionality without CareLink® access (OptiVol® "OFF").
STUDY CENTERS	20-30 centers specialized in ICD and CRT-D implantation and about 100 active satellite HF-management centers with access to Medtronic CareLink® Network
OBJECTIVE	To demonstrate a reduction in hospitalizations, number of deaths due to heart failure (35 and more days after the implantation) in ICD or CRT-D subjects with heart failure
INCLUSION CRITERIA	• Subjects have a Medtronic Virtuoso™ ICD single- **or** dual-chamber **or** Concerto™ CRT-D **or** subsequently market released Medtronic device providing at least the same functionality implanted, including device

replacement. Subjects with CRT-D must fulfill CRT-indication as described in the ESC guidelines for cardiac pacing and cardiac resynchronization therapy 2007: EF ≤ 35% and NYHA **III**, and LVEDD > 55 mm, and **QRS ≥ 120 ms**, and optimized therapy,

- Subjects with stable chronic heart failure (CHF) in New York Heart Association (NYHA) class II or III for at least 30 days and left ventricular ejection fraction of no more than 35% (most recent measurement within 6 months prior to randomization by echocardiography or contrast ventriculography, magnetic resonance or nuclear imaging, based on local practice), on optimal target or maximal tolerated dose of ACE-inhibitors or angiotensin receptor blockers, ß-blockers and diuretics if clinically indicated to reduce fluid retention and one of the following criteria:

  At least one hospitalization due to the heart failure within the last 12 months before enrollment or one course of ambulatory IV-or oral diuretic treatment or a BNP value of > 400 pg/ml or a NT-proBNP values > 450 pg/ml in subject < 50 years, > 900 pg/ml (50-75 years) and > 1800 pg/ml in subject of more than 75 years old within 30 days of enrolment,

- Written informed consent by the subject for study participation prior to clinical investigation plan specific procedures,
- The subject must be able and willing to comply with the clinical investigation plan and willing to remain available for follow-up visits to the study closure,
- Subjects or the subject's caregiver must be willing and able to use the Medtronic CareLink® monitor as instructed and to perform the required duties, if subject is randomized to the access arm.

EXCLUSION CRITERIA

- Subjects with chronic renal failure needing renal dialysis,
- Subjects with serum creatinine > 2.5 mg/dl, measured within 14 days prior to enrollment,
- Subjects with severe to very severe Chronic Obstructive Pulmonary Disease (COPD) as determined by physician and documented in medical records (Stage III and Stage IV),

  Subjects with suspected or confirmed COPD require a current test of lung function (not more than 12 months before inclusion). If the "forced expiratory volume" is < 1.0 L/sec, the subject may not participate in the study.

- Subjects on the heart transplantation list or subjects with transplanted hearts,
- Subjects listed for valve replacement or interventional valve therapy,
- Subjects with myocardial infarction (MI) within the last 40 days before implant. MI is defined by typical changes in biochemical markers

including troponin levels > 3 times the upper limits of normal and creatinine kinase < 2 times of upper limit, or with CKMB greater than the upper limit of normal, combined (for all enzymes) with at least one of the following ischemic symptoms, ECG changes consistent of diagnostic ST-T wave changes or pathologic Q waves or new LBBB,

- Subjects with stroke within 40 days prior randomization,
- Subjects who have had a percutaneous coronary intervention within 3 months prior to randomization,
- Subjects with cardiac surgery within 90 days of randomization,
- Subjects with complex and uncorrected Congenital Heart Disease,
- Subject's life expectancy is less than 18 months in the opinion of the physician,
- Subjects in situations that would limit participation, not eligible to receive a CareLink® monitor (e.g. hearing or speech impaired with no family member or caregiver available to assist, or those who spend extended periods abroad, or those who intend to enroll in a study that would preclude use of the monitor),
- Subject is participating in a concurrent intervention study,
- Subject or the subject's caregiver is unwilling to give consent for the release of information for the evaluation or to give additional consent for the release of subject medical and privacy data for CareLink® subjects,
- Subjects with exclusion criteria required by local law (age < 18, women who are pregnant or breastfeeding).

DURATION OF THE STUDY (PER SUBJECT)	At least 18 months per subject Data collection at baseline / enrollment, randomization, 6 months and every 6 months thereafter until the study exit
DURATION OF THE STUDY (OVERALL)	Planned duration of recruitment: 24 months First subject first visit: September 15, 2008 Last subject last visit: the end of March 2012
EFFICACY DATA AND SAFETY DATA	**Primary endpoint:** All-cause of death or unplanned admission to hospital for cardiovascular reason from day 35 after implantation until 18-month follow-up visit will be considered to determine the **rate of all-cause deaths or cardiovascular related hospitalizations within 18 months**. **Hospitalization is defined as an overnight stay or longer in a hospital**

environment or similar facility including admission to a day care facility.

Cardiovascular hospitalizations are defined as hospitalizations for:

- Heart failure (first or subsequent),
- Acute myocardial infarction,
- Unstable angina pectoris,
- Symptom-driven hospitalization for cardiac arrhythmia (atrial fibrillation, atrial flutter, supraventricular arrhythmias or ventricular arrhythmias),
- Stroke / cerebral vascular accidents.

Hospitalizations for elective CV procedures do not qualify as CV endpoint, this included planned admission for elective cardioversion of atrial fibrillation.

Secondary objectives and endpoints:

1) Number of HF-related hospitalizations during follow-up,
2) HF-related hospitalization,
3) Sum of follow-up days minus days alive and out of the hospital,
4) All-cause mortality,
5) Cardiovascular mortality,
6) HF-related hospitalization and all-cause mortality,
7) Quality of Life (QOL),
8) Health Economics.

Exploratory endpoint:

Number of all-cause hospitalizations during 18 months follow-up.

SAMPLE SIZE

1.000 subjects with single- or dual-chamber Virtuoso™ ICD system or Concerto™ CRT-D or subsequent market released devices providing at least the same functionality (500 per study arm, 60% subjects with stable chronic heart failure NYHA class III and 40% with NYHA class II)

STATISTICAL ANALYSES

Confirmative analyses: It is intended to show the superiority of OptiVol® fluid status monitoring with automatically generated wireless CareAlert® notification of clinician via the Medtronic CareLink® in comparison to standard clinical assessment related to the primary variable rate of all-cause death or cardiovascular related hospitalization. This will be investigated by means of Fisher's Exact test one-sided.

Additional analyses exploratorily: The number of days alive out of hospital as well as the number of hospitalizations of different types will be determined and investigated using Wilcoxon rank-sum test. Time to event analyses

(hospitalization or death, hospitalization, death each of different types etc.) will be performed using survival time methods. Rates for different types of mortality and/or hospitalization will be determined and investigated by means of Fisher's exact test.

All other variables will be analyzed descriptively i.e. summary statistics for location and dispersion will be determined for continuous variables and frequencies and percentages for discrete variables.

Randomization: according to risk-stratification.

STUDY SPONSOR	Medtronic GmbH
STUDY MANAGEMENT	Dr. Manfred Eichenlaub

2 INTRODUCTION

2.1 Purpose of the Study

The purpose of the study is to demonstrate that an automatic, implantable monitoring system identifying increased pulmonary volume status should be able to identify subjects at risk for imminent decompensation and, consequently hospitalization of worsening of heart failure. We hypothesize that early recognition and ambulatory management of progressive pulmonary congestion avoids HF- decompensation and hospitalization. In this respect, we anticipate that the use of an event-triggered heart failure disease management through Medtronic's OptiVol® fluid status monitoring with automatically generated wireless CareAlert® notification of the clinician via the Medtronic CareLink® Network (access arm) can prolong the time to hospitalization, reduce hospitalizations, the number of deaths and all other interventions for worsening of heart failure in subjects with heart failure that have an indication for ICD or CRT-D implantation (CRT-indication as described in the ESC guidelines for cardiac pacing and cardiac resynchronization therapy 2007: EF ≤ 35% and NYHA III, and LVEDD> 55 mm, and QRS ≥ 120 ms, and optimized therapy).

Hospitalizations, secondary to worsening signs and symptoms of HF, represent a major challenge in the management of heart failure. Early intervention after detection of pulmonary congestion may be a key element in avoiding hospitalizations due to cardiovascular decompensation. The OptiVol® fluid status monitoring may reduce the rate of hospitalizations in subjects suffering from decompensated heart failure. We anticipate that OptiVol® will enable early ambulatory intervention in subjects with HF in whom OptiVol® has detected increased pulmonary congestion. Previous observations (MID-HeFT-study[a], In-Sync-Sentry-Registry[b]) have shown a significant correlation between the beginning of a pulmonary congestion and measured intrathoracic impedance. In fact, about 70% of all alert events revealed the beginning of a pulmonary congestion, despite the fact that clinical symptoms of decompensated heart failure are not identifiable yet.

The use of CareLink® Network allows both the study center and the satellite clinic to have access at the same time to the information about the appearance of CareAlert® by a text message (SMS) or an e-mail. The satellite-clinics can be a cardiologic/internistic out-patient clinic or in-patient clinic. This enables an event-triggered HF-disease management, as a CareAlert® of the responsible satellite-clinic and the study center results in a phone contact with the affected subject as first and early disease management step.

[a] Yu CM, Wang L, Chau E *et al.* Intrathoracic impedance monitoring in patients with heart failure: correlation with fluid status and feasibility of early warning receding hospitalization. *Circulation.* 2005; 112: 841–848.

[b] Vollmann D, Nägele H, Schauerte P *et al.* Clinical utility of intrathoracic impedance monitoring to alert patients with an implanted device of deteriorating chronic heart failure. *European Heart Journal*. 2007; 28: 1835–1840.

2.2 Background

Over the last 5 years, the indications for implantable defibrillators (ICDs and CRT-Ds) have expanded greatly[c,d,e], resulting in an increase in ICD and CRT-D utilization, and also burden on healthcare providers. Currently, in Germany follow-up visits for routine ICD / CRT-D device check are scheduled every 3-6 months according to international recommendations[f,g], however many of these routine device checks result in no programming or device changes, and many patients have no clinically significant events between visits. The follow-up process is an ambulatory care and depends on the "initiative of the patient". Usually patients go to general practitioners (GPs) first with possible subsequent referral to an ambulatory cardiological specialist, either in an out-patient or in-patient clinic. In case of emergency the patient in addition gets referral to a hospital specialist sector. The existing separation between out-patient and in-patient care results in duplication of service and procedures, lack of coordination between sectors, and high travel costs by multiple transportations of the patient. In addition to the increased number of patients a clinic needs to manage, these patients have increasingly more complex comorbidities, such as heart failure. The diagnostic features in ICDs / CRT-Ds, such as those in Medtronic's HF-Management Report and Cardiac Compass® Trends, provide clinicians access to more data to help to manage these situations. However, as the amount of data increases, clinicians need tools to help them turn it from data into meaningful information. Patient management initiatives focusing on streamlining access to data, as well as allowing clinicians to better triage patients could increase efficiencies and reduce the burden on the health care system. Monitoring disease progression is also important to managing ICD / CRT-D patients. Many of these

[c] Moss AJ, Zareba W, Hall WJ *et al.* Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med*. 2002; 346: 877-883.

[d] Bardy GH, Lee KL, Mark DB *et al.* Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med*. 2005; 352: 225–237.

[e] Bristow MR, Saxon LA, Boehmer J *et al.* Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med*. 2004; 350: 2140–2150.

[f] Gregoratos G, Abrams J, Epstein AE *et al.* for the American College of Cardiology/American Heart Association Task Force on Practice Guidelines/North American Society for Pacing and Electrophysiology Committee to Update the 1998 Pacemaker Guidelines. ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee to Update the 1998 Pacemaker Guidelines). *Circulation*. 2002; 106: 2145–2161.

[g] Wilkoff, BL, Auricchio A, Brugada J *et al.* HRA/EHRA Expert Consensus on the monitoring of cardiovascular implantable electronic devices (CIEDs): Description of Techniques, Indications, Personnel, Frequency and Ethical Considerations Europace 2008; 10(6): 707-725.

patients have heart failure. There is a need for the ability to monitor patients efficiently for changes in disease status.

Recently, two technologies to meet this need have been developed and already have been proven to work effectively. Both of them either measure directly or indirectly intra-cardiac pressure changes that occur during congestion in heart failure. Pulmonary and systemic congestion are earlier steps in the process of cardiac decompensation. Abnormal systolic and diastolic function lead to increase left ventricular diastolic pressure and impaired volume regulation. These in turn may be further aggravated by progressive activation of neurohormonal systems (sympathetic nervous system, rennin-angiotensin-aldosterone system, vasopressin). The increased blood volume and increased left ventricular diastolic pressure, often aggravated by mitral regurgitation, increase pulmonary capillary wedge pressure, which, in turn, lead to increased pulmonary artery pressure, increased right ventricular and atrial pressures, and tricuspid regurgitation. In addition, depending on the hydrostatic pressure of the pulmonary capillaries, the plasma oncotic pressure, the permeability and integrity of the alveolar capillary membrane, and the pulmonary lymphatic drainage of the lungs, the increased pulmonary capillary wedge pressure leads to redistribution of the excess fluid in the pulmonary vascular bed, interstitial edema and alveolar edema. All these processes constitute to the development of dyspnea in heart failure patients[h,i].

As mentioned before, technologies in implantable devices to measure physiologic signs for monitoring and early warning purposes of acute decompensated heart failure all use measures which can be obtained within the (patho)physiologic mechanism described above. For instance, the Chronicle Hemodynamic Monitor uses the Estimated Pulmonary Arterial Wedge Pressure (EPAD), defined as the right ventricular pressure at the time of maximal shown dp/dt.

The OptiVol® algorithm is an other way of measuring within the (patho)physiological process described before. Instead of measuring intracardial pressures, the change in thoracic impedance, resulting from the accumulation of excess fluid in the lungs is monitored and used as indicator for a deterioration of the patient's heart failure status. Both of these technologies, the Chronicle Hemodynamic Monitor as well as the OptiVol® algorithm use measures that change early in the process of cardiac decompensation.

Another attempt of observing the patients fluid status is measuring the body weight which should indicate fluid accumulation. However, whereas dyspnea and edema can be observed in the majority of patients seeking medical attention for decompensated heart failure, weight gain as result of fluid

[h] Constanza MR. Management of Volume Overload in Acute Heart Failure: Diuretics and Ultrafiltration, in: Acute Heart Failure. Springer 2008; Section 2.3, 503-518.

[i] Mebazaa A, Gheorghiade M, Zannad FM, Parrillo JE (Eds.). Acute Heart Failure. Springer 2008. XXVI, ISBN: 978-1-84628-781-7.

accumulation is a relatively late development in the process of decompensation representing only a late and unreliable measure to alert patients and caregivers.[j,k]

Pulmonary congestion rather than general fluid overload in peripheral organs is the primary cause of cardiac decompensation; i.e. fluid re-distribution rather than fluid overload may be the early key pathophysiological alteration as suggested by Cotter *et al.*[l]. This pathophysiological mechanism preceding clinical signs and symptoms of cardiac decompensation is thought to be related vascular mechanisms such as vasoconstriction as well as neurohormonal and inflammatory activation, renal dysfunction and inappropriate use of some medications. Both the slow development of elevated left ventricular filling pressures and pulmonary congestion are present in a majority of patients presenting with acute heart failure syndrome, however they are often clinically silent in these patients[m].

This early phase of hemodynamic congestion can be detected by the OptiVol® algorithm allowing early intervention to prevent clinical decompensation. The continuous monitoring of measures is key to early detect changes. Mullens *et al.*[n] demonstrated in a setting where patient data including intrathoracic impedance- and OptiVol®-data were transmitted and checked by caregivers every three months, that in 94% of the patients where OptiVol® values that crossed the fluid threshold signs and symptoms such as dyspnea, edema and weight gain could be observed. However, as 18% of these patients had HF-hospitalizations, the three-months interval of data check was not sufficient for a prevention of almost one fifth of these patients. In contrast, the combination of OptiVol® and CareLink® with a continuous daily check of threshold crossings offers the possibility to react within a very short time frame instead of three months as described in the setting used by Mullens *et al.*. Therefore, hospitalizations could be prevented by early detection of changes already in the phase of hemodynamic decompensation before signs and symptoms of clinical decompensation occur later in this continuum.

The Medtronic CareLink® Network (CareLink®) is one solution for continuously monitoring and to help clinicians targeting subjects that most need their attention and at the same time to reduce routine and interim clinic visits. With CareLink®, device data can either be transmitted automatically via

[j] Lewin JM, Ledwidge M, O'Loughlin C *et al.* Clinical deterioration in established heart failure: What is the value of BNP and weight gain in aiding diagnosis? *Eur. J. Heart Failure.* 2003; 7: 953-957.

[k] Verwey HF, Sweeney R. Patients Symptoms and device based activity for decompensated vs. nondecompensated heart failure patients. *J.Card. Fail*. 2005; 12: 170.

[l] Cotter G, Metra M, Milo-Cotter O *et al.* Fluid overload in acute heart failure — Re-distribution and other mechanisms beyond fluid accumulation. *Eur. J. Heart Failure*. 2008; 10: 165-169.

[m] Gheorghiade M, Filippatos G, De Luca L, *et al.* Congestion in Acute heart Failure Syndromes. *The American Journal of Medicine.* 2006; (12A) 119: 3-10.

[n] Mullens W, Abrahams Z, Skouri HN *et al.* Elevated Intra-Abdominal Pressure in Acute Decompensated Heart Failure: A Potential Contributor to Worsening Renal Function? *J. Am. Coll. Cardiol.* 2008; 51: 300-306.

wireless Conexus™ Telemetry or manually by the subject over the Internet. Clinicians can then login to a website and view the same data they would have access to if they had brought the subject in for a routine in-office clinic visit. Patients who need further attention can then be called in for a visit, and patients with no need to come in can avoid a trip to the office. In addition to reducing unnecessary routine visits, CareLink® can also reduce interim visits to the clinic or Emergency Department (ED), after an event such as a shock by allowing physicians remote access to subjects' data.

The new generation of Medtronic Concerto™ CRT-D or Virtuoso™ ICD provides wireless Conexus™ telemetry. These systems are able to automatically transmit data wirelessly to a monitor in the home. They also have enhanced diagnostic features, as well as the ability to deliver wireless (non-audible) alerts (CareAlerts®) that initiate a wireless transmission to notify physicians when clinical events occur. The combination of Medtronic's proprietary OptiVol® fluid status monitoring with automatically generated wireless CareAlerts® through the CareLink® Network alerts the clinician early about increased fluid accumulation in the subject's chest as a presymptomatic indictor of pulmonary congestion. Early intervention after detection of pulmonary congestion may be a key element in avoiding hospitalizations due to cardiovascular decompensation. For example, by being notified that a subject's thoracic impedance has crossed the OptiVol® threshold, it is possible that the subject's compliance regarding medication and the intake of fluid as well as the dose of heart failure medication can be adjusted, potentially reducing the need for an in-clinic visit or even hospitalization due to worsened heart failure condition and decompensation. The presymptomatic notification of worsening heart failure condition by OptiVol®, before decompensation status leads in a serious worsening/HF-hospitalization, is expected to provide adequate time for clinical decision making within the next days. Earlier detection and notification, combined with remote management may also have an economic effect of shifting healthcare utilization from emergency department visits and possibly subsequent hospitalization to ambulatory clinic visits, reducing cost and burden on the healthcare system. In addition, remote monitoring may improve subject well being by increasing quality of life.

This study has been designed to evaluate whether the combination of OptiVol® Fluid Status Monitoring and automatically generated CareAlerts® through CareLink® Network may help physicians to prevent cardiovascular hospitalizations and reduces mortality.

2.3 Product Descriptions and Intended Use

Subjects must be implanted with a Medtronic Inc., market approved, single- or dual-chamber Virtuoso™ ICD or Concerto™ CRT-D device or subsequent devices providing at least the same functionality, used within approved indication:

1) Access arm: Medtronic Virtuoso™ ICD system or Concerto™ CRT-D or subsequent devices providing at least the same functionality providing fluid status monitoring OptiVol® and with CareLink® access (OptiVol® "ON" and CareAlert® "ON"),

2) Control arm: Medtronic Virtuoso™ ICD system or Concerto™ CRT-D or subsequent devices providing at least the same functionality without CareLink® access (OptiVol® "OFF") in order to be considered for participation in the study.

2.3.1 Virtuoso™ ICD and Concerto™ CRT-D Study Device with Conexus™ Telemetry

The Medtronic Virtuoso™ ICDs and Concerto™ CRT-Ds provide technological advancements such as wireless telemetry (Conexus™ Telemetry), Cardiac Compass® Trends including OptiVol® fluid status monitoring and expanded alerts (Medtronic CareAlerts®) including wireless alerts for OptiVol® fluid status monitoring.

Optionally any future CE-approved and market-released Medtronic ICD / CRT-D device with Cardiac Compass® and OptiVol® fluid status monitoring that is supported by the Medtronic CareLink® Network may be incorporated into the study.

Model D164AWC Virtuoso™ DR / D164VWC Virtuoso™ VR devices are indicated to provide ventricular antitachycardia pacing and ventricular defibrillation for automatic treatment of life-threatening ventricular arrhythmias. The Virtuoso™ DR device is also indicated for use in the above subjects with atrial tachyarrhythmias, or those subjects who are at significant risk of developing atrial tachyarrhythmias. Atrial rhythm management features, available on the Virtuoso™ DR, such as Atrial Rate Stabilization (ARS), Atrial Preference Pacing (APP), and Post Mode Switch Overdrive Pacing (PMOP) are indicated for the suppression of atrial tachyarrhythmias in ICD-indicated subjects with atrial septal lead placement and an ICD indication.

The Model C154DWK / C174AWK Concerto™ CRT-D is indicated for ventricular antitachycardia pacing and ventricular defibrillation for automated treatment of life-threatening ventricular arrhythmias. In addition the system provides cardiac resynchronization therapy and is therefore indicated for the reduction of the symptoms of moderate to severe heart failure in those patients who remain symptomatic despite stable, optimal medical therapy, and have a left ventricular ejection fraction < 35% and a prolonged QRS duration.

2.3.2 OptiVol® Fluid Status Monitoring

OptiVol® fluid status monitoring calculates average daily intrathoracic impedance values to track changes in the subject's thoracic fluid status over time. In order to start taking impedance measurements, VF detection must be programmed "ON" in the device. OptiVol® fluid status monitoring calculates the average daily thoracic impedance by averaging 16 four-beat impedance measurements taken from the right ventricular defibrillation coil to the device case ("can") every 20 minutes from noon until 5 pm. Measurements are based on the time programmed in the device.

The reference impedance is established by the OptiVol® algorithm as a multi-day average of impedance, which reflects slower adaptations to fluid changes. The reference impedance reflects changes over time against which daily impedance changes can be compared. The reference impedance is initiated 34 days after implant to allow time for pocket healing and lead maturation. Daily impedance values for days 31-34 are averaged to get the initial reference line point. From then on, the reference impedance changes slightly from day to day to slowly adapt to the daily impedance.

The OptiVol® algorithm calculates the accumulated difference between the daily impedance and reference impedance. When the daily impedance values consistently fall below the reference impedance, the OptiVol® fluid index accumulates. When the daily impedance value increases above the reference impedance values, the OptiVol® fluid index returns to zero. The OptiVol® threshold (refer to section 2.3.3) can be programmed from 30 ohm/days to 180 ohm/days in increments of 10 ohm/days, at device implant or at follow-up device checks. If the OptiVol® fluid index crosses the physician-programmed OptiVol® threshold, an observation is triggered. The OptiVol® fluid index crossing the OptiVol® threshold may be an indicator of possible thoracic fluid accumulation. The daily impedance, reference impedance, OptiVol® threshold, and OptiVol® fluid index can be viewed via the OptiVol® fluid trends, a subset of the Cardiac Compass® Trends on the Cardiac Compass® Reports.

Ongoing research and development may lead to improvements of the OptiVol® algorithm used in the implantable ICD and CRT-D devices within the OptiLink HF study. In case such an improved algorithm becomes available as a CE-labeled download intended for use in the study devices, it can be used in patients already enrolled in the study and future patients as well. After information about the technical details and differences between the currently available OptiVol® algorithm and the improved one by the sponsor, the study executive committee will determine the exact mode of device-upgrade and use of such an improved algorithm in case it becomes available.

2.3.3 Reference Impedance Adjustment

There is one enhancement to the OptiVol® feature, which is of relevance for the OptiLink HF study: OptiVol® reference impedance adjustment.

The OptiVol® reference impedance adjustment enhancement provides study investigators with the option of reinitializing the reference impedance for those occasional cases in which the daily impedance measures are persistently lower than the reference impedance and the subject's pulmonary congestion status and daily impedance values are stable (e.g. stable, but changed HF-status after new titration of drugs; or set of original reference at time of hypovolumic status). Resetting the reference impedance will result in a new reference impedance measurement and will reset the OptiVol® fluid index to zero.

The OptiVol® reference impedance adjustment should only be utilized after thorough assessment and review of the subject and OptiVol® fluid trends. The reference impedance should only be adjusted when the following criteria have been met:

- Subject has stable pulmonary fluid status and

- OptiVol® trends show the subject's daily thoracic impedance is stable and

- Reference impedance has not adjusted to the subject's daily impedance.

Conditions known to potentially cause an OptiVol® threshold crossing include: system modification (e.g. lead or pocket revision) and initialization of the reference impedance during hypovolemic states. When the OptiVol® reference impedance adjustment is used, a new reference impedance will be calculated by averaging the last daily impedance measurement and the next 3 daily impedance measurements. The OptiVol® fluid index will also reset to zero. Once the reference impedance is adjusted, it cannot be reversed. Study center personnel must document the rationale for adjusting the reference impedance on the CRF on care alert evaluation form. Failure to provide rationale will result in a study deviation.

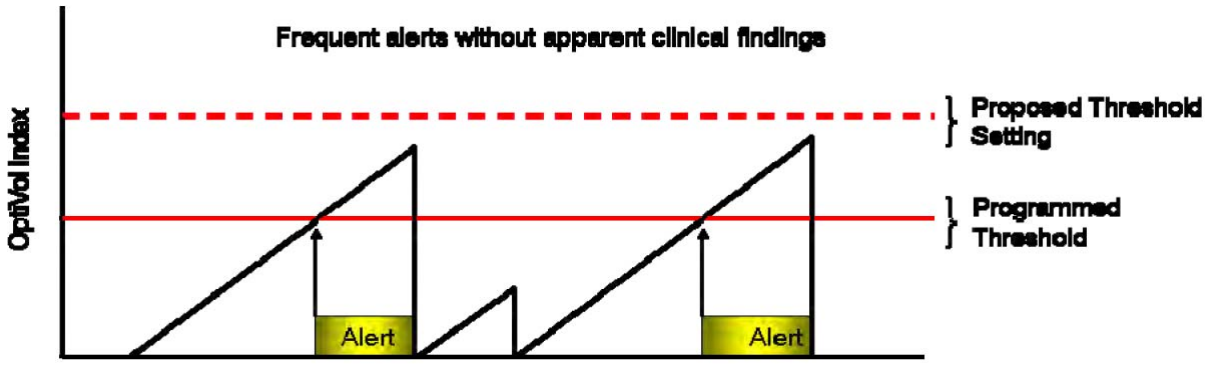
OptiVol® Threshold

The OptiVol® threshold can be programmed at the investigator's discretion to manage the balance between providing sufficient warning prior to significant fluid overload events (such as heart failure hospitalization) versus pre-clinical events and/or premature alerts/too early alerts. Currently, the nominal threshold value is 60 ohm/days, with programming options from 30-180 ohm/days in increments of 10 ohm/days.

It is recommended that the OptiVol® threshold is initially **programmed at 60 ohm/days**. In general, increasing the threshold will reduce the number of alerts, but may also delay or not prevent some clinically relevant alerts. Conversely, reducing the threshold will increase the number of alerts, but a larger portion may be less clinically meaningful. Though the need for threshold programmability is not expected to be high, a few clinical scenarios may warrant consideration for reprogramming the OptiVol® threshold on a subject-by-subject basis.

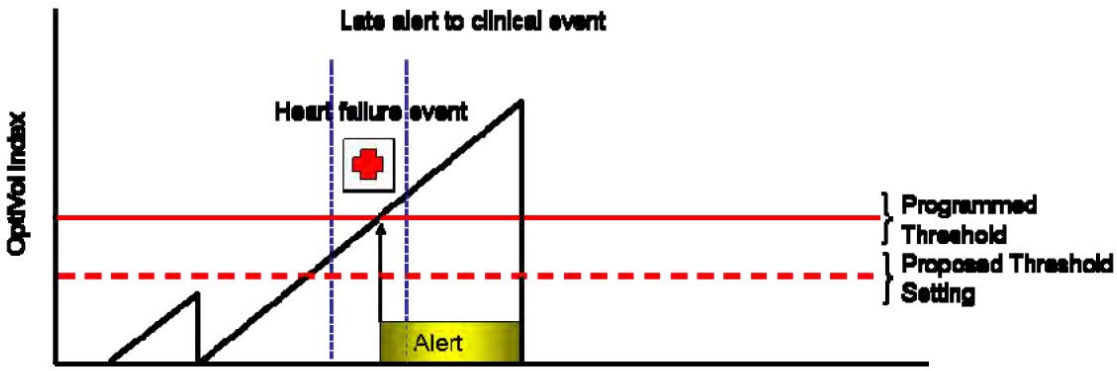
- Consider an increase of the threshold if the subject has frequent, separate low amplitude threshold crossings without any evidence of conditions that could influence intrathoracic impedance, such as new or worsening signs or symptoms congestion or of pocket edema/infection. Increase the threshold to a point above the peak of these threshold crossings. For example, if the threshold crossings that do not appear to be associated with clinical findings peak at about 80 ohm/days, consider reprogramming the OptiVol® threshold to 90 ohm/days.

Figure 1: Frequent alerts without apparent clinical findings



- Consider a decrease of the threshold if the crossing of the OptiVol® threshold occurs too late, meaning when the subject presents with clinical signs or symptoms of fluid overload. Consider reprogramming the OptiVol® threshold to a value that would provide sufficient warning.

Figure 2: Late alert to clinical event



Reprogramming of the OptiVol® threshold should only be done after thorough assessment and review of the subject and OptiVol® fluid trends. Study center personnel must document the rationale for reprogramming the OptiVol® threshold. Failure to provide rationale will result in a study deviation.

2.3.4 Medtronic CareLink® Network and Medtronic CareLink® Monitor

The Medtronic CareLink® Network is designed to monitor the implanted device's performance, as well as physiological aspects of the subject's condition recorded by the implanted device. **CareLink® does not allow for remote implanted device programming.** Reprogramming can only be done during an in-clinic visit. CareLink® consists of the CareLink® Network monitor which sends information to the secure CareLink® server via the telephone connection and the CareLink® Clinician Website with which subjects and/or clinicians interact.

CareLink® Network monitor is CE market approved and will be used for the study within the intended use. The monitor is a small device at the subject's home that interrogates (reads) and transmits data collected by the implanted device, referring to the functionality of the implanted system and data about the physiological and rhythm status of the subject. This data is comparable to the data obtained by interrogating the implanted device with a programmer. The monitor automatically dials a pre-programmed toll-free number to send the information to the secure CareLink® server via the telephone connection.

Monitors are configured to work specifically with an individual, pre-specified subject's implanted device. Therefore, each monitor is for the subject's personal use only and will not function appropriately with another subject's implanted device. Unauthorized use by others with the implanted devices could interrupt the prescribed operation of their device.

The Medtronic CareLink® Monitor Model 2490C for the Concerto™ CRT-D, Virtuoso™ ICD and subsequently released devices with Connexus™ Telemetry are indicated for use in the transfer of subject data from Medtronic implantable cardiac devices to the Medtronic CareLink® Network based on physician instructions and as described in the product manual. These products are not a substitute for appropriate medical attention in the event of an emergency and should only be used as directed by a physician.

The Medtronic CareLink® Network, a tool required at each study center, enables subjects to remotely transfer data from their device to the clinic. **Only subjects in the access arm are required to use the Medtronic CareLink® monitor, which plugs into a phone line, to send their device data from their place of residence to the clinic.** Study center personnel will access the data, including the Heart Failure Management Report and Cardiac Compass® Report (access arm only), by logging onto the CareLink® website via the Internet https://clc.medtroniccarelink.net.

Clinicians involved in the medical management of control arm subjects will not be allowed to view Cardiac Compass® Trends or HF-Management Report information during in-office device follow-up.

Medtronic Conexus™ Telemetry

Medtronic Conexus™ Telemetry is designed to provide clinicians and subjects with an easier and more efficient implant, follow-up, and monitoring experience. The system uses radio frequency (RF) telemetry for wireless communication between the implanted device and Medtronic CareLink®

monitor in the subject's home. This eliminates the need to place a programming head over the implanted device for the monitoring session and allows for communication with the Medtronic CareLink® home monitor without subject intervention, enabling automatic scheduled transmissions as well as alert-based downloads.

2.3.5 Medtronic CareLink® Monitor with Medtronic Conexus™ Telemetry

Subjects randomized to the access arm must be included in the CareLink® Network Service using the OptiVol® CareAlert®–based monitoring and automatic notification of worsening heart failure condition given with CareLink®. Monitor Model 2490C is designed to communicate with Medtronic ICD or CRT-D systems using wireless telemetry (Virtuoso™, Concerto™ or subsequent market released devices providing at least the same functionality). The monitor at the subject's home is plugged into a phone line and an electrical outlet. The system uses RF telemetry for wireless communication between the implanted device and Medtronic CareLink® monitor in the subject's home. This eliminates the need to have a programming head over the implanted device for the monitoring session and allows for communication with the Medtronic CareLink® home monitor without subject intervention, enabling automatic scheduled transmissions as well as CareAlert®-based downloads.

Using the secure Medtronic CareLink® Clinician Website, clinic staff members can preschedule up to six automatic transmissions for each subject without having to make appointments or coordinate calendars with subjects. The device automatically "wakes up" at the scheduled time and communicates with the Medtronic CareLink® monitor, see Figure 3. Data are transmitted wirelessly from the device to the monitor as the subject sleeps. Data are sent automatically from the Medtronic CareLink® monitor via the phone line. The clinician reviews the subject's device data on the secure website.

Figure 3: Medtronic CareLink® Follow-Up with Conexus™ Wireless Telemetry

For alert-based downloads the implanted ICD or CRT-D monitors the device and diagnostic data such as OptiVol® fluid status and detects problems such as a crossing the OptiVol® threshold. If the subject's device is programmed to notify the clinician, the ICD or CRT-D automatically establishes wireless communication with the Medtronic CareLink® monitor, see Figure 4. Device data is sent automatically from the monitor to a secure server via a standard phone line. The clinician receives a Medtronic CareAlert® notification via SMS or e-mail and checks the Medtronic CareLink® Clinician Website for detailed information and reviews the CareAlert®'s device and diagnostic data of the subject. The clinician only calls the subject to provide further instructions, if needed, and also to obtain further information regarding drug compliance, fluid intake and other circumstances preceding a care alert because of a crossing of the OptiVol® threshold.

Figure 4: Continual Monitoring for Medtronic CareAlert® Status

Use of the monitor will not reprogram the functioning of the subject's implanted cardiac device. Reprogramming can only be done during an in-clinic visit.

Medtronic CareLink® Clinician Website ("Website")

Clinicians can monitor the condition of subjects who use the monitor by securely viewing their implanted device information on the Internet-accessible website when and where needed. Only registered clinic users can access implanted device and subject data by logging onto the password-protected website. Implanted device data available on the website are substantially equivalent to the device data available from in-clinic interrogation-only for device evaluation.

2.3.6 OptiVol® Alert and CareAlerts®

The alerts in Virtuoso™ ICD or Concerto™ CRT-D system or subsequent market released devices providing at least the same functionality are designed to alert the subject and/or clinician of certain selectable system or device performance conditions. System performance alerts are intended to help clinicians identify device or system-related issues, component failure, or device replacement timing. In addition to the system and device performance conditions, the Medtronic CareAlert® monitoring in Virtuoso™ ICD or Concerto™ CRT-D (or subsequent market released devices providing at least the same functionality) device is designed to alert the clinician of heart rhythm conditions and functional status including the notification of the OptiVol® Fluid Index crossing the OptiVol® threshold.

The CareAlerts® are available as audible device alerts. Unlike the audible alerts, CareLink® monitor alerts are **silent** to the subjects and are intended to directly notify the clinician using the Medtronic CareLink® Network. The term "silent" refers to automatic transmission of programmable events from the device to the physician via the subject's CareLink® monitor using wireless telemetry. The alerts available in the Virtuoso™ ICD or Concerto™ CRT-D system or subsequent market released devices providing at least the same functionality are outlined in Table 1.

In Virtuoso™ ICD or Concerto™ CRT-D system or subsequent market released devices providing at least the same functionality, the clinician can select whether a specific alert condition will result in an audible device alert, an inaudible CareLink® monitor alert, or both.

In subjects randomized to the access arm, the **OptiVol® alert will be programmed "ON", but not audible to the subject.** This will result in only a CareAlert® to the physician through the CareLink® Network. The CareAlert® notifies the clinician each time the OptiVol® fluid index crosses the OptiVol® threshold.

In addition to the system and device performance conditions, the Medtronic CareAlert® monitoring feature in Virtuoso™ or Concerto™ devices (or subsequent market released devices) is designed to alert the clinician of heart rhythm conditions associated with atrial tachyarrhythmia (AT) and atrial fibrillation (AF) ("AT/AF alerts"). The AT/AF alerts are intended to monitor and convey heart rate and characteristics of AT and AF, similar to the data provided by an external event monitor. **In subjects randomized to the access arm as well as to the control arm the AT/AF alerts will be programmed "OFF".**

When data is transmitted using the CareLink® Network or when the device is interrogated, all alert conditions will be included. The device stores CareAlert® events as log entries. To avoid redundant log entries, an entry is recorded only the first time each CareAlert® condition is met. Each log entry includes the date and time of the alert event, a description of the alert event, and the programmable threshold that was exceeded. The log is also annotated with the date of the last session.

Once the alert criteria for enabled monitor alert conditions are satisfied, the device will immediately attempt to notify the Medtronic CareLink® monitor via wireless telemetry. The Medtronic CareLink®

monitor will communicate back to the device once the transfer of the information is successful. The device will attempt to communicate with the monitor every 3 hours, until successful transfer of the information, for a maximum of 72 hours. If the transfer of information was unsuccessful within 72 hours, the device will emit an audible high urgency alert at the designated device alarm time for that condition.

Table 1: Available alerts in study device Virtuoso™ ICD and Concerto™ CRT-D and alert programming according to randomization

ALERT TYPE VIRTUOSO™ ICD / CONCERTO™ CRT-D	PROGRAMMING			
	ACCESS ARM		CONTROL ARM	
		AUDIBLE Y/N		AUDIBLE Y/N
Clinical Management Alerts				
OptiVol® Fluid Index Threshold Crossing	**ON**	N	**OFF**	N
AT/AF-Burden at Rate Settings	OFF	N	OFF	N
Number of ICD-Shocks Delivered in an Episode	ON	Y	ON	Y
All Therapies in a Zone Exhausted for an Episode	ON	Y	ON	Y
Lead / Device Integrity Alerts	**Per discretion, however it is recommended that alerts are programmed "ON"**			
Lead impedance out of range – A / RV Pacing Impedance	ON	Y	ON	Y
Lead impedance out of range RV / SVC Defibrillation Impedance	ON	Y	ON	Y
Lead impedance out of range LV Pacing Impedance (CRT-D only)	ON	Y	ON	Y
Low Battery Voltage RRT (Recommended Replacement Time)	ON	Y	ON	Y
Excessive Charge Time	ON	Y	ON	Y
VF Detection Off, VT / FVT Therapies Off	ON	Y	ON	Y
Non-Programmable Alerts				
Electrical Reset	ON	Y	ON	Y
Pacing Mode DOO, VOO	ON	Y	ON	Y
Active Can Off without SVC	ON	Y	ON	Y
Charge Circuit Timeout	ON	Y	ON	Y

The OptiVol® alert can only be programmed "OFF (Observation Only)" in access arm subjects in the event of one or more of the following:

- System modification, resulting in dysfunction of the OptiVol® system,
- Study exit.

Study center personnel will document that the OptiVol® alert was programmed to "OFF (Observation Only)" and provide rationale. Study center personnel will reprogram the OptiVol® alert "ON" as outlined per type of system modification in section 4.13.

The OptiVol® alert must be turned "ON" within 2 business days after randomization of a subject to the access arm. OptiVol® reference impedance adjustment can be used anytime after the point of randomization in the access arm. Criteria outlined in section 2.3.3 should be taken into account when such an adjustment is planned.

2.3.7 HF Management Report and Cardiac Compass® Trends

Medtronic Virtuoso™ ICD and Concerto™ CRT-D system (or subsequent market released devices providing at least the same functionality) provide a range of diagnostic tools, including HF-Management Report and Cardiac Compass® Trends. Both are also accessible through a subset of observations on the Quick Look™ Screen and Quick Look™ Report.

Clinicians involved in the medical management of subjects in the control arm should be advised not to use this information through the Medtronic programmer.

The components of the Cardiac Compass® Report include the following:

- OptiVol® Fluid Trends,
- VT/VF episodes per day,
- One or more shocks per day,
- Ventricular rate during VT, FVT and VF,
- AT/AF total (hours) per day,
- Ventricular rate during AT/AF,
- Percent pacing per day,
- Average ventricular rate (day and night),
- Subject activity,
- Heart rate variability,

- Non-sustained VT/VF episodes per day,
- Percent pacing per day.

The Heart Failure Management Report includes the following additional components:

- OptiVol® thoracic impedance and index.

Observations provided by Quick Look™ are based on an analysis of interrogated data and programmed parameters. Four types of observations are provided: parameter, device status, episode data and clinical trends. For observations provided on the Quick Look™ screen and the Quick Look™ Report refer to Table 2.

Table 2: Observations which are accessible through Virtuoso ICD and Concerto™ CRT-D Quick Look™ Screen on the programmer

OBSERVATION	NOTE
Possible fluid accumulation: exceeded OptiVol® threshold <Date fluid index crossed above threshold> <Ongoing> if fluid index is still above threshold at time of interrogation. <Date fluid index crossed below threshold>	**Access arm:** This condition will be associated with an alert and the proceeding text "Alert" will be visible. **Control arm:** **Although OptiVol® is programmed "OFF" these observations will be visible on the Quick Look™ screen. To exclude "Soft-Cross-Over"** by awareness of this information, it is mandatory that the physician in charge of managing subjects of this study does not get this information for subjects of the control arm.
Atrial Tachycardia / Atrial Flutter-Information <Number of days> with more than <Number of hours> of AT / AF **Average Ventricular Rate during AT / AF** <Beats per minute> for <Number of hours> during AT / AF	**Access and control arm:** Even if AT/AF alerts are programmed "OFF" these observations will be visible on the Quick Look™ screen as well as on the CareLink® web page. This may lead in both study arms to interventional action; i.e. cardioversion of VF. The intervention must be documented on the ICD / CRT-D-Safety and Integrity Form (ICD / CRT-D-SIF), or AEF in case that a hospitalization is caused but is not considered to represent a cardiovascular hospitalization as defined in section 4.19.
Subject activity less than 1 hour / day <Number of weeks>	Available information for **access and control arm** This may lead in both study arms to interventional action. This must be documented on the ICD / CRT-D-SIF, or AEF in case that a hospitalization is caused.
Night heart rate over 85 beats per minute for 7 days	Available information for **access and control arm** This may lead in both study arms to interventional action. This must be documented on the ICD / CRT-D-SIF, or AEF in case that a hospitalization is caused.

ICD / CRT-D-SIF: Safety and Integrity Form; AEF: Adverse Event Form

2.3.8 Review of HF Management Report and Cardiac Compass® Trends (Access Arm only)

Whenever review of HF-Management Report and Cardiac Compass® Trends is required, it must include both (i.e. cannot just review the subset of observations on the Quick Look™ Screen or Quick Look™ Report). Data are accessible through the following components:

- HF-Management Report,
- Cardiac Compass® Report,
- Cardiac Compass® Trends on the Quick Look™ Report (Virtuoso™ Concerto™ CRT-D devices or subsequent market released devices providing at least the same functionality),
- A subset of observations on the Quick Look™ Screen and Quick Look™ Report (refer to Table 2),
- Event logs for CareAlert® information.

2.3.9 CareLink® Monitor Distribution

Study center personnel will initiate distribution of the Medtronic CareLink® monitor to subjects by enrolling the subject through the Medtronic CareLink® Network website (if the subject is not already enrolled in the CareLink® Network). Subjects should receive the Medtronic CareLink® monitor approximately two weeks after enrollment on the Medtronic CareLink® website. Study center personnel will provide training and/or demonstrate use of the Medtronic CareLink® monitor to the subject.

2.3.10 Shipment, Storage, Handling and Use

All the devices are commercially available in Europe and will be used within the intended indication. Therefore, no specific procedures to manage the distribution, shipment, storage and handling are required.

3 METHODOLOGY

3.1 Study Design and Rationale

The OptiLink HF study is a prospective, unblinded, randomized, and controlled study performed in multiple centers. It is planned to include 1000 subjects (500 per study arm) and to conduct the study in 20-30 centers specialized in ICD / CRT-D-implantation, and about 100 active satellite HF-management centers with access to Medtronic CareLink® Network. The study is designed with a control group to compare event-triggered HF-disease management through Medtronic's OptiVol® fluid status monitoring with automatically generated wireless CareAlert® notification of the clinician via the Medtronic CareLink® Network (access arm) to standard clinical assessment alone (control arm) in subjects eligible for ICD / CRT-D therapy suffering from heart failure.

The study is randomized to achieve structurally comparable sequence groups concerning known and unknown influence of confounding factors. Unblinded character results from the study design.

Figure 5 presents subject flow. Subjects will undergo screening to ensure they meet all of the inclusion and none of the exclusion criteria. Medical Ethics Committee (MEC) approval of the OptiLink HF clinical investigation plan and informed consent must be obtained prior to enrolling subjects in the OptiLink HF study. Subjects are considered enrolled upon signing the approved informed consent. Enrollment of the subject **can occur 3 days (72 hours) up to 21 days post-implant** while the OptiVol® algorithm activates 34 days after the implant (the period between implant and day 34 is used to build up the impedance reference value). **Subject will be randomized directly after enrollment and after completion of KCCQ and EQ-5D questionnaires.** The time between randomization and activation of the OptiVol® system is used to organize the individual care link device. Eligible enrolled subjects will be randomized in a 1:1 fashion to the access arm or the control arm. Randomization will be stratified by risk, for details refer to section 4.4.2. Randomization requirements are summarized in appendix O.

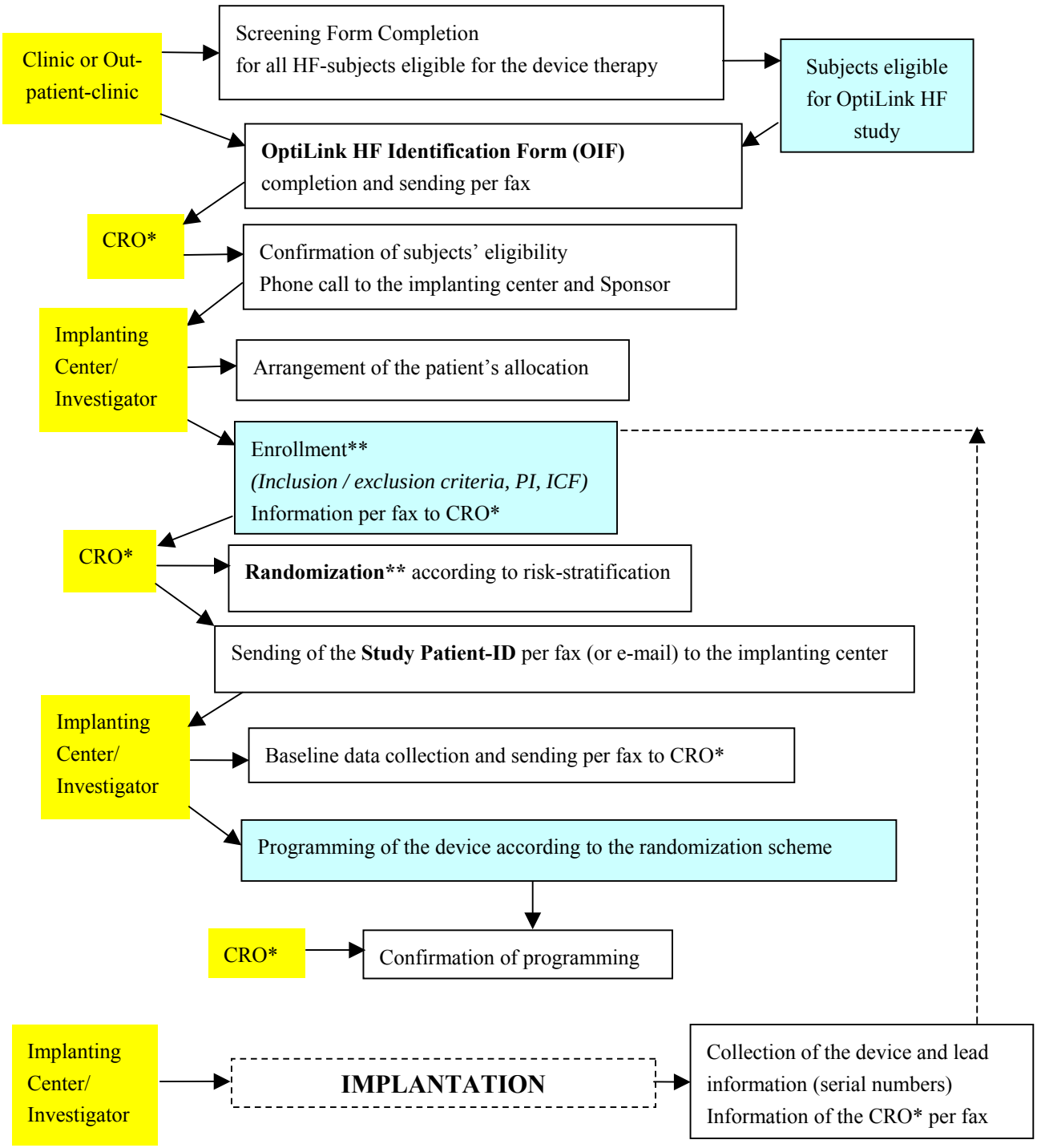
Enrolled subjects who fail to meet final eligibility criteria will not be randomized into the study. The subject will be exited from the study and a study exit form (SEF) will be completed.

Clinical data are required to be collected at baseline/enrollment, randomization, and scheduled follow-up visits at 6 months and every 6 months thereafter until study closure or subject death/exit. Follow-up visit windows are listed in Table 4, section 4.6 and are based on days post-randomization.

Data collected at follow-up visits conducted outside the window will be considered non-compliant to the window but will be included in the final analysis based on intention-to-treat analysis. Data collection requirements are summarized in Table 3, section 4.1.

The study center personnel must report all adverse events and changes in status of these adverse events from time of enrollment until a subject exits the study.

Figure 5: Subject flow



*CRO = Contract Research Organization = IFE Institute for Research and Development
**Enrollment is possible 3 up to 21 days after implantation while the randomization will be performed directly after enrollment
PI = Patient Information, ICF = Informed Consent Form

The study was designed with a control arm in order to adequately investigate the effect of early intervention triggered by CareAlert® notification and evaluation using HF-Management and Cardiac Compass® Report with OptiVol® fluid status monitoring.

Variables that differ between the access arm and the control arm include the following: access to CareLink®, the combination of Medtronic's OptiVol® fluid status monitoring with automatically generated wireless CareAlerts® via the Medtronic CareLink® Network, access to HF-Management-Report and Cardiac Compass® Trends.

In the event the investigator or subject does not comply with the randomization assigned, a deviation must be reported to Medtronic. The subject will continue to be followed on an intent-to-treat principle and should remain within the arm they were initially randomized.

3.2 Study Objectives

Primary objective:
The primary objective of the study is to establish whether the use of "OptiLink" decreases the **combined endpoint of rate of all-cause mortality or cardiovascular hospitalization** over an 18 months follow-up in subjects with HF and ICD or CRT-D treatment. All causes of death and unplanned admissions to hospital for cardiovascular reasons from day 35 after ICD or CRT-D-implantation until 18-months follow-up visit are assessed.

Hospitalization is defined as an overnight stay or longer in a hospital environment or similar facility including admission to a day care facility.

Cardiovascular hospitalizations are defined as hospitalizations for:

- Heart failure (first or subsequent),
- Acute myocardial infarction,
- Unstable angina pectoris,
- Symptom-driven hospitalization for cardiac arrhythmia (atrial fibrillation, atrial flutter, supraventricular arrhythmias or ventricular arrhythmias),
- Stroke/ cerebral vascular accidents.

Hospitalizations for elective CV procedures do not qualify as CV endpoint, this included planned admission for elective cardioversion of atrial fibrillation.

The following secondary objectives and endpoints will be analyzed:

1) Number of HF-related hospitalizations during follow-up;
2) HF-related hospitalization;
3) Sum of follow-up days minus days alive and out of the hospital;
4) All-cause mortality;

5) Cardiovascular mortality;
6) HF-related hospitalization and all-cause mortality;
7) Quality of Life (QOL);
8) Health Economics.

Exploratory endpoint:
Number of all-cause hospitalizations during 18 months follow-up.

3.3 Study Scope

Only subjects implanted with a single- or dual-chamber ICD or CRT-D device will be included in this study. The sample size was estimated using the experience from previous studies (CHARM). The results showed that event rates (i.e. proportion of subjects with at least one event) of 28% in 18 months for the combined event all-cause death or cardiovascular related hospitalization will be a reasonable estimator for the control arm. The assumption of a 30% improvement in the access arm, which results in a difference of 8.4% between the treatment arms, is the basis for the sample size calculation (see 5.6).

3.4 Claims and Intended Performance

The OptiLink HF study intends to establish whether the use of event-triggered HF-disease-management = Medtronic's OptiVol® fluid status monitoring with automatically generated wireless CareAlert® notification of the clinician via the Medtronic CareLink® Network can reduce the number of hospitalizations for worsening of HF in a subject population with HF and ICD / CRT-D treatment by using the diagnostic tools available in the commercially released Medtronic ICD / CRT-D devices in combination with CareLink®. It is not the purpose of the OptiLink HF study to support labeling changes, instructions for use or promotional material claims for these devices.

3.5 Applicable Regulations

The study will be conducted in compliance with ISO 14155 part 1 & 2 and will use ICH-GCP as guidance. The study will comply with the Declaration of Helsinki concerning medical research, CFR part 11 and 54, and in accordance with the laws and regulations in the countries in which it is conducted. A Medical Ethics Committee (MEC) written approval or an investigator approval of a presented opinion from a MEC is required before center participation in this study.
All devices used in this investigation have the CE mark. The devices are manufactured in accordance with the provision of the Active Implantable Medical Device Directive (90/385/EEC) and comply

with all relevant legal requirements. The used devices and leads are market released and used within labeling. Please refer to appendix N for the CE declaration of conformity of the used devices.

3.6 Inclusion and Exclusion Criteria

Subjects of both genders who comply with all inclusion and none of the exclusion criteria are eligible for this clinical study.

Inclusion Criteria:

- Subjects have a Medtronic Virtuoso™ single- **or** dual-chamber ICD **or** Concerto™-CRT-D **or** subsequently market released Medtronic device providing at least the same functionality implanted, including device replacement. Subjects with CRT-D must fulfill CRT-indication as described in the ESC guidelines for cardiac pacing and cardiac resynchronization therapy 2007: EF ≤ 35% and NYHA III, and LVEDD> 55 mm, and QRS ≥ 120 ms, and optimized therapy,
- Subjects with stable chronic heart failure (CHF) in New York Heart Association (NYHA) class II or III for at least 30 days and left ventricular ejection fraction of no more than 35% (most recent measurement within 6 months prior to randomization by echocardiography or contrast ventriculography, magnetic resonance or nuclear imaging, based on local practice), on optimal target or maximal tolerated dose of ACE-inhibitors or angiotensin receptor blockers, ß-blockers and diuretics if clinically indicated to reduce fluid retention and one of the following criteria:
  At least one hospitalization due to the heart failure within the last 12 months before enrollment or one course of ambulatory IV- or oral diuretic treatment or a BNP value of > 400 pg/ml or a NT-proBNP values > 450 pg/ml in subjects < 50 years, > 900 pg/ml (50-75 years) and > 1800 pg/ml in subjects of > 75 years old within 30 days of enrollment,
- Written informed consent by the subject for study participation prior to clinical investigation plan specific procedures,
- The subject must be able and willing to comply with the clinical investigation plan and willing to remain available for follow-up visits to the study closure,

- Subjects or the subject's caregiver must be willing and able to use the Medtronic CareLink® monitor as instructed and to perform the required duties.

Exclusion Criteria:

- Subjects with chronic renal failure needing renal dialysis,
- Subjects with serum creatinine > 2.5 mg/dl, measured within 14 days prior to enrollment,
- Subjects with severe to very severe Chronic Obstructive Pulmonary Disease (COPD) as determined by physician and documented in medical records (Stage III or Stage IV),

  Subjects with suspected or confirmed COPD require a current test of lung function (not more than 12 months before inclusion). If the "forced expiratory volume" is < 1.0 L/sec, the subject may not participate in the study.

- Subjects on the heart transplantation list or subjects with transplanted hearts,
- Subjects listed for valve replacement or interventional valve therapy,
- Subjects with myocardial infarction within the last 40 days before ICD / CRT-D-implant. MI is defined by typical changes in biochemical markers including troponin levels > 3 times the upper limits of normal and creatinine kinase < 2 times of upper limit, or with CKMB greater than the upper limit of normal, combined (for all enzymes) with at least one of the following ischemic symptoms, ECG changes consistent of diagnostic ST-T wave changes or pathologic Q waves or new LBBB,
- Subjects with stroke within 40 days prior randomization,
- Subjects who have had a percutaneous coronary intervention within 3 months prior to randomization,
- Subjects with cardiac surgery within 90 days of randomization,
- Subjects with complex and uncorrected Congenital Heart Disease,
- Subject's life expectancy is less than 18 months in the opinion of the physician,
- Subjects in situations that would limit participation, not eligible to receive a CareLink® monitor (e.g. hearing or speech impaired with no family member or caregiver available to assist, or those who spend extended periods abroad, or those who intend to enroll in a study that would preclude use of the monitor),
- Subject is participating in a concurrent intervention study,
- Subject or the subject's caregiver is unwilling to give consent for the release of information for the evaluation or to give additional consent

for the release of subject medical and privacy data for CareLink® subjects,

- Subjects with exclusion criteria required by local law (age < 18, women who are pregnant or breastfeeding).

The enrolling physician will be responsible for identifying subjects who might participate in the evaluation and discussing participation with them.

3.7 Intended Blinding to HF-Management Report and Cardiac Compass® Trends

Study center personnel involved in the medical management of subjects in the control arm will be asked not to view HF-Management Report and Cardiac Compass® Trends for subjects in the control arm in order to adequately study the effect of review on the rate of hospitalizations and mortality. All efforts will be made to maintain this advice for subjects in the control arm.

3.8 General Center Requirements

A center may be included in the investigation if the center complies with the following requirements:

- Physician with expertise in subject therapy management,
- Absence of simultaneous competing clinical protocols that may interfere with this trial's subject enrollment and study compliance,
- Appropriate supplies, resources and equipment as required by the clinical investigation plan (e.g. Internet access, Medtronic CareLink® Network access, Medtronic 2090 or 2090W Programmer, required for implanting center, optional for active study center),
- Sufficient staff to carry out the clinical investigation plan requirements in a timely fashion and maintain compliance to the clinical investigation plan,
- Investigator with no known history of misconduct resulting in withdrawal of investigator's privileges / responsibilities by MEC or regulatory authorities,
- Acknowledgement of and agreement to comply with local regulatory requirements as well as with the clinical investigation plan and MEC requirements,
- Investigator permits monitoring and auditing by Medtronic or the CRO and inspection by regulatory authorities.

3.9 Investigator Agreement

A clinical trial agreement must be signed by each center and returned to IFE prior to the commencement of any study activities.

The investigator is indicating his/her approval of the clinical investigation plan and subsequent amendments, by signing and dating the agreement. Recent dated and signed curriculum vitae that reflect the investigator's current position and title will be required from each investigator participating in this study.

3.10 Medical Ethics Committee

MEC approval of the study and clinical investigation plan must be received and the contents of the approval letter accepted by Medtronic or the CRO before commencement of the study at a clinical site.

The MEC approval letter must contain the following elements:

- Name of study,
- Name of MEC and MEC composition / letter of compliance,
- Date of approval,
- Sufficient identification of version/date of clinical investigation plan, version/date of amendments (if applicable), version/date of center-specific subject information and informed consent form (see appendix A for the template version), and version/date of any other study specific documents approved by the MEC,
- If the investigator or any other member of the study team at the site is a member of the MEC, Medtronic shall be provided with written documentation that he/she did not participate in the voting approval process for this study.

3.11 Access to Center and Study Material

The principal investigator(s), his/her delegate(s) and the study coordinator(s) shall be accessible to the Medtronic field clinical support, the CRO-personnel and the study manager. This accessibility is of particular importance for reviewing data in the Case Report Forms (CRFs). For the study monitors, direct access to the subject records for source data verification will need to be granted and prepared prior to any monitoring visits.

3.12 Study Training

Center personnel (investigators, coordinators, other clinical staff) participating in the OptiLink HF clinical study will be trained in study activities relevant to their role prior to conducting any OptiLink HF study activities. Investigators and study coordinators will be trained on their responsibilities, investigational product usage and handling, ISO-14.155, obtaining informed consent, and the clinical investigation plan. Training on worksheet completion and CRF completion, will also be provided. Investigator and/or study coordinator meeting(s) or conference call(s) may be held to discuss the study, clinical investigation plan, training, study results, etc. Interim meetings or telephone conference calls may be organized to discuss relevant study issues. The investigator will agree to attend investigator meetings and/or conference calls or send a co-investigator if they are unable to attend, whenever possible.

The coordinator will agree to attend all coordinator meetings and/or conference calls, whenever possible.

3.13 Bias Reduction

The following methods were incorporated into the study to minimize bias:

- Subject demographics will be assessed by collecting information on possible differences that may affect the outcome. Information will be gathered on the subject's gender, ethnicity, medical background, diagnosis, and indications for ICD / CRT-D device therapy at time of implant,
- Subjects are assigned to the access arm or control arm by a randomization procedure, which is stratified by risk. This ensures statistical validity as well as a high probability of balanced confounding influences, refer to section 4.4.2,
- All centers will use the same version of the OptiLink HF clinical investigation plan,
- An independent committee of physicians will regularly assess, review and classify all hospitalizations, ED visits, urgent and non-urgent unscheduled office visits.
- To ensure a widespread distribution of data, the number of enrollments per center should not exceed 100 subjects,
- Data will be collected using standardized CRFs,

- Only subjects in the access arm are required to be enrolled on the Medtronic CareLink® Network,
- All study center personnel and Medtronic personnel will be trained on their respective aspects of the study using standardized training materials,
- Regular monitoring visits will be conducted for adherence to the clinical investigation plan and source data verification, refer to section 8,
- A Data Safety Monitoring Board (DSMB) will provide oversight of the study, refer to section 11.4,

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

3.14 Early Termination or Suspension

Suspension of a clinical investigator or a clinical center may occur for the following reasons:

- Non compliance to the inclusion/exclusion criteria,
- Failure to follow through with MEC/authority for approval or compliance to MEC conditions or continuation of the clinical study,
- Failure to follow subjects per scheduled follow-ups,
- Failure to submit data in a timely manner,
- Failure to follow-up with findings on monitoring reports,
- Failure to comply with adverse event reporting requirements.

4 STUDY PROCEDURES

4.1 Data Collection Overview

Clinical data is required to be collected at baseline/enrollment, randomization, and scheduled follow-up visits at 6 months and every 6 months thereafter until study closure or subject death/exit. Follow-up visit windows are listed in Table 4 and are based on days post-randomization.
Data collected at follow-up visits conducted outside the window will be considered non-compliant to the window but will be included in the final analysis based on intention-to-treat analysis.

Scheduled follow-up visits can be performed either by the study EP/implanting clinician or out-patient-clinic. The actual dates and windows for each follow-up will be obtained from the external CRO (IFE) performing monitoring. It is recommended that the study center personnel file the follow-

up schedule in the subject binder. If a follow-up visit falls outside the window, the original follow-up schedule will be maintained for subsequent visits. If a scheduled visit is missed, does not occur within the defined follow-up visit window, or the visits are more than ten days apart, a study deviation form (DEF) will be required with a justification.

Requirements for data collection during the follow-up visit:

- NYHA class,
- Current HF symptoms,
- Cardiovascular medication,
- Arrhythmia-episode review,
- ICD- / CRT-D-Device Therapy Safety and Integrity Information,
- Adverse events (AEs),
- Study deviation,
- Health Care Utilization (HCU),
- Programming check,
- Save-to-disk (control arm, access arm until save-to-disk equivalent data-files for analyses can be retrieved from the CareLink® Network).

Explicit elements for access arm (not for the control arm):

- Review of HF-Management Report and Cardiac Compass® Trends.

Clinical data will be collected via standard Case Report Form (CRFs), device interrogation and save-to-disk storage (control arm). In the access arm device interrogation and save-to-disk storage will be substitute by automatically transferred data-transmission to the CareLink® Network. The sponsor might decide to collect save-to-disk files also on the access arm in case equivalent data can not be retrieved from the CareLink® Network in order to secure the availability of data. Otherwise, only in case of in-office, hospital-visits, combined with reprogramming of the device a save-to-disk storage may be required, unless manual data-upload to the CareLink® website after reprogramming can not be performed within 3-4 days after visit. Medtronic and IFE will have read-only access to all CRF-data and to individual CareLink® Network accounts for all study centers upon completion of study-specific training.

CRFs will be entered by the trained, delegated and authorized study site personnel. Once data has been entered and submitted, there may be discrepancies that require clarification. Data clarifications are generated by queries and send to the center.

The study site personnel are responsible for timely review and resolution of all queries. Investigators will be required to sign off on data as communicated by the study team.

Data collection requirements are summarized in Table 3.

Table 3: Data Collection Requirements

CRF or CareLink-Session or Visit	Baseline (BLF)	Randomi-zation (RRF)	Scheduled/ Unscheduled visit (ICD /CRT-D-SIF)	Tel. Contact by OptiVol® Alert (CAEF)	Hospitali-zation or AE (AEF)	Study Exit/ Subject Death (SEF)	Deviation (DEF)
Requirements	**A: Access Arm; C: Control Arm**						
Inclusion criteria	X						
NYHA class	II or III		X C: during office visit		X	X	
LVEF measurement	≤ 35%						
1. HF-related hospitalization within last 12 months	Yes, only one of this 3 items						
2. IV- or oral diuretics							
3. BNP value of > 400 pg/ml or a NT-proBNP values > 450 in subjects < 50 years, > 900 (50-75 years) and > 1800 in subjects of > 75 years old within 30 days of enrollment							
Exclusion criteria	X						
Informed consent signed	X						
Demographic data	X						
Medical history	X						
Weight and/or changes	X			X	X		
Medication and/or changes	X		C: during office visit A: via telephone contact	X	X	X	X
HF symptom status (or death information),	X			X	X	X	X
Continuous hospitalization check							
Blood sample	X		X[1] (Optionally at 6-month follow-up)		X[1] (Optionally)	X	

CRF or CareLink-Session or Visit	Baseline (BLF)	Randomi-zation (RRF)	Scheduled/ Unscheduled visit (ICD /CRT-D-SIF)	Tel. Contact by OptiVol® Alert (CAEF)	Hospitali-zation or AE (AEF)	Study Exit/ Subject Death (SEF)	Deviation (DEF)
Requirements	**A: Access Arm; C: Control Arm**						
Kansas City Cardiomyopathy Questionnaire (KCCQ) and EQ-5D	X		X[2] (Only at 6-month follow-up)			X	
Randomization assignment; handover of subject ID card to subject		X					
CareLink® enrollment		Only A					
Assign subject to CareLink® satellite		Only A					
ICD / CRT-D-therapy assessment		X	C: during office visit A: via CareLink®		X	X	X
Review Cardiac Compass® Trends and HF Management Report			C: should be limited A: via CareLink®	X	X	X	C: Review is unavoida-ble
Device interrogation StD	Only C		Only C A: via CareLink®		A and C	Only C A: via Care Link®	Only C A: via Care Link®
Intervention algorithm				Only A	A and C		
Health Care Unit Documentation				A and C	A and C		

[1] Optionally a blood sample will be collected at 6-month follow-up in-office visit or in the case of hospitalization after CareAlert®.
[2] Questionnaires will be filled in at 6-month. Subjects from the control arm will fill in the questionnaires at follow up visit, whereas subjects from the access arm will received questionnaires per post and fill them in at home.
[3] After randomization.

4.2 Implant/Pre-hospital Discharge

The surgical procedure for ICD / CRT-D implantation in the implanting center will be at the discretion of the implanting physician. Device information obtained from the implantation until hospital discharge will be documented on the Baseline Form (BLF) after enrollment.

The following device programming is required after randomization for the subjects in the access arm:

- OptiVol® is programmed "ON", but not audible to the subject,
- CareAlert® through CareLink® Network is programmed "ON".

4.3 Subject Informed Consents

Subject Informed Consent:

The study informed consent process is under the responsibility of the implanting center.
A MEC-approved subject information and informed consent form (see appendix A) shall be used for the informed consent procedure.

An initial review of a subject's medical record shall be performed by the center prior to approaching the subject with intent to present this study. If the subject appears to meet study inclusion and exclusion criteria, the trial should be presented to the subject. Since no procedures are necessary for the sole purpose of screening the subject for enrollment into the study, no subject informed consent shall be signed and dated prior to carrying out any study related procedures (e.g. randomization).

The informed consent process has to be conducted by a member of the investigator's team qualified and authorized to conduct this procedure. The completed form shall include the dated signatures of both subject and the investigator / co-investigator acknowledging that participation in the study is voluntary. The complete and original signed subject information and informed consent form shall be kept in the hospital/clinic with the subject's medical files or with the study documentation. These are available to Medtronic or CRO study personnel upon request during site visits. A copy of the complete signed and dated subject information and informed consent form will be provided to the subject.

In the event the subject cannot read and/or write, an informed consent procedure witnessed by an impartial third party will be allowed. Such a procedure requires detailed documentation in the subject's medical record as well as signature of the witness on the informed consent document.

The process of informed consent shall:

- Avoid any coercion of or undue influence of subjects to participate,
- Not waive or appear to waive subject's legal rights,
- Use language that is non-technical and understandable to the subject or his/her legal representative,
- Provide ample time for the subject to consider participation.

Subjects shall be required to provide written informed consent for enrollment.

When a subject signs an informed consent form for this clinical study, he/she is considered enrolled in the study. If, at any time, the subject does not wish to continue participation in the study, a study exit CRF shall be completed.

CareLink® Privacy Principles Statement:

Subjects randomized to the access arm are required to be enrolled in CareLink® Network. For this all eligible subjects need to be informed about the requirement to provide written informed consent for the data collection and handling given with CareLink® Network service prior to enrollment in the study. This information will be combined with the subject informed consent form (see appendix A). The information about CareLink® Privacy Principles Statement before enrollment as well as the sign off process following randomization for the access arm is under the responsibility of the implanting center.

Revisions in Subject Information and Informed Consent Forms:

Medtronic shall update the subject information and informed consent whenever relevant new information becomes available. This revised document shall be sent to the investigator for approval by their MEC. Once the MEC and Medtronic approve the informed consent, a copy of this information shall be provided to the participating subjects. If the new information is related to increased subject risk, all previously enrolled subjects shall be approached for their re-consent for participation in the study.
The investigator or his designee shall inform the subject in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the investigation. The investigator shall document the communication of this information in the subject file at the hospital.

Informed Consent in Emergency Situations:

All devices used in the study are market-released. Therefore guidelines related to emergency use of investigational devices are not applicable.

4.4 Baseline/Enrollment

A subject is enrolled in the OptiLink HF study when the subject has signed the informed consent form. Baseline/enrollment data will be collected for subjects meeting all eligibility requirements. If a consented subject fails to meet final eligibility criteria, the center will enter the screening information and reason for eligibility failure in a study exit form. Additionally, if a subject is enrolled

but not randomized, a study exit CRF will be completed. If the subject did not meet eligibility requirements and was randomized, a study deviation will be completed but the subject will remain in the study.

The following information is required as part of a subject's baseline evaluation for the OptiLink HF study and must be recorded on the CRFs within the baseline/enrollment visit:

Eligibility Criteria

Verify and document that the subject met the eligibility criteria for the study.

Serum creatinine measurement

The subject's serum creatinine measurement will be reported on the baseline/enrollment CRF.

This blood test is intended to provide evidence of adequate renal function as required by inclusion criteria. It is acceptable to report lab results drawn within the 14 days prior to enrollment. In the case several creatinine measurements are available, the worst result must be taken into consideration.

Other baseline testing/procedures must not be performed until it has been confirmed that the subject met the creatinine eligibility requirement. If the center fails to obtain a serum creatinine measurement within 14 days prior to enrollment or at baseline, a study exit form for not meeting eligibility criteria must be completed.

Informed consent

Record the date the informed consent was signed by the subject or subject's legally authorized representative.

Blood sample

After the informed consent procedure a blood sample (10 ml serum Monovette® and 10 ml EDTA-Monovette®) will be collected to detect a level of different biomarkers, like NT-proBNP in subject's blood. No further processing of the sample, i.e. no centrifugation or cooling of the sample is required. The sample will be subsequently sent to the Central Laboratory (CoreLab of the Hannover Medical School; MHH, for the contact information refer to Section 12) and the biomarkers will be detected using a commercial diagnostic kit. The samples should be labeled with the subject no., time of sampling („Randomization"), and date on the serum or EDTA-Monovette®.

Subject demographics and medical history

Information will be collected on the subject's date of birth, gender, and ethnicity. The subject's medical history will include information on the subject's heart failure etiology, cardiovascular history, cardiovascular surgical history, respiratory-related history, pulmonary-related history, vascular-related history, arrhythmia history and renal/endocrine-related history.

Intrinsic QRS duration and LVEF measurements

Study center personnel will record the subject's most recent intrinsic QRS duration and LVEF measurement within the last 6 months prior to randomization obtained prior to enrollment (see Section 3.6, inclusion criteria). The clinical investigation plan does not require that new measurements be obtained at baseline/enrollment.

Implant information

The following information will be collected:
a) Date of device implant,
b) NYHA classification (most recent prior to or at implant),
c) Primary indication for implant.

Weight and its changes and other HF signs or symptoms

Kansas City Cardiomyopathy Questionnaire (KCCQ)[o, p, q, r] and EQ-5D Questionnaire

Health status of subjects will be additionally assessed using the Kansas City Cardiomyopathy Questionnaire and the EQ-5D Questionnaire. Subjects should fill in the questionnaires after signing the informed consent form, but necessary before the randomization.

Device interrogation StD (only for subjects from the control arm).

Medication collection (cf. below, section 4.4.1).

4.4.1 Medication Collection

All cardiovascular medications will be collected. Study center personnel will verify the status of all cardiovascular medications at baseline/randomization, follow-up, telephone contact, in case of hospitalization or an AE, and study exit. Advised changes of medication during visits, adverse event

[o] Spertus J, Peterson E, Conard MW *et al.* Monitoring clinical changes in patients with heart failure: A comparison of methods. *American Heart Journal* 2005, 150 (4): 708-715.

[p] Soto GE, Jones P, Weintraub WS *et al.* Prognostic Value of Health Status in Patients With Heart Failure After Acute Myocardial Infarction. *Circulation.* 2004; 110: 546-551.

[q] Heidenreich PA, Spertus JA, Jones PG *et al.* for the Cardiovascular Outcomes Research Consortium. Health Status Identifies Heart Failure Outpatients at Risk for Hospitalization or Death. Journal of the American College of Cardiology. 2006; 47 (4): 752–6.

[r] Green CP, Porter CB, Bresnahan DR *et al.* Development and Evaluation of the Kansas City Cardiomyopathy Questionnaire: A New Health Status Measure. Journal of the American College of Cardiology. 2000; 35 (5): 1245–55.

situations or hospitalization must be recorded on the CRF. It is not necessary to report non-cardiovascular oral medications.

4.4.2 Randomization

After center confirmation that inclusion/exclusion study criteria have been fulfilled, and informed consent and baseline data have been obtained, subjects will be randomized. Enrollment of subjects is possible **3 days up to 21 days** after Virtuoso™ ICD or Concerto™ CRT-D (or subsequent market released devices providing at least the same functionality) implant. Eligible enrolled subjects will be randomized in a 1:1 fashion to the access arm or the control arm. **Subject will be randomized directly after enrollment and completion of KCCQ and EQ-5D questionnaires.** Randomization will be risk-stratified: by NYHA class II/III (40% NYHA class II / 60% NYHA class III), ischemic/non-ischemic cardiovascular disease, atrial fibrillation and occurred VT/VF episodes before implant.

Access Arm:

- Medtronic Virtuoso™ ICD or Concerto™ CRT-D system or subsequently market released system providing fluid status monitoring OptiVol® and with CareLink® access (OptiVol® "ON" and CareAlert® "ON"),

Control Arm:

- Medtronic Virtuoso™ ICD or Concerto™ CRT-D system or subsequently market released system without CareLink® access (OptiVol® "OFF").

Randomization requirements are summarized in appendix O.

A statistician from the involved Contract Research Organization (CRO), IFE will create a randomization schedule. Randomization will be performed centrally through the responsible CRO through a randomization request form, which will be submitted via fax to CRO, IFE to receive a randomization result.

Study center notifies CRO (IFE) per fax about subject enrollment by sending the Randomization Request Form (RRF). Randomization is performed by IFE by sending of the study subject-ID per fax (or optionally per e-mail) to the study center (Randomization Result Form, RRF). Randomization result of the subject will be recorded on the Baseline Form (BLF).

To ensure a widespread distribution of data, the maximum number of enrollments per center is 100 subjects. To attempt to ensure adequate numbers in each group, centers will be ranked by the number of subjects enrolled, and the top 25% of centers will be considered "high" enrolling centers. The high enrolling centers will be compared to the remaining 75% of "low" enrolling centers.

In the event the investigator or subject does not comply with the randomization assignment, a deviation must be reported to the sponsor.

Cross-over

Study participants are required to remain in the randomized arm to which they are assigned. Crossover is prohibited unless deemed clinically necessary by the investigator and approved by a designated member of the OptiLink HF steering committee who will review rationale for crossovers. To achieve approval the investigator must inform the CRO upfront about intended cross-over.

An approved crossover is defined as any instance when the study center personnel make a permanent, deliberate, medically intended decision to use Cardiac Compass® Trends and/or HF-Management Report to manage a subject in the control arm.

In the event the study center personnel do not comply with the randomization assigned, a deviation must be reported to the sponsor.

Refer to section 11.2 for the contact information of the steering committee members.

- In the event of a system modification when a study device is removed and not replaced with another study device, subjects initially randomized to the access arm will be crossed over to the control arm, but analyzed in the access arm (intention-to-treat). Prior approval by a designated member of the steering committee will not be required, however study center personnel must contact Medtronic and a study deviation must be recorded on the deviation form (DEF).

4.5 Subject Enrollment in CareLink® Network

Enrollment in CareLink® Network of subjects randomized to the access arm is under the responsibility of the study center. Enrollment in CareLink® Network is required to be done after enrollment into the study and randomization of the subject, up to 25 days after implantation. Information needed for enrollment in the CareLink® Network is based on the baseline form (BLF) completion for all subjects.

In order to ensure CareLink® functionality, subjects in the access arm will be trained on the usage of the CareLink® monitor conducted by a member of the investigator's team qualified to conduct this procedure. Moreover the following additional documentation is required for the access arm:

- CareLink® enrollment,
- CareLink® training,
- OptiLink HF programming.

4.6 Follow-up Visits

After enrollment of the subject into the study, subjects will be monitored via follow-up visits or contacts. Regular follow-ups are necessary to monitor the condition of the ICD / CRT-D therapy system and subject status. The follow-ups are required at six months, and every six months thereafter post-randomization, until study closure, or subject exit due to death or other cause.

The required follow-up or contact windows for this study are described in Table 4.

Visits to the clinician can be conducted remotely via CareLink®. The ICD / CRT-D programming will allow automatic routine data interrogation and transmission into the CareLink® Network every 6 months for subjects from the access arm.

Table 4: Follow-up Schedule/Visit Windows

Follow-up Visit (Months)	Window Start* (Days)	Target Day*	Window end (Days)
6	150	180	210
12	330	360	390
18	510	540	570

*Days post-randomization

The following information is required as part of every 6 months follow-up and must be recorded:

- Follow-up information,
- HF symptom status changes, if applicable,
- ICD / CRT-D-Device-Therapy Safety & Integrity Information,
- Changes in cardiovascular medication, if applicable,
- HCU information: hospital, emergency department, unscheduled clinic/office, urgent care or remote visits, if applicable
- Study deviations,
- Adverse events,
- Subject questionnaires (KCCQ and EQ-5D) as part of 6-month follow-up.

Optionally (control arm):

- Programming check,

- New York Heart Association (NYHA) classification,

Final ICD / CRT-D interrogation (all) to save-to-disk, if ICD / CRT-D interrogation performed in-office, and if CareLink® transmission not performed.

Additionally for all subjects a blood sample will be collected during the **in-office follow-up visit at 18 months** (10 ml serum Monovette® and 10 ml EDTA-Monovette®). No further processing of the sample i.e. no centrifugation or cooling of the sample is required. The sample will be sent to the Central Laboratory (CoreLab of the Hannover Medical School; MHH, for the contact information refer to Section 12) and the biomarkers will be detected using a commercial diagnostic kit. The samples should be labeled with the subject no., time of sampling („18 months") and date on the serum or EDTA-Monovette®.

Optionally

A blood sample (10 ml serum Monovette® and 10 ml EDTA-Monovette®, compare above) for examination of a level of biomarkers should also be collected during the in-office follow-up visit at 6 months and in the case of a hospitalization (as a result of CareAlert®). The samples should be labeled with the subject no., time of sampling („6 months" or „Hospitalization") and date on the serum or EDTA-Monovette®.

4.7 Scheduled Follow-up Contacts

In case of a scheduled CareLink® remote visit, the subject must be contacted within 7 days to complete the follow-up contact related questions.
The following information is required as part of all follow-up contacts for both access arm and control arm and **the following that have occurred since the last scheduled contact must be recorded:**

- Contact information,
- HF symptom status changes, if applicable,
- ICD / CRT-D-Device-Therapy Safety & Integrity Information,
- Changes in cardiovascular medication, if applicable
- HCU information: hospital, emergency department, unscheduled clinic/office, urgent care or remote visits, if applicable,
- HF-related intervention, if applicable,
- Study deviations,
- Adverse events,

- Final ICD / CRT-D interrogation (all) to save-to-disk, if ICD / CRT-D interrogation performed in-office, and if CareLink® transmission not performed.

The following additional documentation as part of the follow-up contact documentation is required for the access arm:

- Review and classification of HF-Management and Cardiac Compass® Trends OptiVol® or CareAlert® reprogramming, if applicable.

4.8 Unscheduled Visits

Any interim/additional subject's contacts are at the discretion of the center schedule and may include follow-ups both for the technical ICD / CRT-D device testing and/or for heart failure management. Additional data will be collected at urgent and non-urgent unscheduled office visits, emergency department visits, hospitalizations, data associated with an intervention algorithm, telephone contacts, system modifications, adverse events, study deviations, and study exit/death.
The study center personnel must report all adverse events and a change in status of these adverse events from time of enrollment until a subject exits the study.
A **CareAlert® Evaluation Form (CAEF)** must be completed whenever a study personnel-initiated therapeutic action based on the **CareAlert®** is taken, or HF-Management Report and/or Cardiac Compass® is reviewed and treatment decisions are made (**access arm**).

An **Adverse Event Form (AEF)** must be completed whenever a study personnel-initiated therapeutic actions based on new or worsening signs and/or symptoms of cardiovascular decompensation occur, which are not notified through the CareLink® Network, and treatment decisions are made (**access and control arm**).

4.9 Health Care Utilization

Health Care Utilization will be measured by data received from the completion of an Adverse Event Form (AEF) or CareAlert® Evaluation Form (CAEF) in the following situations:

- Hospitalizations,
- Emergency Department (ED) visit,
- Unscheduled office visit (a visit to an out-patient clinic that is not a study scheduled follow-up but fulfills one or more of the following criteria):

a) OptiVol® alert and/or subject notified of possible fluid accumulation (access arm only).

b) Subject has new or worsening signs or symptoms of cardiovascular decompensation (including fluid overload or dehydration) and/or weight gain and the subject comes into the office.

c) In-office visits in conjunction with an intervention algorithm.

An unscheduled office visit will be defined as **"urgent"** if the visit occurs within 24 hours from when the subject communicates distress.

An unscheduled office visit will be defined as **"non-urgent"** if it is a visit to an out-patient clinic more than 24 hours from when the subject communicates distress.

The following information is required to be recorded on the AEF: date, type, name of facility, and primary reason of visit.

4.10 Intervention Algorithm

An intervention algorithm is required to be performed and documented when the subject currently meets the criteria:

- the OptiVol® fluid index exceeding the OptiVol® threshold (access arm),
- new or worsening signs and/or symptoms of cardiovascular decompensation (access and control arm).

Table 5: Intervention Algorithm Requirements – Access Arm with CareLink® vs. Control Arm

Access Arm	Control Arm
CareAlert® notification via SMS and/or e-mail of responsible study personnel based on OptiVol® fluid index exceeding OptiVol® threshold **Cardiac Compass® and HF-Management Report Review** **Signs and Symptoms Assessment** via telephone contact of the subject **Manual data transmission advice** to subject, **Follow-up of data transmissions**	**CareAlert® notification due to OptiVol® threshold-crossing is not possible** **HF-Management Report Review must be avoided, but it could happen. If it happens through programmer this must be documented** **(no protocol deviation)**
Up to the investigator, depending what is the best for the subject (both arms)	Up to the investigator, depending what is the best for the subject (both arms)

Access Arm:

If the subject contact occurs over the phone, study center personnel must instruct the subject to transmit data via CareLink®. Study center personnel will review the data received via CareLink® within 2 business days of receiving the transmission.

Once OptiVol® alert has been occurred, study center personnel (either the implanting center or the referring cardiologist) is notified on the OptiVol® alert condition. The HF-Management-Report and Cardiac Compass® Trends must be reviewed in association with **contacting subject within 2 business days** to evaluate the subject's condition and heart failure status.

When the subject is initially contacted additional CareLink® remote visits are required to be scheduled with the subject who will be asked to interrogate and send ICD / CRT-D data via CareLink® Network **every 4 days for a maximum of 3 times** until the OptiVol® fluid index decreases below the physician-programmed OptiVol® threshold. Again the study center personnel is required to review HF-Management Report and Cardiac Compass® Trends and to **contact subject at least within 2 business days** to evaluate the subject's condition and heart failure status. This intervention algorithm must be followed until the OptiVol® fluid index decreases below the physician-programmed OptiVol® threshold. The following algorithm is encouraged to be followed: as outlined in Figure 6.

Figure 6: Intervention algorithm

If anything is identified, the following actions are encouraged

OPTIVOL ALARM (OPTIVOL® index above threshold)?

↓

Contact subject within 2 business days

Indications for imminent cardiac decompensation?

- Has the subject been compliant regarding limit of fluid intake and regularly taken his medication?
- Body weight increased, blood pressure increased?
- Are there any peripheral edema; are there any signs of (pulmonary) infection (fever, cough, sputum)?
- Obtain procalcitonin.
- Has adverse medication been added (Glitazones, NSAIDS, Antiarrythmics)? BNP/NT-pro BNP values increased over baseline?

↓

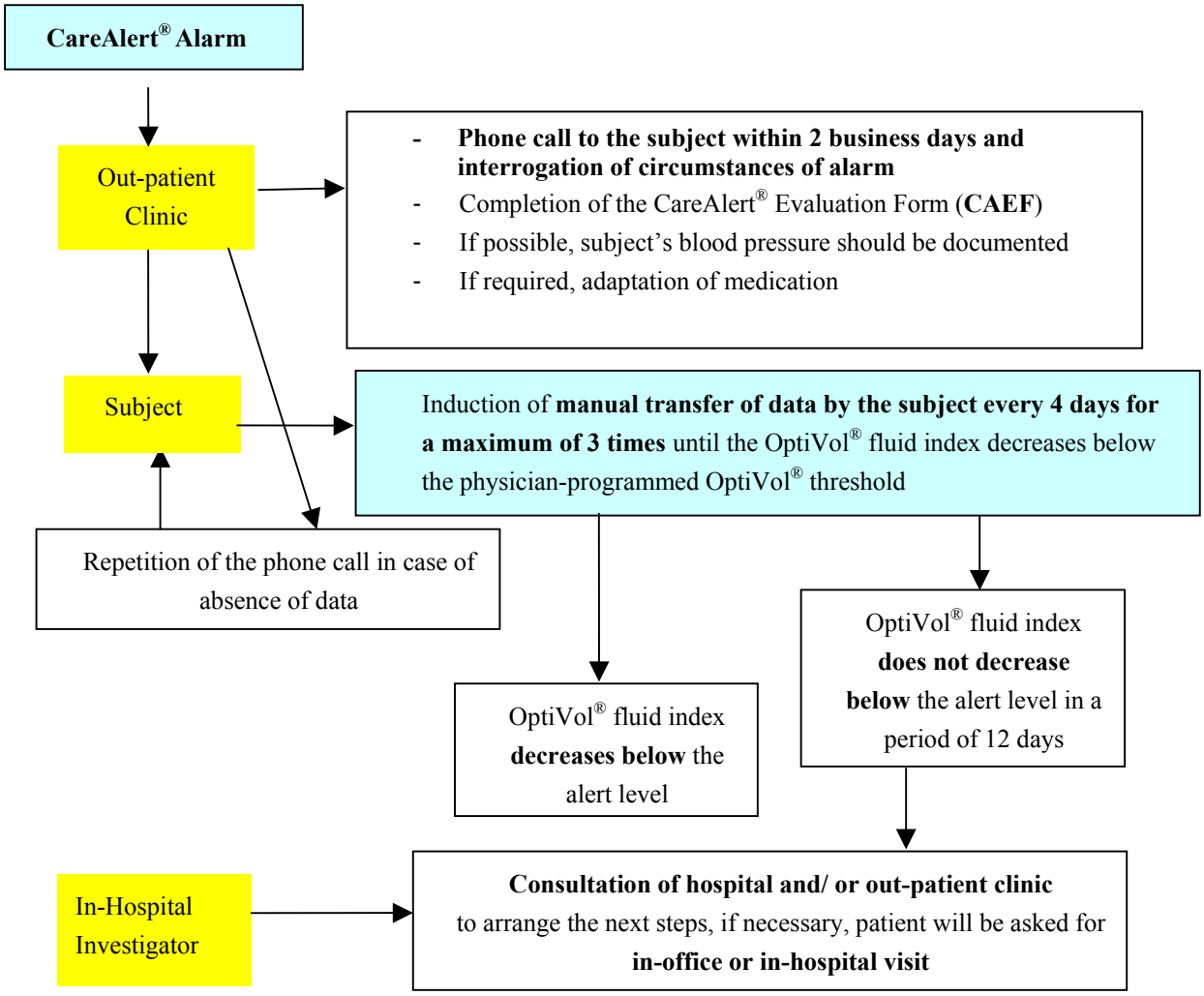
Optimize Heart Failure diagnostic and therapy according to eliciting causes
Re-enforce regular intake of medication and restriction of fluid intake, start antibiotic if indicated, increase oral diuretics, stop adverse medication if possible.

↓

Check for improvement of fluid index & symptoms **every 4 days for a maximum of 3** times until the OptiVol® fluid index decreases below the physician-programmed OptiVol® threshold

A scheme of the intervention is presented in Figure 7.

Figure 7: Intervention (CareLink® Access Arm) notice



If, at any point in the intervention algorithm determination, the clinician identifies an audible alert other than the OptiVol® alert, the EP/implanting clinician (if different) must be notified and the subject will be managed per routine practice.

Study center personnel will document rationale if no action is taken upon initial notification of OptiVol® threshold crossing and/or new or worsening signs/symptoms of cardiovascular decompensation.

If the active peripheral HF-management center is completing the intervention algorithm, the clinician must notify the EP/implanting clinician (if different) and vice versa.

Control Arm:

An intervention is an action required and documented as an AE in the AEF in case of clinical deterioration either notified by the subject or recognized by a study physician.

4.11 Device Interrogation and Save-to-Disk

Save-to-disk (StD) data will be obtained using the Medtronic CareLink® Model 2090 and 2090W programmers. Data will be saved on a 3.5-inch computer diskette that is IBM compatible having capacity of either 720 Kb (DS, DD) or 1.44 Mb (DS, HD). Diskettes will be provided with attached labels. The Medtronic CareLink® model 2090 and 2090W programmers will automatically assign a unique name to each file and hence will not overwrite any existing session export file or memory report file. To indicate which file was saved for a particular session, the diskette file directory will automatically list the date and time each file was created.

Save-to-disk data with final programming are always required for subjects from the control arm, whenever a device reprogramming is performed.

If device reprogramming is performed for subjects from the access arm, the save-to-disk requirement is substituted by manual data transmission to CareLink® Network within a 2 days window after the in-office-/hospital visit. Save-to-disk data can also be required for subjects of the access arm, depending on the availability of data from the CareLink® Network for analysis.

Every save-to-disk must be sent to external CRO (IFE) and copy retained in the subject binder.

Table 6: Device Interrogation and Save-to-Disk-Requirements

Time	Type of Interrogation and Save-to-Disk (StD)
Baseline	**C:** If not yet received during implant then initial and final interrogation and StD with final programming
Scheduled follow-up visits and study exit	**Only C:** Initial and final interrogation and StD with final programming **A:** Verification of automatically transferred interrogation with unchanged programming
Unscheduled follow-up visits	**C:** Initial and final interrogation and StD with final programming **A – in case of office visit:** Save-to-disk is substituted by manual data transmission of device data to CareLink® Network
System modification	**A & C:** Final interrogation and StD with final programming of revised system / explanted device Final interrogation and StD with final programming of new implanted device

A: Access Arm
C: Control Arm

4.12 Study Exit

All consented subjects will be documented in the database. Enrolled subjects who fail to meet final eligibility criteria will not be randomized. The subject will be exited from the study and a study exit CRF will be completed.

A study exit will be documented for any of the following:

- Subject death,
- Study closure,
- Subject withdrawal/investigator withdrawal of subject/lost to follow-up.

The investigator shall complete the study exit form (SEF). The following information will be collected (if applicable):

- NYHA class,
- Medication and/or changes,

- HF symptom status (or death information),
- KCCQ and EQ-5D,
- ICD / CRT-D-therapy assessment,
- Review of Cardiac Compass® Trends and HF Management Report,
- Device interrogation, StD.

4.12.1 Subject Death

If the death occurs at a center remote from the investigational center, it is the investigative center's responsibility to make every attempt to retrieve all subject's information related to the subject's death and submit the investigator's summary of the known events surrounding the death.

In the event of a subject death, the following information related to the death will be documented on the study exit form (SEF) and reported to the CRO:

- Date of death,
- Date study center became aware of death,
- Description of death (see section 4.15),
- Primary cause of death,
- Location of death,
- Time of death (if known),
- Any adverse events leading up to the death,
- Investigator death relatedness classification (i.e. cardiac related, procedure related, system related),
- Death summary/autopsy report/death certificate, if available,
- Save-to-disk, if available,
- Whether or not the device and leads, if explanted, were sent to the sponsor.

If a physician's death summary report is available or an autopsy is performed, submit a copy of the autopsy report to the OptiLink HF study clinical trial leader. If the death occurs at a center remote from the investigational center, it is the study center's investigator responsibility to make every attempt to retrieve all pertinent information related to the subject's death and submit the investigator's summary of the known events surrounding the death.

4.12.2 Study Closure

Study closure is defined as a specific date that is determined when the clinical investigation plan requirements and/or regulatory requirements have been satisfied.

4.12.3 Subject Withdrawal/Investigator Withdrawal/Lost to Follow-Up

Any subject withdrawn from the study before the scheduled completion will be considered an early withdrawal, regardless of the reason for the withdrawal. The subject is free to withdraw from the study for any reason and at any time without giving any explanation for doing so and without penalty or loss of future medical care. The investigational center should indicate if the withdrawal was related to the investigational system.

The investigator is also free to terminate a subject's involvement in the study at any time if it would be to the subject's detriment to continue. It is also possible that the sponsor or the competent authorities request termination of the study, if there are concerns about conduct or safety. In particular cases the study may be terminated at a single investigational site, if the sponsor has relevant reasons (e.g. no compliance with the Good Clinical Practice or clinical investigation plan). In such cases subject's participation in the study can be terminated and the subject's consent is not needed.

A subject may withdraw from the study after enrollment, if he failed to meet eligibility criteria.

All data available at the time of withdrawal or last visit will be used for analysis. There will be no future required study-related follow-up visit for this subject.

The written documentation shall be provided stating the reason, why the subject was withdrawn:

- To the sponsor and subject, if the investigator withdraw a subject from the study,
- To the investigator with the request to inform the subject, if the sponsor decides to withdrawn a subject from the study,
- The investigator shall complete the study exit form (SEF).

The study investigator or Medtronic may terminate the subject's participation in the study without the subject's consent if two consecutive follow-up visits are missed, if subject routinely fails to complete required procedures, and/or if the investigator feels it is medically necessary. If the subject fails to comply with follow-up visits, the study center must make repeated attempts to contact the subject. At least three documented attempts must be made to contact the subject, documenting the method used (e.g. telephone contacts, registered letters). At least one attempt must be made in writing.

4.13 System Modification

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

In the event of a system modification, including removal and/or modification of the entire or a portion of the implantable system, the follow-up schedule for the subject will remain unchanged (i.e. the subject should continue to be followed and scheduled follow-up CRFs should be completed based on the original follow-up schedule). Study center personnel will report the adverse event as described in section 4.15 to document the underlying cause or events related to the system modification.

a) Explanted Devices

- Prior to device explant, interrogate the study device and perform a save-to-disk. An "Interrogate all" must be performed at the initial interrogation to collect all data from the device before it is reprogrammed as described below.
- Disable all VT/VF detection capabilities prior to removal to avoid inadvertent shock delivery. Whenever possible, disable the OptiVol® alert prior to device or RV lead explant.

For information on how to return an explanted device the local Medtronic representative should be contacted.

If the device is explanted and a replacement "study" device is not immediately re-implanted, continue to collect any adverse events, health care utilizations, telephone contacts, study deviations, and scheduled follow-up visit data through the time period where subject is without a study device. If the device is explanted and a replacement device will not be implanted, complete a study deviation and continue to follow the subject. If the subject was initially randomized to the access arm, the subject will be crossed over to the control arm and prior approval by a designated member of the steering committee will not be required, however study center personnel must contact Medtronic or the CRO. Not obtaining prior approval by a designated member of the steering committee for this purpose will not result in an additional study deviation. If the subject was initially randomized to the control arm, the subject will remain in the control arm.

b) Replaced Devices:

- Interrogate the replacement study device and perform a save-to-disk, unless the subject's replacement device is a non-study device,
- Enroll the subject in CareLink® under the new device serial number, unless the subject's replacement device is a non-study device (access arm only),

- If the subject's replacement device is a non-study device, complete a study deviation form. The subject will not be exited but will be followed per their original follow-up schedule. If the subject was initially randomized to the access arm, the subject will be crossed over to the control arm and prior approval by a designated member of the steering committee will not be required. Not obtaining prior approval by a designated member of the steering committee for this purpose will not result in a study deviation. If the subject was initially randomized to the control arm, the subject will remain in the control arm. Note that primary and secondary objectives will be analyzed using the intent to treat principle.

c) Lead replaced / repositioned / capped / explanted or the subject had a pocket revision:

- Perform an initial interrogation and save to disk prior to the revision. The initial interrogation must be "Interrogate all",
- If the lead or pocket is modified and the subject is randomized to the access arm, consider programming the OptiVol® alert to "OFF (Observation only)" for a minimum of 30 days or until the time of the subject's post-operative visit, but no more than 60 days post-system modification. Consider adjusting the reference impedance once the subject's pulmonary fluid status is stable, the OptiVol® trends show the subject's daily thoracic impedance is stable, and if the reference impedance has not adjusted to the subject's daily impedance,
- Perform a final interrogation and save-to-disk with final programming after the revision.

In addition to the requirements outlined above, the system modification is required to be recorded on the study deviation form CRF.

4.14 Study Deviation

A study deviation is defined as an event within a study that does not occur according to the clinical investigation plan or the Clinical Trial Agreement.

Prior approval by the Study Management 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 life or physical well being of a subject in an emergency. Prior approval is not expected in situations where unforeseen circumstances are beyond the investigator's control (e.g. subject failure to attend scheduled follow-up visits, inadvertent errors, equipment failure, or inability to perform required procedures due to subject illness). Refer for study Sponsor contact information to section 12.

All study deviations must be reported to IFE. In the case that the deviation involves a failure to obtain subject informed consent or is made to protect the life or physical well being of a subject in an

emergency, the deviation must be reported immediately to IFE. Reporting of all other study deviations should be completed as soon as possible and should comply with MEC policies and/or local laws. All deviations must be reported to IFE on the study deviation form (DEF).

Record any deviation together with an explanation for the deviation and corrective action. Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions. Medtronic will review study deviations and assess the need to amend the clinical investigation plan, conduct additional training, or to terminate the investigation. When relevant, deviations will be reported to the MEC or appropriate regulatory body. A center-specific report of study deviations will be provided to the investigator on regular basis (approximately every six months).

4.15 Adverse Events and Deaths

The following adverse event information will be collected throughout the study and reported to IFE on an adverse event form as described below:

Adverse Event

An adverse event is defined as any untoward medical occurrence in a subject. (ISO 14.155)
NOTE 1: This definition does not imply that there is a relationship between the adverse event and the device under investigation.

Adverse Device Effect (ADE)

Any untoward and unintended response to a medical device. (ISO 14.155)
NOTE 1: This definition includes any event resulting from insufficiencies or inadequacies.
NOTE 2: This definition includes any event that is a result of a user error.

Serious Adverse Event (SAE) (ISO 14.155)

An adverse event that

a) led to death

b) led to a serious deterioration in the health of a subject that

1) resulted in a life-threatening illness or injury,

2) resulted in a permanent impairment of a body structure or a body function,

3) required in-patient hospitalization or prolongation of existing hospitalization, or

4) resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function

c) led to fetal distress, fetal death or a congenital abnormality or birth defect.

An adverse event is considered "serious" if condition 1, 2, 3, or 4 apply in combination with a serious deterioration in health e.g. a planned hospitalization for a pre-existing condition, without a serious deterioration in health is not considered to be a SAE.

Serious Adverse Device Effect (SADE)

An ADE that has resulted in any of the consequences characteristic of a Serious Adverse Event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

Unavoidable Adverse Event - An adverse event inherent to a surgical procedure that is expected to occur in all subjects for a projected duration according to the investigator's opinion, including, but not limited to the unavoidable adverse events listed in Table 7. **The implantation is not a part of the study thus the list below should be considered as additional information.**

Table 7: Unavoidable Adverse Events

EVENTS DESCRIPTION	TIME FRAME (HOURS) FROM THE SURGICAL PROCEDURE
Anesthesia related nausea / vomiting	24
Low grade fever (100°F or 37.8°C)	48
Pocket site / incisional pain	72
Mild to moderate bruising / ecchymosis (at pocket site)	72
Sleep problems (insomnia)	72
Back pain related to laying on table	72

Relatedness

System Related Adverse Event

An adverse event that results from the presence or performance of the system. In this study, the system includes the Medtronic Virtuoso™ ICD or Concerto™ CRT-D (or subsequently market released devices providing at least the same functionality), pace/sense leads and cardioversion/defibrillation leads, and the Medtronic CareLink® 2090 or 2090W programmer and its market released software.

Non-System Related Adverse Event

An adverse event that does not result from the presence or performance of the system.

Death Reporting

All subject deaths will be collected from time of enrollment until the subject is exited from the study or study closure. The investigator will report deaths using the study exit form (SEF) as soon as possible upon notification and classify the event based on the following categories:

- Cardiac (Y/N),

If cardiac, sudden vs. non-sudden

- Relatedness,
- Cause of death.

Death Review and Classification

An independent events committee will assess, review and classify all deaths. The committee will regularly review and adjudicate reported deaths.

All reported deaths will be reviewed and classified by the events committee based on the following categories:

- Cardiac (Y/N),

If cardiac, sudden vs. non-sudden:

- Witnessed vs. not witnessed,
- Relatedness,
- Cause of death.

Death Definitions

All reported deaths will be reviewed and classified by the events committee based on the following definitions:

Cardiac

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

Sudden Cardiac Death (SCD)

Natural death due to cardiac causes, heralded 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

A death not classified as a cardiac death.

Witnessed

The death is considered witnessed if someone was able to give a firsthand account of the death by either having seen or heard the subject at the time of death. In addition, the event will be considered witnessed if the subject was hospitalized and being monitored at the time of death.

Non-Witnessed
All deaths not classified as witnessed will be considered non-witnessed

System Related

A death will be considered system related if it results from the presence or performance of any component of the implantable system, investigational software, CareLink® monitor or the programmer and its market released software. The "system" includes the ICD / CRT-D device, CareLink® monitor (access arm only), pace/sense leads, and cardioversion/defibrillation leads.

Non-System Related

A death that does not meet the definition of "system related".

4.16 Recording and Reporting of Adverse Events

All new and/or worsening adverse event (AE) information, except for unavoidable adverse events, will be collected from time of enrollment until the event is resolved, the subject exits the study, or study closure. The investigator will report adverse events to the CRO using the adverse event form (AEF) as soon as possible. All adverse events, regardless of relatedness or outcome must be reported.

Investigators are provided with a list of previously reported adverse events for the subject population identified for the study in appendix K. For any changes in status of an adverse event (i.e. change in action, change in outcome), an adverse event update CRF will be completed until the adverse event is resolved, the subject exits the study, or until study closure, whichever occurs first.

Information reported on the adverse event form will include a description of the event, the diagnosis, the date of event onset, the relatedness of the event to the procedure, the relationship of the event to the device/system, actions taken as a result of the event and the outcome of the event and the date the event was first noticed by the investigator.

In case the investigator requires information from the sponsor in an emergency situation, the investigator can contact the sponsor. Contact details are given in section 12.

The investigator shall report serious adverse device effects and serious adverse events immediately after learning of the effect.

Medtronic shall report the serious adverse events and device effect to MEC and relevant competent authorities based on regulatory requirements in addition to reporting events through the standard vigilance reporting system, as required.

The adverse events need to be reported according to Table 8.

Table 8: Adverse event reporting requirements

Serious Adverse Events (SAE) and Serious Adverse Device Effects (SADE)	
Investigator submit to:	
IFE	Immediately via fax after the investigator first learns of the event.
MEC	Submit to MEC per local MEC requirement.
Sponsor submit to:	
Regulatory Authorities	Reporting timeframe as per local requirement.
MEC	Submit to MEC per local reporting requirement.

The following information shall be collected on the AE CRF:

- Subject ID and center address
- Date of report
- Date of event onset
- Date study center became aware of event
- Description of the event
- Primary diagnosis best representing the event
- Seriousness
- Device and procedure relatedness shall be assessed
- Action(s) taken
- The outcome of the event.

The sponsor will review all AEs. This review will include the determination whether the adverse event meets regulatory reporting requirements. The sponsor will ensure timely adverse event reporting to meet global regulatory requirements.

4.17 Event Review

MedDRA, the Medical Dictionary for Regulatory Activities, will be utilized to assign a key term for each event based on the information provided by the investigator. The key term will be reviewed and adjudicated by an independent events committee. The committee will regularly assess, review and classify all adverse events including hospitalizations, emergency department visits, urgent and non-urgent unscheduled office visits. The committee will **consist of a minimum of three and a maximum of nine physicians** including a chairperson appointed either by Medtronic or the events committee. The chairperson must either be present at each meeting or provide their input for the meeting attendees to discuss.

At least three committee members must review at a minimum all deaths, serious and system adverse events. At least one physician member of the committee will review all other adverse events. The committee will regularly review and adjudicate reported adverse events.

All reported adverse events will be reviewed and classified by the events committee based on the following categories:

- Relatedness to system/procedure (Y/N),
- Serious vs. not serious,
- Is the safety composite event definition met? (see below for definition),
- Is the Clinically Relevant Thoracic Event definition met? (see below for definition).

Additionally, an arrhythmia committee will review and classify device-detected sustained VT/VF episodes to determine which episodes were appropriately detected sustained VT/VF episodes for the safety composite event definition.

4.18 Emergency Contact Details in Case of Serious Adverse Event

In case of an immediately reportable adverse event the investigator should contact:

Dr. Michael Berghahn
IFE Europe GmbH
Zeche Katharina 6
D-45307 Essen, Germany
Phone: +49(0) 201/8990-123
Fax: +49(0) 201 8990-251
safety@ife-europe.com

4.19 Study Specific Definitions

A) HF Event

Heart Failure Hospitalization

A therapeutic, in-patient hospitalization extending over a calendar date change where admission occurs after consent for worsening heart failure associated with signs and symptoms of:

- congestion treated with administration of diuretic and/or vasodilators and/or inotropes and/or other parenteral therapy

  OR

- low cardiac output due to heart failure indicated by organ compromise treated with IV therapy

B) Safety Composite Event

A safety composite event is an event that includes one or more of the following:

- Syncope,
- Worsening renal function resulting in IV therapy, ultrafiltration, or dialysis,
- Hypotension and/or hypovolemia resulting in the administration of fluids,
- Clinically significant electrolyte abnormalities resulting in IV replacement or ER/hospitalization for correction,
- Appropriately detected sustained VT/VF episode,
- Death.

C) Cardiovascular related hospitalization

A hospitalization extending over a calendar date change that is due to causes including, but not limited to, the following: heart failure, myocardial infarction, coronary insufficiency, acute coronary syndrome/unstable angina, non-ischemic atrial or ventricular dysrhythmias, symptomatic bradycardia/heart block, syncope, cardiac procedures (percutaneous or surgical), peripheral vascular disease or resulting complications, pulmonary or vascular emboli, aortic aneurysm / dissection, stroke, TIA, vascular surgery/procedure, or heart transplant.

D) Clinically Relevant Thoracic Event

An event that may impact thoracic impedance including but not limited to:

- Acute dialysis
- Pulmonary edema

- Pericardial effusion
- Pneumonia
- Pleural effusion
- Ultrafiltration for HF management
- Protocol required scheduled follow-up visits, ED, hospitalization, urgent or non-urgent unscheduled office visit with evidence of congestion.

4.20 Post Market Surveillance

All devices used in this study are marked released. Therefore Post Market Surveillance is applicable. It is the responsibility of the investigator to report all product complaints and malfunctions immediately via the regular channels for CE marked products.

The reporting of product complaints and malfunctions is not part of the clinical study and should be done in addition to the adverse event reporting requirements. The investigator must report issues with non-Medtronic leads to its manufacturer, not to Medtronic.

Product Complaint:

Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a device after it is released for distribution.

Malfunction:

Failure of a device to perform as claimed by the manufacturer. This includes all performance specifications and all claims made in the instruction for the device.

Medtronic will notify the Competent Authority of the following incidents immediately on 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 subject, 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 impairment of a body function or permanent damage to a body structure.

4.21 Health Economics

Cost Effectiveness:
A payer perspective is used, covering the major cost drivers of hospitalization, emergency department visits, medication and "out-patients" visits.

Data Collection:
Healthcare utilization of emergency department visits, hospitalization, out-patient and all further utilization of healthcare will be collected based upon discharge summaries (if applicable) and CRF based information. Utilization of medication will be based on CRF information assessed at follow-up visits or any other subject contacts, e.g. phone contact, by the implanting center and HF management center over time. Life expectancy will be derived from the mortality data collected within the trial. HRQOL data will be assessed by questionnaire leading to determination of QALY's and ICER's.

5 STATISTICAL METHODS AND DATA ANALYSIS

This chapter describes the statistical analysis as it is foreseen at the time of planning the study. Any major deviations from this plan, the reasons for such deviations, and all alternative or additional statistical analyses that may be performed will be mentioned in the **Statistical Analysis Plan (SAP)**, which gives a detailed technical description of all statistical analyses. All deviations and/or alterations will be summarized in the clinical study report (CSR).

Because of the unpredictability of potential problems, it may be necessary to decide about the manner of dealing with irregularities in a data review meeting.

5.1 Study Populations

Analyses will be based on the following sets: total set, safety set, full analysis set, and per protocol set. The definitions of the analysis sets follow those given in the ICH E9 guideline.

5.2 Total Population

The total set consists of all subjects enrolled including subjects withdrawn from the study.

5.3 Safety Population

The safety population includes all enrolled subjects after implantation.

5.4 Intention-to-treat Population

The intention to treat (ITT) population consists of all subjects from the safety population who are eligible for the study, i.e. all subjects, who have post-baseline data available and who did not fail to satisfy major entry criteria (details see ICH E9 guideline).

5.5 Per Protocol Population

The per protocol (PP) population consists of all subjects of the ITT population who completed the study without major protocol violations or who terminated the study prematurely due to an adverse event with at least likely relation to the study device or due to lack of efficacy. Decisions on protocol violations will be made individually in the data review meeting.

5.6 Statistical Analysis of Primary Objective

The OptiLink HF study is powered to detect whether the "OptiLink" functionality causes a clinically relevant decrease of 30% in the rate of all-cause death or cardiovascular related hospitalization within 18 month.

For the analysis of the primary variable the rate of all-cause death or cardiovascular related hospitalization will be determined **for the 18 month following day 34 (the day of activation of the OptiVol® algorithm; the period between the implant and day 34 is used to build up the impedance reference value** see section 2.3.2).

The following hypothesis will be investigated:

$$H_0: \; p_{control} - p_{alert} \leq \theta \quad \text{vs} \quad H_1: \; p_{control} - p_{alert} > \theta$$

whereby $p_{control}$ denotes the rate of all-cause death or cardiovascular related hospitalization within 18 months for the control arm, p_{alert} denotes the respective rate of all-cause death or cardiovascular related hospitalization in 18 months for the access arm and θ corresponds to the difference of the

rates of the treatment arms, which is assumed to be 8.4%, if 30% improvement from the control arm can be expected (see 3.3) .
Group comparison will be performed on an α-level of 2.5%. Fisher's exact test one-sided will be used. Additionally the corresponding confidence intervals will be calculated for the rates and their differences.
If the p-value is below 0.025 the superiority of the OptiVol® fluid status monitoring with automatically generated wireless CareAlert® notification of clinician will be concluded.

Sample Size Calculation

The calculation of the sample size for the present study is based on available study data using the experience from previous studies (see 3.3). Only ICD / CRT-D subjects will be included in this study.

For sample size calculation the following assumptions are made:

type I error α=0.025 and power β=0.8,

rate control arm = 28%, difference between treatment arms = 30% of control arm → 8.4%

The method for analysis of the primary criterion is the Fisher's Exact test one-sided.
Based on these assumptions the total sample size of 848 will have 80% power to detect a difference of 8.4% between the rates of all-cause death or cardiovascular related hospitalization of the two treatment arms. Taking into account early study termination 1000 subjects will be enrolled in the study (drop-out rate: ≈18%).

Interim analysis:
An interim analysis is planned after 150 (40% NYHA II and 60% NYHA III) subjects will have finished the study. The focus of this interim analysis will be to check if the assumptions for the rates of all-cause death or cardiovascular related hospitalization of the treatment groups and the corresponding difference fit. Depending on these results (see 3.3) the sample size can be adapted following the rules of an adaptive design.

5.7 Secondary Objectives

All secondary variables will be analyzed by descriptive statistical methods. For discrete variables frequencies and percentages will be determined, for continuous variables parameters for location and dispersion will be calculated. Shift-tables and pre-post differences can be determined, if applicable.

In general hospitalizations or deaths will be classified according to the following causes:

1) Cardiovascular related,
2) Heart failure related,
3) Related to other causes,

4) All causes,
5) Sudden cardiac death*

*only death.

The following secondary objectives will be tested on an α of 5% each. P-values will only be interpreted in an exploratory sense.

The number of hospitalizations according to the above-mentioned causes will be compared for both study arms by means of Wilcoxon rank-sum test two-sided. The corresponding rates of first hospitalization will be compared using Fisher's exact test.

The number of days in hospital and the number of days alive out of hospital according to the above-mentioned causes will be compared using Wilcoxon rank-sum test two-sided.

Mortality rates according to the above mentioned causes will be determined and compared by means of Fisher's exact test. Furthermore mortality rates as well as HF-related mortality rates after the first HF-related hospitalization and after the first decompensation will be determined.

Time to event analyses will be performed for the time to first all-cause hospitalization or death, the time to first all-cause hospitalization, time to first HF-related hospitalization, time to first cardiovascular related hospitalization, time to first hospitalization because of decompensation, time to first all-cause death, time to first HF-related death, time to cardiovascular related death and time to first death because of decompensation. The time to event analyses will be carried out using Kaplan-Meier method and Log-rank tests will be performed to compare the risk for both access arms.

The number of adverse events, and the number of HF-related events and cardiovascular related events only will be compared for both study arms using Fisher's exact test.

The quality of life assessed by means of the Kansas City Cardiomyopathy Questionnaire (KCCQ) and EQ-5D questionnaire will be compared by means of Wilcoxon rank-sum test.

Additionally all demographic data, medical history, previous and concomitant diseases and medication, vital signs and results from physical examination will be analyzed descriptively.

5.8 Subgroup Analyses

Subgroup analyses will be carried out for ischemic and non-ischemic cardiovascular diseases, subjects with or without atrial fibrillation and subjects with or without VT/VF episodes before implant.

5.9 Adverse Events

The recorded adverse events will be coded according to MedDRA. The adverse events will be summarized by treatment, System Organ Class, preferred-term and intensity.
Nature, incidence and intensity, as well as the investigator's and the sponsor's causality assessment will be reported for each treatment-emergent adverse event. Descriptive summary statistics, e.g. with regard to the incidence of symptoms and the causality assessment, will be presented for the study period.

5.10 Handling of Missing Values

A worst-case scenario will be used for replacing missing values for the primary variable. Missing values will be taken into account as an event (death or hospitalization). For all other variables missing values will not be replaced.

5.11 Data Entry and Validation

Data management procedures will be specified in the data management plan (e.g. double data entry, plausibility checks).

6 RISK ANALYSIS AND RISK ASSESSMENT

6.1 General Potential Risk associated with ICD or CRT-D Systems and CareLink®

The safety and clinical performance of the Medtronic market-released ICD or CRT-D systems have been demonstrated through previous pre-clinical testing and previous clinical studies. Model C154DWK / C174AWK Concerto™ CRT-D and D164AWC Virtuoso™ DR / D164VWC Virtuoso™ VR or subsequent devices providing at least the same functionality used in this study are market-released. Should subsequently market released devices be used within the study, their safety and clinical performance will have been assessed equally through clinical studies before market release.
Therefore, it is not anticipated that subjects implanted with these devices enrolled in this study will be exposed to any risks beyond those normally associated with ICD or CRT-D and transvenous lead systems.

Medtronic has attempted to minimize the risk of implanting Medtronic ICD or CRT-D systems through careful design and pre-clinical testing. Pre-clinical testing includes bench testing to verify

performance, software validation testing, biocompatibility tests, destructive analysis and shock tests and packaging qualifications.

6.2 Risk Minimization

Medtronic has attempted to minimize risk to subjects by requiring routine, scheduled follow-ups, training of study center personnel and Medtronic personnel, and implementing a Data Safety Monitoring Board to review safety issues as part of the study.

6.3 Potential Benefits

Literature has supported that subject outcomes improve during the course of participating in a clinical study. This may be a result of study subjects having increased interaction with study center personnel. Consequently, the clinician may evaluate their HF status more frequently.

The information gained from this study may help clinicians understand how to better manage HF in the future. The implementation of this study may provide insight into how subjects can be better served by reinforcing the interaction between HF and EP clinicians. Additionally, information collected from this study may assist in the design of new product(s)/therapy(ies) and/or instructions for use.

7 WARRANTY AND INSURANCE

7.1 Warranty

Warranty information is provided in the product packaging for the commercially released Concerto™, Virtuoso™, and subsequently market released devices and the Medtronic leads used in this study. Warranty information will be provided in the product packaging for any future CE-approved Medtronic devices with OptiVol® fluid status monitoring. This study does not affect the warranty.

7.2 Insurance

The following statement of the provisions made for subject compensation and of insurance to cover liability:

Medtronic GmbH 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 MEC.

8 MONITORING AND AUDIT

8.1 Monitoring

It is the responsibility of the study sponsor, Medtronic GmbH, to ensure that proper monitoring of the study is conducted and that MEC review and approval of the investigation is obtained. Trained Medtronic personnel or delegates from the CRO appointed by the study sponsor will conduct monitoring activities in order to ensure that the investigation is conducted, recorded and reported in accordance with the clinical investigation plan, signed clinical trial agreement, and applicable regulatory requirements of the local law. The following factors will be taken into account when determining the frequency of the monitoring visit:

- Subject enrollment rate at each center,
- Total number of subjects enrolled at each center,
- Clinical investigation plan compliance at each center,
- Any suspected inconsistency in data that requires investigation.

Monitors shall require direct access to subject medical records, study management documents, regulatory documents, and subject informed consent documents, as well as other potential applicable records not listed here. Monitors may ensure the clinical investigator have and continue to have staff and facilities to conduct the clinical investigation safely and effectively.

Monitors may conduct the following monitoring activities throughout the study:

- Verification that the current MEC-approved informed consent was signed and dated by each subject prior to participating in study required procedures,
- Verification of documentation in the subject's record that informed consent was signed prior to initiation of study procedures,
- Comparison of CRFs against source documentation for accuracy and completeness of information,
- Verification that subjects met study enrollment criteria,
- Confirmation that the study is being conducted according to the clinical investigation plan and applicable regulations,
- Verification that study deviations are documented and reported,

- Verification that the procedures for recording and reporting adverse events to the sponsor are followed,
- Ensuring proper error correction,
- Reviewing subject documentation with regard to subjects deemed lost to follow-up and subject drop-outs (to determine accuracy and ensure valid attempts to locate subject lost to follow-up),
- Verification of training documentation of all study personnel participating in study-related activities,
- Reviewing all correspondence and regulatory documents, including confirmation of MEC-approved clinical investigation plan or amendments,
- Resolution of outstanding issues and completion of assigned tasks will be documented by the monitors.
- Other monitoring items as they arise.

New and previous findings (ongoing or resolved) and recommended corrective/preventative actions (if applicable) will be communicated with the study staff during the visit and will also be addressed in a final letter that will be sent to the investigator after the visit. Items requiring resolution will be documented on an action item worksheet maintained by the sponsor.

Study closure visits (for definition refer to section 4.12.2) will be conducted at all enrolling clinical sites in order to review record retention requirements, device/software disposition requirements, etc., with site personnel. A telephone contact may take the place of a study closure visit if appropriate (e.g. low subject enrollment, recent monitoring visit, etc.). For contact information on the CRO performing study monitoring refer to administrative page. A separate monitoring plan will specify details on the monitoring process and source data verification

8.2 Auditing

All records and other information about subjects participating in this study will be treated as confidential. IFE will collect data and monitor study records. The sponsor or regulatory authority may audit the study center to evaluate the conduct of the study. The clinical investigator(s)/center(s) shall allow auditing of this study by providing direct access to source data/documentation. Participating subjects will not be identified by name in any published reports about this study.

9 RECORDS AND REPORTS

9.1 Investigator Records and Reports

The investigator is responsible for the completion (review and signature, if applicable) and retention of the records cited below. The following records are subject to inspection by the regulatory bodies and must be retained for a period of two years after the date on which the investigation is terminated or completed or according to local regulatory requirements, whichever is greater. Study closure is defined as a specific date that is determined when the clinical investigation plan requirements and/or regulatory requirements have been satisfied.

The investigator shall maintain the following accurate, complete and current records relating to the investigator's participation in this study:

- Relevant correspondence/documentation with another investigator, an MEC, competent authorities, Medtronic, monitors including required reports that relate to this study,
- Delegated tasks list,
- Subjects' case history records including:
  - Signed subject informed consent documents,
  - Medical history,
  - All CRFs and supporting data (source documents),
  - All relevant subject complaints,
  - Observations of adverse events.
- All clinical investigation plans and amendments,
- Final CRFs,
- Documentation of the dates and reasons for any deviation from the clinical investigation plan,
- Study center personnel training records,
- Investigator Agreement,
- Signed clinical trial agreements/Co-Investigator addenda including Financial Disclosure information,
- Current curriculum vitae for principal investigator and any co-investigators,
- MEC/authorities approvals, renewals, and correspondence,

- MEC approved Patient Informed Consent Form,
- Insurance statement/certificate.

IFE will supply required paper CRFs. The investigator is responsible for the accurate and correct preparation (review and signature) and submission to the sponsor of all CRFs, all deaths and reportable adverse events and any deviations from the clinical investigation plan. All reports are subject to inspection and to the retention requirements described above for investigator records. If an MEC takes any action related to this clinical study, copies of all pertinent documentation shall be forwarded to the sponsor.

Table 9: Investigator Reports

REPORT	SUBMIT TO	DESCRIPTION/CONSTRAINTS
Withdrawal of MEC Approval (either suspension or termination)	Sponsor	Report if required by local law.
Deviation from clinical investigation plan	Sponsor & MEC/authorities	Any deviation from the CIP shall be recorded together with an explanation for the deviation. (EN ISO 14155-2:2003(E)4.9) For MEC: deviations associated with emergency situations to protect the life and well being of the subject. Informed consent shall be obtained in writing and documented before a subject is enrolled into the clinical investigation. (EN ISO 14155-1:2003(E))

9.2 Sponsor Records and Reports

Records are subject to inspection by regulatory bodies. Medtronic will maintain (but is not limited to) the following records:

- Relevant correspondence (including correspondence with authorities and MEC, as applicable) which pertains to the investigation, including MEC approval letter,
- Signed clinical trial agreement, recent curriculum vitae of investigators (signed and dated), and confidential disclosure agreement,
- Study reportable adverse events, deaths,
- All CRFs submitted by investigator and center-specific samples of subject informed consents,

- Clinical investigation plan and any amendments,
- Training documentation of all IFE study personnel,
- Insurance statement / certificate,
- Name of principal investigator and institution in which the clinical investigation is conducted,
- Approvals of study documents,
- CIP deviations.

Table 10: Sponsor Reports

REPORT	SUBMIT TO	DESCRIPTION/CONSTRAINTS
Premature termination or suspension of the clinical investigation	Investigators, MECs/ competent authority	Medtronic will provide prompt notification of termination or suspension and reason(s).
Final Report	All MECs and competent authority	A final report will be submitted to the MECs after completion or termination of the study.

10 PUBLICATIONS

10.1 Publication Committee

The publication committee will be composed of members of the executive board, the steering committee, at least one member of the sponsor study team and physicians participating in the study and demonstrating a high scientific interest and subject contribution to the study. It will convene at or near the time of the first enrollment to further refine the publication strategy. Participating investigators, members of the executive board and members of steering committee, may submit publication ideas through the publication committee and may author publications. The publication committee is responsible for overseeing the development of case reports, manuscripts and abstracts according to the publication strategy, identifying and appointing the manuscript/abstract first author(s)/writer(s), and identifying Medtronic personnel responsible for assisting the first author. The publication committee will meet approximately every year to refine the publication strategy. The publication committee may refine the publication strategy during the course of the study if needed.

The publication committee reviews not only main publications, but also ancillary publications. If necessary, specified authorship criteria may be applied for ancillary publications. The committee may

decide that no case reports, publications or abstracts will be prepared prior to the end of the study. The timelines for submission are dependent upon the clinical study timelines.

10.2 Authorship Selection

Authorship is determined on the basis of the following, at a minimum:

1) Substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data,

2) Drafting the article or revising it critically for important intellectual content,

3) Final approval of the version to be published.

Authors must meet conditions 1, 2, and 3 (including Medtronic CRM clinical personnel).

Being a member of the publication committee does not guarantee authorship.

Once authorship is determined, the following criteria, at a minimum, will be considered in selecting co-authorship:

1) Demonstration of a high level of interest in the disease state, product and unique product feature(s) being studied,

2) The ability to write, review, edit, and present the publication within a reasonable time frame,

3) Author contributes to the high quality of study data for assessment of the study endpoint,

4) A demonstration of a good publication history.

Criteria for selecting first and subsequent authors will be determined and documented in a publication strategy. All investigators not listed as co-authors may be acknowledged as the "OptiLink HF clinical study investigators" and may be individually listed according to the guidelines of the scientific journal.

10.3 Ancillary Publications

Ancillary publications include those reporting on a subset of the subject population or reporting a specific aspect of the study that requires either Medtronic resources or data from the OptiLink HF clinical study. The publication committee must approve publication of ancillary requests and will need to ensure that requests do not present conflicts with other previously submitted requests. Requests for publications utilizing clinical study data will be evaluated for scientific validity and the ability of Medtronic to provide resources. If multiple geographies contribute data, co-authorship will be representative, using the guidelines for authorship selection described above.

11 ADDITIONAL COMMITTEES

11.1 Executive Committee

The executive committee consisting of 10 physicians from Germany, a member of the sponsor study team. It will be established to guide the development of the study. For detail list of the executive committee members refer to the appendix P.

11.2 Steering Committee

A steering committee consisting of physicians including also members of the executive committee and a member of the sponsor study team will be utilized to assist with planning, organizing and performance of the study. The steering committee members are listed below and may participate as investigators in the study. For detail list of the steering committee members refer to appendix R.

11.3 Events Committee

An events committee consisting of approximately nine physicians (minimum three, maximum nine) will assist in the following:

- Protocol development,
- Establishing committee guidelines and processes,
- Adjudicating events for study objectives,
- Documenting event classifications,
- Attending meetings as requested.

The events committee members are listed in appendix S and will **not be otherwise participating** in the study (i.e. no study center investigator will be involved) to assure that the transmission of information to the study center investigators about events triggering per study arm or per subject does not take place. Medtronic personnel may facilitate the events committee meeting (e.g. statistician, clinical trial leader), but they will not be voting members. The events committee will consist of two working groups (one for adjudication of HF-related events and the other for arrhythmia-related events).

The events committee will not be made aware of the randomization assignment of study subjects.

For detail list of the events committee members refer to appendix S.

11.4 Data Safety Monitoring Board

An independent, unblinded Data Safety Monitoring Board (DSMB) will be established by Medtronic to review the interim data analyses as well as to periodically review the total incidence of adverse events and deaths in this study. The DSMB for this study will consist of a minimum of three and up to seven members with study related backgrounds. Medtronic will appoint members of the DSMB and the chairperson. Up to two additional investigators participating in this study may participate in the open meetings to offer clarification of events, but will not be given voting privileges. Medtronic personnel may facilitate the DSMB meeting (e.g. clinical trial leader, statistician), but they will not be voting members.

A quorum of the committee will review the results of each interim analysis in which the results are analyzed against the primary objective. A summary of adverse events will be reviewed at this time also. Review and consensus by the entire committee is required to recommend that the study should be stopped.

All documentation will be de-identified of clinical center and subject identifiers.

12 CONTACT INFORMATION

Sponsor:	Medtronic GmbH Cardiac Rhythm Disease Management Clinical Cooperation Earl-Bakken-Platz 1 D-40670 Meerbusch Germany Phone: +49 (0) 2159-8149-0 Fax: +49 (0) 2159-8149-100 Dr. Manfred Eichenlaub Study Management Phone: +49 (0) 2159-8149-195
Contract Research Organization:	IFE Europe GmbH Zeche Katharina 6 D-45307 Essen Germany Phone: +49(0) 201/89900 Fax: +49(0) 201 8990 101
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Vice-Principal Investigator:	Prof. Dr. med. Johannes Brachmann Klinikum Coburg gGmbH II. Medizinische Klinik Ketschendorfer Str. 33 D-96450 Coburg Germany
Central Laboratory:	Dr. K. Bethmann AG Wollert (OE 6889) Klinik für Kardiologie und Angiologie Hans-Borst Zentrum für Herz- und Stammzellforschung Gebäude: K11 (HBZ); Ebene: SO; Raum: 6570 Medizinische Hochschule Hannover Carl-Neuberg-Str. 1 D-30625 Hannover Germany Phone: +49 (0) 511 532-5365

APPENDIX

APPENDIX A: SUBJECT INFORMATION AND INFORMED CONSENT TEMPLATE

APPENDIX B: CARELINK INSTRUCTIONS

APPENDIX C: SUBJECT ID CARDS

APPENDIX D: QUALITY OF LIFE QUESTIONAIRES

KANSAS CITY CARDIOMYOPATHY QUESTIONAIRE (KCCQ)

EQ-5D QUESTIONNAIRE

APPENDIX E: SAMPLE HEART FAILURE MANAGEMENT REPORT

APPENDIX F: QUICK LOOK SCREEN

APPENDIX G: CARDIAC COMPASS REPORT

APPENDIX H: DETAIL COMOPARISON OF CARDIAC COMPASS REPORT; HF-MANAGEMENTREPORT AND QUICK LOOK SCREEN

APPENDIX I: NEW YORK HEART ASSOCIATION CLASSIFICATION

APPENDIX J: CRFS

APPENDIX K: ANTICIPATED ADVERSE EVENTS

APPENDIX L: LIST OF ACRONYMS USED IN CLINICAL INVESTIGATION PLAN

APPENDIX M: BIBLIOGRAPHY

APPENDIX N: CE DECLARATION OF CONFORMITY OF THE USED DEVICES

APPENDIX O: RANDOMIZATION REQUIREMENTS

APPENDIX P: EXECUTIVE COMMITTEE MEMBERS

APPENDIX R: STEERING COMMITTEE MEMBERS

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APPENDIX T: GOLD CLASSIFICATION OF COPD SEVERITY

APPENDIX U: MODIFICATIONS TO CLINICAL INVESTIGATION PLAN

1 TITLE PAGE

AMENDMENT NUMBER TO CLINICAL INVESTIGATION PLAN	
Title: OptiLink HF Study (Optimization of Heart Failure Management using Medtronic **Opti**Vol® Fluid Status Monitoring and Medtronic Care**Link**® Network)	**Amendment No. 1**, **Version 1.0**, to Clinical Investigation Plan Version 3.0, dated October 12, 2008, **Release date: April 26, 2011**
Principal Investigator:	Prof. Dr. med. Michael Böhm Klinik für Innere Medizin III Kirrberger Straße 66424 Homburg/Saar Germany Phone: ++49-(0)6841-16-23372 Fax: ++49-(0)6841-16-23369
Sponsor:	Medtronic GmbH Cardiac Rhythm Disease Management Clinical Cooperation Earl-Bakken-Platz 1 40670 Meerbusch Germany Phone: ++49-(0)2159-8149-0 Fax: ++49-(0)2159-8149-100
Contract Research Organization:	Pierrel Research Europe GmbH Zeche Katharina 6 45307 Essen Germany Phone: ++49-(0)201-8990-0 Fax: ++49-(0)201-8990-101
The information provided in this document is strictly confidential. No disclosure should be performed without the written authorization of Medtronic GmbH.	

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3 RATIONALE FOR AMENDMENT

This Amendment No. 1, Version 1.0, dated April 26, 2011, adjusts several topics outlined in the Clinical Investigation Plan (CIP) Version 3.0, dated October 12, 2008. The adjustments are:

1) The Follow-up period of subjects who are already participating or who will be enrolled into the study in the future may be prolonged until the last subject who entered the study will have reached the 18-month Follow-up Visit. This additional follow-up of more than 18 months will only be performed if a subject consents to this optional prolongation by signing an additional "Longterm Follow-Up" Patient Informed Consent form (PIC).

   In case, a subject does not consent, the study will end for him/her as soon as the 18-month Follow-up Visit is completed.
2) Wording changes with reference to the conditional prolongation of the Follow-up period are performed throughout the entire CIP.
3) The statistical evaluation is adapted.
4) An optional blood sampling and evaluation of quality of life using the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the EQ-5D questionnaire are introduced at the 24-month Follow-up.
5) The Principal Investigator and the company name of the Contract Research Organization (CRO) have changed.

In the following sections, rationales for the respective change, if applicable, and the affected sections of the CIP are given.

4 CHANGES TO THE CLINICAL INVESTIGATION PLAN

4.1 Follow-Up Period

According to a recommendation of the DSMB stated on August 28, 2010, the Follow-up period of subjects who are already participating or who will be enrolled into the study in the future may be prolonged until the last subject who entered the study will have reached the 18-month Follow-up Visit. This additional follow-up of more than 18 months will only be performed if a subject consents to this optional prolongation by signing an additional "Longterm Follow-Up" PIC.

In case, a subject does not consent, the study will end for him/her as soon as the 18-month Follow-up Visit is completed.

All subjects will be asked for the additional consent during the 18-month Follow-up Visit. This serves to guarantee an identical study conduct for all subjects (i.e. for those already enrolled and those to be enrolled) and scientific integrity of the results.

Sections involved:

- Page 11, Section 1, [Synopsis, Duration of the Study (per Subject)]
- Page 11 and 12, Section 1, (Synopsis, Efficacy Data and Safety Data)
- Page 34 and 35, Section 3.2 (Study Objectives)
- Page 35, Section 3.3 (Study Scope)
- Page 51 and 52, Section 4.6 (Follow-up Visits):

  The visit window for the Follow-up Visit at 24 months was added in Table 4 as displayed below.

Table 4 Follow-up Schedule/Visit Windows

Follow-up Visit (Months)	Window Start* (Days)	Target Day*	Window End (Days)
6	150	180	210
12	330	360	390
18	510	540	570
24	*720*	*750*	*780*
Every further 12 months *Until last subject has reached 18 months of Follow-up*	*720* *+ every 12 months* *Until last subject has reached 18 months of Follow-up*	*750* *+ every12 months* *Until last subject has reached 18 months of Follow-up*	*780* *+ every 12 months* *Until last subject has reached 18 months of Follow-up*

*Days post-randomization

For the long-term Follow-up Visits following the 24-month visit, the respective time windows will be + 12 months ± 30 days

Study Exit will be performed for all subjects as soon as last subject enrolled has reached 18 months of Follow-up.

- Page 72 and 73, Section 5.6 (Statistical Analysis)

4.2 Statistical Evaluation

The description of the statistical evaluation was adapted according to the input by the DSMB In the following, an updated version of CIP Section 5 and of the respective paragraph in the synopsis is presented.

1 SYNOPSIS

STATISTICAL ANALYSES

Confirmative analyses (primary objective): It is intended to show the superiority of OptiVol® fluid status monitoring with automatically generated wireless CareAlert® notification of clinician via the Medtronic CareLink® in comparison to standard clinical assessment related to the incidence rate of all-cause death or first unplanned cardiovascular related hospitalization. This will be investigated by means of a two-sided log-rank test.

Additional exploratory analyses (secondary objectives): The

number of days alive and out of hospital as well as the number of hospitalizations of different types will be determined and investigated using the Wilcoxon rank-sum test. Time to event analyses (hospitalization or death, hospitalization, death each of different types etc.) will be performed using survival time methods.

All other variables will be analyzed descriptively, i.e. summary statistics for location and dispersion will be determined for continuous variables, and frequencies and percentages for discrete variables.

Randomization: according to risk-stratification.

5.1 Study Populations

Analyses will be based on the following sets: total population, intention-to-treat (ITT) population, and per protocol (PP) population. The definitions of the analysis sets follow those given in the ICH E9 guideline.

5.2 Total Population

The total population consists of all subjects enrolled including subjects withdrawn from the study.

5.3 Intention-to-treat Population

The ITT population consists of all randomized subjects. Under strict conditions, subjects who have no post-baseline data available or subjects who fail to satisfy major entry criteria may be excluded (details see ICH E9 guideline).

5.4 Per Protocol Population

The PP population consists of all subjects of the ITT population who completed the study without major protocol violations or who terminated the study prematurely due to an adverse event with at least likely relation to the study device or due to lack of efficacy. Decisions on protocol violations will be made individually in the data review meeting.

5.5 Statistical Analysis of Primary Objective

The primary objective of the OptiLink HF study is to demonstrate that the “OptiLink” functionality causes a clinically relevant decrease in the incidence rate of all-cause death or first unplanned cardiovascular related hospitalization within Follow-up period. The primary objective will look at the time to first event and the analysis will use survival analysis methods.

The following hypothesis will be investigated:

$$H_0: \; S_{control} = S_{access} \quad \text{vs} \quad H_1: \; S_{control} \neq S_{access}$$

where $S_{control}$ and S_{access} denote the survival functions for freedom from all-cause death or unplanned cardiovascular related hospitalization within 18 months for the control arm and the access arm, respectively. For example, S_{access} is the proportion of subjects in the access arm that is alive and free from unplanned cardiovascular hospitalizations at 1 year after implant.
Group comparison will be performed with an α-level of 5% using a two-sided log-rank test. The ITT population will be used for the primary analysis. Additionally, the confidence interval will be calculated for the hazard ratio using Cox regression.

Sample Size Calculation

The calculation of the sample size for the present study is based on available study data using the experience from previous studies (see 3.3)). Only ICD / CRT-D subjects will be included in this study.
For sample size calculation the following assumptions are made:

- type I error $\alpha = 0.05$
- power = 0.80
- control arm proportion event-free at 18 months = 72.0%
- difference between treatment arms = 30% of control arm → 8.4%
- access arm proportion event-free at 18 months = 80.4%
- all subjects are followed up for at least 18 months

The method for analysis of the primary criterion is the two-sided log-rank test. Based on these assumptions the total sample size of 798 subjects will have 80% power to detect a difference between the rates of all-cause death or cardiovascular related hospitalization of the two treatment arms. This is based on the method from Lakatos (1988)[1] and Cantor (1997)[2], setting accrual time to 0 to model subject exit after 18 months (SAS Power and Sample Size module, version 3.1). Taking into account early study termination and treatment non-compliance including cross-over, 1000 subjects will be enrolled in the study. This increase in sample size will ensure that power is maintained when 5.0% of subjects cross over (based on simulation, with cross-over equally distributed over arms, assuming full compliance on other elements of the protocol). Then, the expected number of events is 238 (simulation).

1 Lakatos, E. (1988), "Sample Sizes Based on the Log-Rank Statistic in Complex Clinical Trials," Biometrics, 44, 229–241
2 Cantor, A. B. (1997), Extending SAS Survival Analysis Techniques for Medical Research, Cary, NC: SAS Institute Inc.

Interim analysis:
Two interim analyses are planned when 33% and 67% of the 238 expected primary endpoints has been accrued. At the interim analyses, minimally the primary endpoint and the secondary mortality endpoint will be analyzed. The DSMB will review the results and will advise the Study Executive Committee about continuation of the study. The DSMB will consider to stop for success if the primary endpoint occurs significantly more often in the control arm with $p < 0.0001$ for the first and $p < 0.001$ for the second interim analysis. The DSMB will consider to stop for harm if the primary endpoint occurs significantly more often in the access arm with $p < 0.01$ or if mortality is significantly higher in the access arm with $p < 0.05$. The final analysis will use a modified alpha to compensate for the interim analyses, maintaining total type I error at 0.05.

5.6 Secondary Objectives

All secondary variables will be analyzed by descriptive statistical methods. For discrete variables frequencies and percentages will be determined, for continuous variables parameters for location and dispersion will be calculated. Shift-tables and pre-post differences can be determined, if applicable.

In general hospitalizations or deaths will be classified according to the following causes:

1) Cardiovascular related,
2) Heart failure (HF) related,
3) Related to other causes,
4) All causes,
5) Sudden cardiac death*

*only death.

The following secondary objectives will be tested on an α-level of 5% each. P-values will only be interpreted in an exploratory sense.

The number of hospitalizations per subject according to the above-mentioned causes will be compared for both study arms by means of a two-sided Wilcoxon rank-sum test. The corresponding rates of first hospitalization will be compared using a log-rank test.

The number of days in hospital and the number of days alive out of hospital according to the above-mentioned causes will be compared using a two-sided Wilcoxon rank-sum test.

Mortality rates according to the above mentioned causes will be determined and compared by means of a log-rank test. Furthermore mortality rates as well as HF-related mortality rates after the first HF-related hospitalization and after the first decompensation will be determined.

Time to event analyses will be performed for the time to first all-cause hospitalization or death, the time to first all-cause hospitalization, time to first HF-related hospitalization, time to first cardiovascular related hospitalization, time to first hospitalization because of decompensation, time to first HF-related death, time to cardiovascular related death and time to first death because of decompensation. The time to event analyses will be carried out using the Kaplan-Meier method and log-rank tests will be performed to compare the risk for both access arms.

Where appropriate, repeat-events survival analysis methods may be used to analyze recurring events, including adverse events, HF-related events and cardiovascular related events.

The quality of life assessed by means of the Kansas City Cardiomyopathy Questionnaire (KCCQ) and EQ-5D questionnaire will be compared by means of a Wilcoxon rank-sum test.

Additionally, demographic data, medical history, previous and concomitant diseases and medications, vital signs, and results from the physical examination will be analyzed descriptively.

5.7 Subgroup Analyses

Subgroup analyses will be carried out for ischemic and non-ischemic cardiovascular diseases, subjects with or without atrial fibrillation and subjects with or without VT/VF episodes before implantation (primary vs. secondary prevention).

5.8 Adverse Events

The recorded adverse events will be coded according to MedDRA. The adverse events will be summarized by treatment, System Organ Class, preferred-term and intensity.

Nature, incidence and intensity, as well as the investigator's and the sponsor’s causality assessment will be reported for each treatment-emergent adverse event. Descriptive summary statistics, e.g. with regard to the incidence of symptoms and the causality assessment, will be presented for the study period.

5.9 Handling of Missing Values

Procedures will be in place to ensure complete reporting of subject visits and events. The statistical analysis will be based on available data. For the primary objective, subjects will be censored according to their last documented visit.

5.10 Data Entry and Validation

Data management procedures will be specified in the data management plan (e.g. double data entry, plausibility checks).

4.3 Optional Blood Sampling and Quality of Life Assessment

Based on the prolongation of the Follow-up period, an optional blood sampling and assessment of quality of life by the KCCQ and EQ-5D during the 24-month Follow-up Visit are introduced.

Sections involved:

- Page 41 to 44, Section 4.1, (Data Collection Requirements)
- Page 51 and 52, Section 4.6 (Follow-up Visits)

4.4 Wording Changes

Some sections of the CIP were adapted to enhance comprehensibility and concision. In the following, the sections changed are displayed in their updated form.

<u>Primary objective</u>

- Page 9, Section 1 (Synopsis, Objective):

  To demonstrate a reduction in the incidence rate of the composite endpoint of all-cause death or first unplanned cardiovascular hospitalization in ICD or CRT-D subjects with HF

- Page 11, Section 1 (Synopsis, Efficacy Data and Safety Data):

  Primary endpoint:

  All-cause of death or first unplanned admission to hospital for cardiovascular reason from randomization until last subject enrolled has reached 18 months Follow-up will be considered to determine the rate of all-cause deaths or first unplanned cardiovascular related hospitalizations

  […]

- Page 34, Section 3.2 (Study Objectives):

  The primary objective of the study is to establish whether the use of “OptiLink” decreases the incidence rate of the combined endpoint of all-cause mortality or first unplanned cardiovascular hospitalization in subjects with HF and ICD or CRT-D treatment. All causes of death and unplanned admissions to hospital for cardiovascular reasons from randomization until last subject enrolled has reached 18-months Follow-up Visit are assessed.

Claims and Intended Performance

- Page 35, Section 3.4 (Claims and Intended Performance):

  The OptiLink HF study intends to establish whether the use of event-triggered HF-disease-management = Medtronic's OptiVol® fluid status monitoring with automatically generated wireless CareAlert® notification of the clinician via the Medtronic CareLink® Network can reduce the number of unplanned cardiovascular hospitalizations in a subject population with HF and ICD / CRT-D treatment by using the diagnostic tools available in the commercially released Medtronic ICD / CRT-D devices in combination with CareLink®. It is not the purpose of the OptiLink HF study to support labeling changes, instructions for use or promotional material claims for these devices.

Study Exit

- Page 58 and 59, Section 4.12 (Study Exit):

  All consented subjects will be documented in the database. Enrolled subjects who fail to meet final eligibility criteria will not be randomized. The respective subject will be withdrawn from the study and a study exit CRF will be completed. If failure to meet eligibility criteria is discovered after randomization, the subject will stay in the study.

  A study exit will be documented for any of the following:

  - Subject death,
  - Study closure,
  - Subject withdrawal/investigator withdrawal of subject/lost to Follow-up. In case withdrawal is considered, it is preferred to stop only those study procedures that are problematic and to continue the procedures that are still feasible. In particular, data collection on the primary endpoint should continue whenever possible.

  The investigator shall complete the study exit form (SEF). The following information will be collected (if applicable):

  - NYHA class,
  - Medication and/or changes,
  - HF symptom status (or death information),
  - KCCQ and EQ-5D,
  - ICD / CRT-D-therapy assessment,
  - Review of Cardiac Compass® Trends and HF Management Report,
  - Device interrogation, StD.

Subject Withdrawal

- Page 60 and 61, Section 4.12.3 (Subject Withdrawal/Investigator Withdrawal/Lost to Follow-Up):

  Any subject withdrawn from the study before the scheduled completion will be considered an early withdrawal, regardless of the reason for the withdrawal.

  The subject is free to withdraw from the study for any reason and at any time without giving any explanation for doing so and without penalty or loss of future medical care. The investigational center should indicate if the withdrawal was related to the investigational system.

  The investigator is also free to terminate a subject's involvement in the study at any time if it would be to the subject's detriment to continue.

  It is also possible that the sponsor or the competent authorities request termination of the study, if there are concerns about conduct or safety.

  In particular cases, the study may be terminated at a single investigational site, if the sponsor has relevant reasons (e.g. no compliance with Good Clinical Practice or the CIP). In such cases, participation of subjects enrolled in this particular center can be terminated. For this purpose, the subjects consent is not needed.

  A subject may be withdrawn from the study after enrollment (equals signature and date of PIC), if eligibility criteria are not met, but only before randomization. Once randomized, subjects should be followed up according to the investigational plan.

  All data available at the time of withdrawal or last visit will be used for analysis. There will be no future required study-related Follow-up Visit for this subject.

  Written documentation shall be provided stating the reason why the subject was withdrawn:

  - To the sponsor and subject, if the investigator withdrew a subject from the study,
  - To the investigator with the request to inform the subject, if the sponsor decides to withdraw a subject from the study,
  - The investigator shall complete the SEF.

  The study investigator or Medtronic may terminate a subject's participation in the study without the subject's consent if two consecutive Follow-up Visits are missed, if the subject routinely fails to complete required procedures, and/or if the investigator deems it as medically necessary. If the subject fails to comply with Follow-up Visits, the study center must make repeated attempts to contact the subject.

It is important to distinguish between withdrawal and stopping following study required procedures. If study procedures cannot be followed any more, it is preferable to continue data collection and to not completely withdraw the subject.

4.5 Administrative Changes

Principal Investigator

As the originally Principal Investigator in charge, Prof. Dr. med. Helmut Drexler, deceased, Prof. Dr. med. Michael Böhm was appointed as successor in December 2009. Therefore, name and contact details are changed to the following:

Prof. Dr. med. Michael Böhm
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CRO company name

The company name of the CRO, IFE Europe GmbH, changed to Pierrel Research Europe GmbH on December 16, 2009. Thus, in every occasion IFE Europe GmbH is mentioned in the CIP version 3.0, it has to be read and understood as Pierrel Research Europe GmbH.

This applies also to all other documents related to the clinical investigation referring to the CRO (e.g. Case Report Forms).

5 MEC APPROVAL

A copy of this amendment will be sent to the Medical Ethics Committees (MEC) as well as to the competent/regulatory authorities, to achieve acceptance before implementation.

For signatures of the Principal Investigators and all responsible persons on behalf of the sponsor and the CRO, please refer to Section 6.

6 APPROVAL OF CHANGES

Principal Investigator:

I, herewith, confirm that I have read, understood, and approve the Amendment No. 1, Version 1.0, dated: **April 26, 2011**, to the Clinical Investigation Plan Version 3.0, dated October 12, 2010.

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_____

Date, signature

Vice-Principal Investigator:

I, herewith, confirm that I have read, understood, and approve the Amendment No. 1, Version 1.0, dated: **April 26, 2011**, to the Clinical Investigation Plan Version 3.0, dated October 12, 2010.

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_____

Date, signature

On Behalf of the Sponsor

I, herewith, confirm that I have read, understood, and approve the Amendment No. 1, Version 1.0, dated: **April 26, 2011**, to the Clinical Investigation Plan Version 3.0, dated October 12, 2010.

Study Manager:

Dr. Manfred Eichenlaub

_____

Date, signature

On Behalf of the CRO:

I, herewith, confirm that I have read, understood, and approve the Amendment No. 1, Version 1.0, dated: **April 26, 2011**, to the Clinical Investigation Plan Version 3.0, dated October 12, 2010.

Project Manager:

Verena Seitz

_____

Date, signature

Medtronic OptiLink HF Study
Clinical Investigation Plan

Version 3.3
October 02, 2009

Medtronic GmbH
Cardiac Rhythm Disease Management Clinical Cooperation

Earl-Bakken-Platz 1
D-40670 Meerbusch

Germany

Confidential

This clinical investigation plan was subject to critical review and has been approved by the following:

Principal Investigators

I agree that this clinical investigation plan contains all the information required to conduct this study.

By my signature below, I hereby certify that I have read, understood and agree to abide by all conditions, instructions and restrictions contained in this clinical investigation plan.

Principal Investigator
Prof. Dr. med. Michael Böhm
Universitätsklinikum des Saarlandes
Direktor der Klinik für Innere Medizin III
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_____ _____
(place, date) (signature)

Vice-Principal Investigator
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_____ _____
(place, date) (signature)

Approval on behalf of the Sponsor

Study Manager

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1 SYNOPSIS

TITLE	OptiLink HF Study (Optimization of Heart Failure Management using Medtronic **Opti**Vol® Fluid Status Monitoring and Medtronic Care**Link**® Network)
AIM OF THE STUDY	The objective of the study is to establish whether the use of event-triggered HF-disease management through Medtronic's OptiVol® fluid status monitoring with an automatically generated wireless CareAlert® notification of the clinician via the Medtronic CareLink® Network can reduce cardiovascular related hospitalizations and the number of deaths in a subject population with HF and ICD / CRT-D treatment as compared to standard clinical assessment. As a measure for the reduction of hospitalizations and deaths the rate of all-cause deaths or cardiovascular related hospitalizations will be determined.
INDICATION	ICD / CRT-D indication for subjects with chronic heart failure
STUDY DESIGN	Prospective, multi-center, unblinded, 1:1 randomized, controlled study
STUDY DEVICES	Medtronic Inc., market approved, single- or dual-chamber ICD or CRT-D devices used within approved indication: 1) Access arm: Medtronic Virtuoso™ ICD or Concerto™ CRT-D system or subsequently market released devices providing at least the same functionality with fluid status monitoring OptiVol® and with CareLink® access (OptiVol® "ON" and CareAlert® "ON"), 2) Control arm: Medtronic Virtuoso™ ICD or Concerto™ CRT-D system or subsequent market released devices providing at least the same functionality without CareLink® access (OptiVol® "OFF").
STUDY CENTERS	20-30 centers specialized in ICD and CRT-D implantation and about 100 active satellite HF-management centers with access to Medtronic CareLink® Network
OBJECTIVE	To demonstrate a reduction in the incidence rate of the composite endpoint of death or unplanned cardiovascular hospitalization in ICD or CRT-D subjects with heart failure
INCLUSION CRITERIA	• Subjects have a Medtronic Virtuoso™ ICD single- **or** dual-chamber **or** Concerto™ CRT-D **or** subsequently market released Medtronic device providing at least the same functionality implanted, including device

replacement. Subjects with CRT-D must fulfill CRT-indication as described in the ESC guidelines for cardiac pacing and cardiac resynchronization therapy 2007: EF ≤ 35% and NYHA **III**, and LVEDD > 55 mm, and **QRS ≥ 120 ms**, and optimized therapy,

- Subjects with stable chronic heart failure (CHF) in New York Heart Association (NYHA) class II or III for at least 30 days and left ventricular ejection fraction of no more than 35% (most recent measurement within 6 months prior to randomization by echocardiography or contrast ventriculography, magnetic resonance or nuclear imaging, based on local practice), on optimal target or maximal tolerated dose of ACE-inhibitors or angiotensin receptor blockers, ß-blockers and diuretics if clinically indicated to reduce fluid retention and one of the following criteria:

  At least one hospitalization due to the heart failure within the last 12 months before enrollment or one course of ambulatory IV-or oral diuretic treatment or a BNP value of > 400 pg/ml or a NT-proBNP values > 450 pg/ml in subject < 50 years, > 900 pg/ml (50-75 years) and > 1800 pg/ml in subject of more than 75 years old within 30 days of enrolment,

- Written informed consent by the subject for study participation prior to clinical investigation plan specific procedures,
- The subject must be able and willing to comply with the clinical investigation plan and willing to remain available for follow-up visits to the study closure,
- Subjects or the subject's caregiver must be willing and able to use the Medtronic CareLink® monitor as instructed and to perform the required duties, if subject is randomized to the access arm.

EXCLUSION CRITERIA

- Subjects with chronic renal failure needing renal dialysis,
- Subjects with serum creatinine > 2.5 mg/dl, measured within 14 days prior to enrollment,
- Subjects with severe to very severe Chronic Obstructive Pulmonary Disease (COPD) as determined by physician and documented in medical records (Stage III and Stage IV),

  Subjects with suspected or confirmed COPD require a current test of lung function (not more than 12 months before inclusion). If the "forced expiratory volume" is < 1.0 L/sec, the subject may not participate in the study.

- Subjects on the heart transplantation list or subjects with transplanted hearts,
- Subjects listed for valve replacement or interventional valve therapy,
- Subjects with myocardial infarction (MI) within the last 40 days before implant. MI is defined by typical changes in biochemical markers

including troponin levels > 3 times the upper limits of normal and creatinine kinase < 2 times of upper limit, or with CKMB greater than the upper limit of normal, combined (for all enzymes) with at least one of the following ischemic symptoms, ECG changes consistent of diagnostic ST-T wave changes or pathologic Q waves or new LBBB,

- Subjects with stroke within 40 days prior randomization,
- Subjects who have had a percutaneous coronary intervention within 3 months prior to randomization,
- Subjects with cardiac surgery within 90 days of randomization,
- Subjects with complex and uncorrected Congenital Heart Disease,
- Subject's life expectancy is less than 18 months in the opinion of the physician,
- Subjects in situations that would limit participation, not eligible to receive a CareLink® monitor (e.g. hearing or speech impaired with no family member or caregiver available to assist, or those who spend extended periods abroad, or those who intend to enroll in a study that would preclude use of the monitor),
- Subject is participating in a concurrent intervention study,
- Subject or the subject's caregiver is unwilling to give consent for the release of information for the evaluation or to give additional consent for the release of subject medical and privacy data for CareLink® subjects,
- Subjects with exclusion criteria required by local law (age < 18, women who are pregnant or breastfeeding).

DURATION OF THE STUDY (PER SUBJECT)	At least 18 months per subject Data collection at baseline / enrollment, randomization, 6 months and every 6 months thereafter until the study exit
DURATION OF THE STUDY (OVERALL)	Planned duration of recruitment: 24 months First subject first visit: September 15, 2008 Last subject last visit: the end of March 2012
EFFICACY DATA AND SAFETY DATA	**Primary endpoint:** All-cause of death or unplanned admission to hospital for cardiovascular reason from randomization until 18-month follow-up visit will be considered to determine the **rate of all-cause deaths or cardiovascular related hospitalizations within 18 months**. **Hospitalization is defined as an overnight stay or longer in a hospital**

environment or similar facility including admission to a day care facility.

Cardiovascular hospitalizations are defined as hospitalizations for:

- Heart failure (first or subsequent),
- Acute myocardial infarction,
- Unstable angina pectoris,
- Symptom-driven hospitalization for cardiac arrhythmia (atrial fibrillation, atrial flutter, supraventricular arrhythmias or ventricular arrhythmias),
- Stroke / cerebral vascular accidents.

Hospitalizations for elective CV procedures do not qualify as CV endpoint, this included planned admission for elective cardioversion of atrial fibrillation.

Secondary objectives and endpoints:

1) Number of HF-related hospitalizations during follow-up,
2) HF-related hospitalization,
3) Sum of follow-up days minus days alive and out of the hospital,
4) All-cause mortality,
5) Cardiovascular mortality,
6) HF-related hospitalization and all-cause mortality,
7) Quality of Life (QOL),
8) Health Economics.

Exploratory endpoint:

Number of all-cause hospitalizations during 18 months follow-up.

SAMPLE SIZE

1.000 subjects with single- or dual-chamber Virtuoso™ ICD system or Concerto™ CRT-D or subsequent market released devices providing at least the same functionality (500 per study arm, 60% subjects with stable chronic heart failure NYHA class III and 40% with NYHA class II)

STATISTICAL ANALYSES

Confirmative analyses (primary objective): It is intended to show the superiority of OptiVol® fluid status monitoring with automatically generated wireless CareAlert® notification of clinician via the Medtronic CareLink® in comparison to standard clinical assessment related to the incidence rate of all-cause death or cardiovascular related hospitalization. This will be investigated by means of a two-sided log-rank test.

Additional analyses exploratorily (secondary objectives): The number of days alive out of hospital as well as the number of hospitalizations of different types will be determined and investigated using Wilcoxon rank-sum test. Time to

event analyses (hospitalization or death, hospitalization, death each of different types etc.) will be performed using survival time methods.

All other variables will be analyzed descriptively, i.e. summary statistics for location and dispersion will be determined for continuous variables, and frequencies and percentages for discrete variables.

Randomization: according to risk-stratification.

STUDY SPONSOR	Medtronic GmbH
STUDY MANAGEMENT	Dr. Manfred Eichenlaub

2 INTRODUCTION

2.1 Purpose of the Study

The purpose of the study is to demonstrate that an automatic, implantable monitoring system identifying increased pulmonary volume status should be able to identify subjects at risk for imminent decompensation and, consequently, hospitalization of worsening of heart failure. We hypothesize that early recognition and ambulatory management of progressive pulmonary congestion avoids HF- decompensation and hospitalization. In this respect, we anticipate that the use of an event-triggered heart failure disease management through Medtronic's OptiVol® fluid status monitoring with automatically generated wireless CareAlert® notification of the clinician via the Medtronic CareLink® Network (access arm) can prolong the time to hospitalization, reduce hospitalizations, the number of deaths and all other interventions for worsening of heart failure in subjects with heart failure that have an indication for ICD or CRT-D implantation (CRT-indication as described in the ESC guidelines for cardiac pacing and cardiac resynchronization therapy 2007: EF ≤ 35% and NYHA III, and LVEDD> 55 mm, and QRS ≥ 120 ms, and optimized therapy).

Hospitalizations, secondary to worsening signs and symptoms of HF, represent a major challenge in the management of heart failure. Early intervention after detection of pulmonary congestion may be a key element in avoiding hospitalizations due to cardiovascular decompensation. The OptiVol® fluid status monitoring may reduce the rate of hospitalizations in subjects suffering from decompensated heart failure. We anticipate that OptiVol® will enable early ambulatory intervention in subjects with HF in whom OptiVol® has detected increased pulmonary congestion. Previous observations (MID-HeFT-study[a], In-Sync-Sentry-Registry[b]) have shown a significant correlation between the beginning of a pulmonary congestion and measured intrathoracic impedance. In fact, about 70% of all alert events revealed the beginning of a pulmonary congestion, despite the fact that clinical symptoms of decompensated heart failure are not identifiable yet.

The use of CareLink® Network allows both the study center and the satellite clinic to have access at the same time to the information about the appearance of CareAlert® by a text message (SMS) or an e-mail. The satellite-clinics can be a cardiologic/internistic out-patient clinic or in-patient clinic. This enables an event-triggered HF-disease management, as a CareAlert® of the responsible satellite-clinic and the study center results in a phone contact with the affected subject as first and early disease management step.

[a] Yu CM, Wang L, Chau E *et al.* Intrathoracic impedance monitoring in patients with heart failure: correlation with fluid status and feasibility of early warning receding hospitalization. *Circulation.* 2005; 112: 841–848.

[b] Vollmann D, Nägele H, Schauerte P *et al.* Clinical utility of intrathoracic impedance monitoring to alert patients with an implanted device of deteriorating chronic heart failure. *European Heart Journal*. 2007; 28: 1835–1840.

2.2 Background

Over the last 5 years, the indications for implantable defibrillators (ICDs and CRT-Ds) have expanded greatly[c,d,e], resulting in an increase in ICD and CRT-D utilization, and also burden on healthcare providers. Currently, in Germany follow-up visits for routine ICD / CRT-D device check are scheduled every 3-6 months according to international recommendations[f,g], however many of these routine device checks result in no programming or device changes, and many patients have no clinically significant events between visits. The follow-up process is an ambulatory care and depends on the "initiative of the patient". Usually patients go to general practitioners (GPs) first with possible subsequent referral to an ambulatory cardiological specialist, either in an out-patient or in-patient clinic. In case of emergency the patient in addition gets referral to a hospital specialist sector. The existing separation between out-patient and in-patient care results in duplication of service and procedures, lack of coordination between sectors, and high travel costs by multiple transportations of the patient. In addition to the increased number of patients a clinic needs to manage, these patients have increasingly more complex comorbidities, such as heart failure. The diagnostic features in ICDs / CRT-Ds, such as those in Medtronic's HF-Management Report and Cardiac Compass® Trends, provide clinicians with access to more data to help to manage these situations. However, as the amount of data increases, clinicians need tools to help them turn it from data into meaningful information. Patient management initiatives focusing on streamlining access to data, as well as allowing clinicians to better triage patients could increase efficiencies and reduce the burden on the health care system. Monitoring disease progression is also important to managing ICD / CRT-D patients. Many of these patients have heart failure. There is a need for the ability to monitor patients efficiently for changes in disease status.

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[c] Moss AJ, Zareba W, Hall WJ *et al.* Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med*. 2002; 346: 877-883.

[d] Bardy GH, Lee KL, Mark DB *et al.* Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med*. 2005; 352: 225–237.

[e] Bristow MR, Saxon LA, Boehmer J *et al.* Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med*. 2004; 350: 2140–2150.

[f] Gregoratos G, Abrams J, Epstein AE *et al.* for the American College of Cardiology/American Heart Association Task Force on Practice Guidelines/North American Society for Pacing and Electrophysiology Committee to Update the 1998 Pacemaker Guidelines. ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee to Update the 1998 Pacemaker Guidelines). *Circulation*. 2002; 106: 2145–2161.

[g] Wilkoff, BL, Auricchio A, Brugada J *et al.* HRA/EHRA Expert Consensus on the monitoring of cardiovascular implantable electronic devices (CIEDs): Description of Techniques, Indications, Personnel, Frequency and Ethical Considerations Europace 2008; 10(6): 707-725.

Recently, two technologies to meet this need have been developed and already have been proven to work effectively. Both of them either measure directly or indirectly intra-cardiac pressure changes that occur during congestion in heart failure. Pulmonary and systemic congestion are earlier steps in the process of cardiac decompensation. Abnormal systolic and diastolic function lead to increase left ventricular diastolic pressure and impaired volume regulation. These in turn may be further aggravated by progressive activation of neurohormonal systems (sympathetic nervous system, rennin-angiotensin-aldosterone system, vasopressin). The increased blood volume and increased left ventricular diastolic pressure, often aggravated by mitral regurgitation, increase pulmonary capillary wedge pressure, which, in turn, lead to increased pulmonary artery pressure, increased right ventricular and atrial pressures, and tricuspid regurgitation. In addition, depending on the hydrostatic pressure of the pulmonary capillaries, the plasma oncotic pressure, the permeability and integrity of the alveolar capillary membrane, and the pulmonary lymphatic drainage of the lungs, the increased pulmonary capillary wedge pressure leads to redistribution of the excess fluid in the pulmonary vascular bed, interstitial edema and alveolar edema. All these processes constitute to the development of dyspnea in heart failure patients[h,i].

As mentioned before, technologies in implantable devices to measure physiologic signs for monitoring and early warning purposes of acute decompensated heart failure all use measures which can be obtained within the (patho)physiologic mechanism described above. For instance, the Chronicle Hemodynamic Monitor uses the Estimated Pulmonary Arterial Wedge Pressure (EPAD), defined as the right ventricular pressure at the time of maximal shown dp/dt.

The OptiVol® algorithm is an other way of measuring within the (patho)physiological process described before. Instead of measuring intracardial pressures, the change in thoracic impedance, resulting from the accumulation of excess fluid in the lungs is monitored and used as indicator for a deterioration of the patient's heart failure status. Both of these technologies, the Chronicle Hemodynamic Monitor as well as the OptiVol® algorithm use measures that change early in the process of cardiac decompensation.

Another attempt of observing the patients fluid status is measuring the body weight which should indicate fluid accumulation. However, whereas dyspnea and edema can be observed in the majority of patients seeking medical attention for decompensated heart failure, weight gain as result of fluid accumulation is a relatively late development in the process of decompensation representing only a late and unreliable measure to alert patients and caregivers.[j,k]

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[h] Constanza MR. Management of Volume Overload in Acute Heart Failure: Diuretics and Ultrafiltration, in: Acute Heart Failure. Springer 2008; Section 2.3, 503-518.

[i] Mebazaa A, Gheorghiade M, Zannad FM, Parrillo JE (Eds.). Acute Heart Failure. Springer 2008. XXVI, ISBN: 978-1-84628-781-7.

[j] Lewin JM, Ledwidge M, O'Loughlin C *et al.* Clinical deterioration in established heart failure: What is the value of BNP and weight gain in aiding diagnosis? *Eur. J. Heart Failure.* 2003; 7: 953-957.

Pulmonary congestion rather than general fluid overload in peripheral organs is the primary cause of cardiac decompensation; i.e. fluid re-distribution rather than fluid overload may be the early key pathophysiological alteration as suggested by Cotter *et al.*[l]. This pathophysiological mechanism preceding clinical signs and symptoms of cardiac decompensation is thought to be related vascular mechanisms such as vasoconstriction as well as neurohormonal and inflammatory activation, renal dysfunction and inappropriate use of some medications. Both the slow development of elevated left ventricular filling pressures and pulmonary congestion are present in a majority of patients presenting with acute heart failure syndrome, however they are often clinically silent in these patients[m].

This early phase of hemodynamic congestion can be detected by the OptiVol® algorithm allowing early intervention to prevent clinical decompensation. The continuous monitoring of measures is key to early detect changes. Mullens *et al.*[n] demonstrated in a setting where patient data including intrathoracic impedance and OptiVol®-data were transmitted and checked by caregivers every three months, that in 94% of the patients where OptiVol® values that crossed the fluid threshold signs and symptoms such as dyspnea, edema and weight gain could be observed. However, as 18% of these patients had HF-hospitalizations, the three-months interval of data check was not sufficient for a prevention of almost one fifth of these patients. In contrast, the combination of OptiVol® and CareLink® with a continuous daily check of threshold crossings offers the possibility to react within a very short time frame instead of three months as described in the setting used by Mullens *et al.*. Therefore, hospitalizations could be prevented by early detection of changes already in the phase of hemodynamic decompensation before signs and symptoms of clinical decompensation occur later in this continuum.

The Medtronic CareLink® Network (CareLink®) is one solution for continuously monitoring and to help clinicians targeting subjects that most need their attention and at the same time to reduce routine and interim clinic visits. With CareLink®, device data can either be transmitted automatically via wireless Conexus™ Telemetry or manually by the subject over the Internet. Clinicians can then login to a website and view the same data they would have access to if they had brought the subject in for a routine in-office clinic visit. Patients who need further attention can then be called in for a visit, and patients with no need to come in can avoid a trip to the office. In addition to reducing unnecessary

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[k] Verwey HF, Sweeney R. Patients Symptoms and device based activity for decompensated vs. nondecompensated heart failure patients. *J.Card. Fail*. 2005; 12: 170.

[l] Cotter G, Metra M, Milo-Cotter O *et al.* Fluid overload in acute heart failure — Re-distribution and other mechanisms beyond fluid accumulation. *Eur. J. Heart Failure*. 2008; 10: 165-169.

[m] Gheorghiade M, Filippatos G, De Luca L, *et al.* Congestion in Acute heart Failure Syndromes. *The American Journal of Medicine.* 2006; (12A) 119: 3-10.

[n] Mullens W, Abrahams Z, Skouri HN *et al.* Elevated Intra-Abdominal Pressure in Acute Decompensated Heart Failure: A Potential Contributor to Worsening Renal Function? *J. Am. Coll. Cardiol.* 2008; 51: 300-306.

routine visits, CareLink® can also reduce interim visits to the clinic or Emergency Department (ED), after an event such as a shock by allowing physicians remote access to subjects' data.

The new generation of Medtronic Concerto™ CRT-D or Virtuoso™ ICD provides wireless Conexus™ telemetry. These systems are able to automatically transmit data wirelessly to a monitor in the home. They also have enhanced diagnostic features, as well as the ability to deliver wireless (non-audible) alerts (CareAlerts®) that initiate a wireless transmission to notify physicians when clinical events occur. The combination of Medtronic's proprietary OptiVol® fluid status monitoring with automatically generated wireless CareAlerts® through the CareLink® Network alerts the clinician early about increased fluid accumulation in the subject's chest as a presymptomatic indictor of pulmonary congestion. Early intervention after detection of pulmonary congestion may be a key element in avoiding hospitalizations due to cardiovascular decompensation. For example, by being notified that a subject's thoracic impedance has crossed the OptiVol® threshold, it is possible that the subject's compliance regarding medication and the intake of fluid as well as the dose of heart failure medication can be adjusted, potentially reducing the need for an in-clinic visit or even hospitalization due to worsened heart failure condition and decompensation. The presymptomatic notification of worsening heart failure condition by OptiVol®, before decompensation status leads in a serious worsening/HF-hospitalization, is expected to provide adequate time for clinical decision making within the next days. Earlier detection and notification, combined with remote management may also have an economic effect of shifting healthcare utilization from emergency department visits and possibly subsequent hospitalization to ambulatory clinic visits, reducing cost and burden on the healthcare system. In addition, remote monitoring may improve subject well being by increasing quality of life.

This study has been designed to evaluate whether the combination of OptiVol® Fluid Status Monitoring and automatically generated CareAlerts® through CareLink® Network may help physicians to prevent cardiovascular hospitalizations and reduces mortality.

2.3 Product Descriptions and Intended Use

Subjects must be implanted with a Medtronic Inc., market approved, single- or dual-chamber Virtuoso™ ICD or Concerto™ CRT-D device or subsequent devices providing at least the same functionality, used within approved indication:

1) Access arm: Medtronic Virtuoso™ ICD system or Concerto™ CRT-D or subsequent devices with at least the same functionality providing fluid status monitoring OptiVol® and with CareLink® access (OptiVol® "ON" and CareAlert® "ON"),

2) Control arm: Medtronic Virtuoso™ ICD system or Concerto™ CRT-D or subsequent devices providing at least the same functionality without CareLink® access (OptiVol® "OFF") in order to be considered for participation in the study.

2.3.1 Virtuoso™ ICD and Concerto™ CRT-D Study Device with Conexus™ Telemetry

The Medtronic Virtuoso™ ICDs and Concerto™ CRT-Ds provide technological advancements such as wireless telemetry (Conexus™ Telemetry), Cardiac Compass® Trends including OptiVol® fluid status monitoring and expanded alerts (Medtronic CareAlerts®) including wireless alerts for OptiVol® fluid status monitoring.

Optionally any future CE-approved and market-released Medtronic ICD / CRT-D device with Cardiac Compass® and OptiVol® fluid status monitoring that is supported by the Medtronic CareLink® Network may be incorporated into the study.

Model D164AWC Virtuoso™ DR / D164VWC Virtuoso™ VR devices are indicated to provide ventricular antitachycardia pacing and ventricular defibrillation for automatic treatment of life-threatening ventricular arrhythmias. The Virtuoso™ DR device is also indicated for use in the above subjects with atrial tachyarrhythmias, or those subjects who are at significant risk of developing atrial tachyarrhythmias. Atrial rhythm management features, available on the Virtuoso™ DR, such as Atrial Rate Stabilization (ARS), Atrial Preference Pacing (APP), and Post Mode Switch Overdrive Pacing (PMOP), are indicated for the suppression of atrial tachyarrhythmias in ICD-indicated subjects with atrial septal lead placement and an ICD indication.

The Model C154DWK / C174AWK Concerto™ CRT-D is indicated for ventricular antitachycardia pacing and ventricular defibrillation for automated treatment of life-threatening ventricular arrhythmias. In addition, the system provides cardiac resynchronization therapy and is therefore indicated for the reduction of the symptoms of moderate to severe heart failure in those patients who remain symptomatic despite stable, optimal medical therapy, and have a left ventricular ejection fraction < 35% and a prolonged QRS duration.

2.3.2 OptiVol® Fluid Status Monitoring

OptiVol® fluid status monitoring calculates average daily intrathoracic impedance values to track changes in the subject's thoracic fluid status over time. In order to start taking impedance measurements, VF detection must be programmed "ON" in the device. OptiVol® fluid status monitoring calculates the average daily thoracic impedance by averaging 16 four-beat impedance measurements taken from the right ventricular defibrillation coil to the device case ("can") every 20 minutes from noon until 5 pm. Measurements are based on the time programmed in the device.

The reference impedance is established by the OptiVol® algorithm as a multi-day average of impedance, which reflects slower adaptations to fluid changes. The reference impedance reflects changes over time against which daily impedance changes can be compared. The reference

impedance is initiated 34 days after implant to allow time for pocket healing and lead maturation. Daily impedance values for days 31-34 are averaged to get the initial reference line point. From then on, the reference impedance changes slightly from day to day to slowly adapt to the daily impedance.

The OptiVol® algorithm calculates the accumulated difference between the daily impedance and reference impedance. When the daily impedance values consistently fall below the reference impedance, the OptiVol® fluid index accumulates. When the daily impedance value increases above the reference impedance values, the OptiVol® fluid index returns to zero. The OptiVol® threshold (refer to section 2.3.3) can be programmed from 30 ohm/days to 180 ohm/days in increments of 10 ohm/days, at device implant or at follow-up device checks. If the OptiVol® fluid index crosses the physician-programmed OptiVol® threshold, an observation is triggered. The OptiVol® fluid index crossing the OptiVol® threshold may be an indicator of possible thoracic fluid accumulation. The daily impedance, reference impedance, OptiVol® threshold, and OptiVol® fluid index can be viewed via the OptiVol® fluid trends, a subset of the Cardiac Compass® Trends on the Cardiac Compass® Reports.

Ongoing research and development may lead to improvements of the OptiVol® algorithm used in the implantable ICD and CRT-D devices within the OptiLink HF study. In case such an improved algorithm becomes available as a CE-labeled download intended for use in the study devices, it can be used in patients already enrolled in the study and future patients as well. After information about the technical details and differences between the currently available OptiVol® algorithm and the improved one by the sponsor, the study executive committee will determine the exact mode of device-upgrade and use of such an improved algorithm in case it becomes available.

2.3.3 Reference Impedance Adjustment

There is one enhancement to the OptiVol® feature, which is of relevance for the OptiLink HF study: OptiVol® reference impedance adjustment.

The OptiVol® reference impedance adjustment enhancement provides study investigators with the option of reinitializing the reference impedance for those occasional cases in which the daily impedance measures are persistently lower than the reference impedance and the subject's pulmonary congestion status and daily impedance values are stable (e.g. stable, but changed HF-status after new titration of drugs; or set of original reference at time of hypovolumic status). Resetting the reference impedance will result in a new reference impedance measurement and will reset the OptiVol® fluid index to zero.

The OptiVol® reference impedance adjustment should only be utilized after thorough assessment and review of the subject and OptiVol® fluid trends. The reference impedance should only be adjusted when the following criteria have been met:

- Subject has stable pulmonary fluid status and

- OptiVol® trends show the subject's daily thoracic impedance is stable and

- Reference impedance has not adjusted to the subject's daily impedance.

Conditions known to potentially cause an OptiVol® threshold crossing include: system modification (e.g. lead or pocket revision) and initialization of the reference impedance during hypovolemic states. When the OptiVol® reference impedance adjustment is used, a new reference impedance will be calculated by averaging the last daily impedance measurement and the next 3 daily impedance measurements. The OptiVol® fluid index will also reset to zero. Once the reference impedance is adjusted, it cannot be reversed. Study center personnel must document the rationale for adjusting the reference impedance on the CRF on care alert evaluation form. Failure to provide rationale will result in a study deviation.

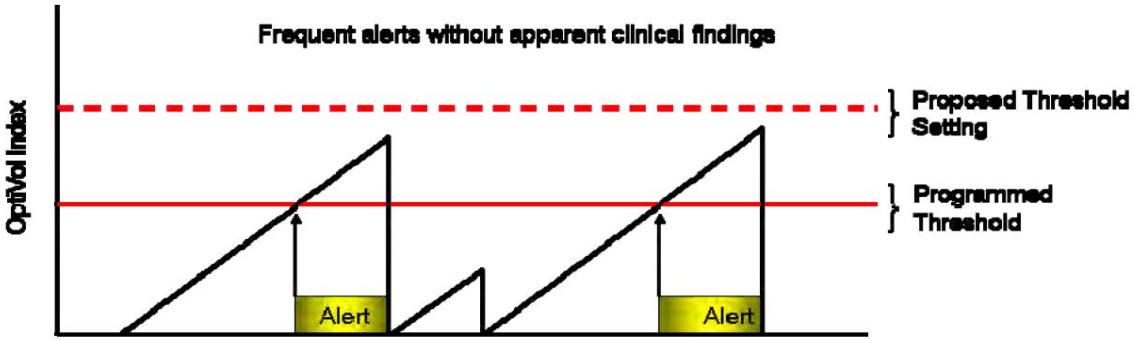
OptiVol® Threshold

The OptiVol® threshold can be programmed at the investigator's discretion to manage the balance between providing sufficient warning prior to significant fluid overload events (such as heart failure hospitalization) versus pre-clinical events and/or premature alerts/too early alerts. Currently, the nominal threshold value is 60 ohm/days, with programming options from 30-180 ohm/days in increments of 10 ohm/days.

It is recommended that the OptiVol® threshold is initially **programmed at 60 ohm/days**. In general, increasing the threshold will reduce the number of alerts, but may also delay or not prevent some clinically relevant alerts. Conversely, reducing the threshold will increase the number of alerts, but a larger portion may be less clinically meaningful. Though the need for threshold programmability is not expected to be high, a few clinical scenarios may warrant consideration for reprogramming the OptiVol® threshold on a subject-by-subject basis.

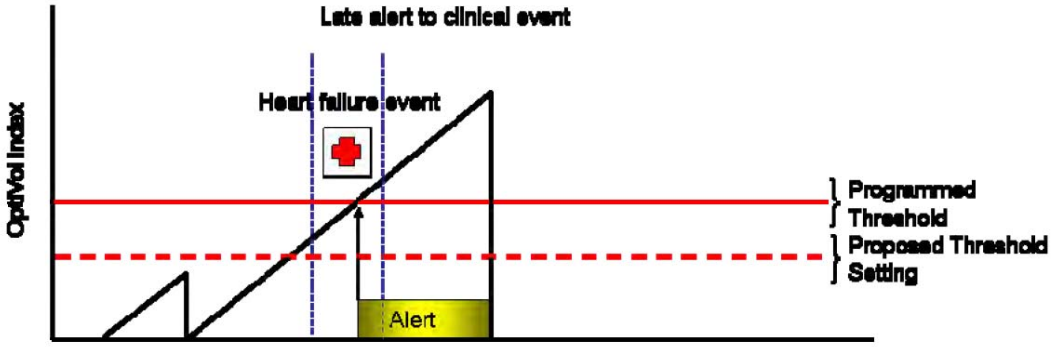
- Consider an increase of the threshold if the subject has frequent, separate low amplitude threshold crossings without any evidence of conditions that could influence intrathoracic impedance, such as new or worsening signs or symptoms congestion or of pocket edema/infection. Increase the threshold to a point above the peak of these threshold crossings. For example, if the threshold crossings that do not appear to be associated with clinical findings peak at about 80 ohm/days, consider reprogramming the OptiVol® threshold to 90 ohm/days.

Figure 1: Frequent alerts without apparent clinical findings



- Consider a decrease of the threshold if the crossing of the OptiVol® threshold occurs too late, meaning when the subject presents with clinical signs or symptoms of fluid overload. Consider reprogramming the OptiVol® threshold to a value that would provide sufficient warning.

Figure 2: Late alert to clinical event



Reprogramming of the OptiVol® threshold should only be done after thorough assessment and review of the subject and OptiVol® fluid trends. Study center personnel must document the rationale for reprogramming the OptiVol® threshold. Failure to provide rationale will result in a study deviation.

2.3.4 Medtronic CareLink® Network and Medtronic CareLink® Monitor

The Medtronic CareLink® Network is designed to monitor the implanted device's performance, as well as physiological aspects of the subject's condition recorded by the implanted device. **CareLink® does not allow for remote implanted device programming.** Reprogramming can only be done during an in-clinic visit. CareLink® consists of the CareLink® Network monitor which sends information to the secure CareLink® server via the telephone connection and the CareLink® Clinician Website with which subjects and/or clinicians interact.

CareLink® Network monitor is CE market approved and will be used for the study within the intended use. The monitor is a small device at the subject's home that interrogates (reads) and transmits data collected by the implanted device, referring to the functionality of the implanted system and data about the physiological and rhythm status of the subject. This data is comparable to the data obtained by interrogating the implanted device with a programmer. The monitor automatically dials a pre-programmed toll-free number to send the information to the secure CareLink® server via the telephone connection.

Monitors are configured to work specifically with an individual, pre-specified subject's implanted device. Therefore, each monitor is for the subject's personal use only and will not function appropriately with another subject's implanted device. Unauthorized use by others with the implanted devices could interrupt the prescribed operation of their device.

The Medtronic CareLink® Monitor Model 2490C for the Concerto™ CRT-D, Virtuoso™ ICD and subsequently released devices with Connexus™ Telemetry are indicated for use in the transfer of subject data from Medtronic implantable cardiac devices to the Medtronic CareLink® Network based on physician instructions and as described in the product manual. These products are not a substitute for appropriate medical attention in the event of an emergency and should only be used as directed by a physician.

The Medtronic CareLink® Network, a tool required at each study center, enables subjects to remotely transfer data from their device to the clinic. **Only subjects in the access arm are required to use the Medtronic CareLink® monitor, which plugs into a phone line, to send their device data from their place of residence to the clinic.** Study center personnel will access the data, including the Heart Failure Management Report and Cardiac Compass® Report (access arm only), by logging onto the CareLink® website via the Internet https://clc.medtroniccarelink.net.

Clinicians involved in the medical management of control arm subjects will not be allowed to view Cardiac Compass® Trends or HF-Management Report information during in-office device follow-up.

Medtronic Conexus™ Telemetry

Medtronic Conexus™ Telemetry is designed to provide clinicians and subjects with an easier and more efficient implant, follow-up, and monitoring experience. The system uses radio frequency (RF) telemetry for wireless communication between the implanted device and Medtronic CareLink®

monitor in the subject's home. This eliminates the need to place a programming head over the implanted device for the monitoring session and allows for communication with the Medtronic CareLink® home monitor without subject intervention, enabling automatic scheduled transmissions as well as alert-based downloads.

2.3.5 Medtronic CareLink® Monitor with Medtronic Conexus™ Telemetry

Subjects randomized to the access arm must be included in the CareLink® Network Service using the OptiVol® CareAlert®–based monitoring and automatic notification of worsening heart failure condition given with CareLink®. Monitor Model 2490C is designed to communicate with Medtronic ICD or CRT-D systems using wireless telemetry (Virtuoso™, Concerto™ or subsequent market released devices providing at least the same functionality). The monitor at the subject's home is plugged into a phone line and an electrical outlet. The system uses RF telemetry for wireless communication between the implanted device and Medtronic CareLink® monitor in the subject's home. This eliminates the need to have a programming head over the implanted device for the monitoring session and allows for communication with the Medtronic CareLink® home monitor without subject intervention, enabling automatic scheduled transmissions as well as CareAlert®-based downloads.

Using the secure Medtronic CareLink® Clinician Website, clinic staff members can preschedule up to six automatic transmissions for each subject without having to make appointments or coordinate calendars with subjects. The device automatically "wakes up" at the scheduled time and communicates with the Medtronic CareLink® monitor, see Figure 3. Data are transmitted wirelessly from the device to the monitor as the subject sleeps. Data are sent automatically from the Medtronic CareLink® monitor via the phone line. The clinician reviews the subject's device data on the secure website.

Figure 3: Medtronic CareLink® Follow-Up with Conexus™ Wireless Telemetry

For alert-based downloads the implanted ICD or CRT-D monitors the device and diagnostic data such as OptiVol® fluid status and detects problems such as a crossing the OptiVol® threshold. If the subject's device is programmed to notify the clinician, the ICD or CRT-D automatically establishes wireless communication with the Medtronic CareLink® monitor, see Figure 4. Device data is sent automatically from the monitor to a secure server via a standard phone line. The clinician receives a Medtronic CareAlert® notification via SMS or e-mail and checks the Medtronic CareLink® Clinician Website for detailed information and reviews the CareAlert®'s device and diagnostic data of the subject. The clinician only calls the subject to provide further instructions, if needed, and also to obtain further information regarding drug compliance, fluid intake and other circumstances preceding a care alert because of a crossing of the OptiVol® threshold.

Figure 4: Continual Monitoring for Medtronic CareAlert® Status

Use of the monitor will not reprogram the functioning of the subject's implanted cardiac device. Reprogramming can only be done during an in-clinic visit.

Medtronic CareLink® Clinician Website ("Website")

Clinicians can monitor the condition of subjects who use the monitor by securely viewing their implanted device information on the Internet-accessible website when and where needed. Only registered clinic users can access implanted device and subject data by logging onto the password-protected website. Implanted device data available on the website are substantially equivalent to the device data available from in-clinic interrogation-only for device evaluation.

2.3.6 OptiVol® Alert and CareAlerts®

The alerts in Virtuoso™ ICD or Concerto™ CRT-D system or subsequent market released devices providing at least the same functionality are designed to alert the subject and/or clinician of certain selectable system or device performance conditions. System performance alerts are intended to help clinicians identify device or system-related issues, component failure, or device replacement timing. In addition to the system and device performance conditions, the Medtronic CareAlert® monitoring in Virtuoso™ ICD or Concerto™ CRT-D (or subsequent market released devices providing at least the same functionality) device is designed to alert the clinician of heart rhythm conditions and functional status including the notification of the OptiVol® Fluid Index crossing the OptiVol® threshold.

The CareAlerts® are available as audible device alerts. Unlike the audible alerts, CareLink® monitor alerts are **silent** to the subjects and are intended to directly notify the clinician using the Medtronic CareLink® Network. The term "silent" refers to automatic transmission of programmable events from the device to the physician via the subject's CareLink® monitor using wireless telemetry. The alerts available in the Virtuoso™ ICD or Concerto™ CRT-D system or subsequent market released devices providing at least the same functionality are outlined in Table 1.

In Virtuoso™ ICD or Concerto™ CRT-D system or subsequent market released devices providing at least the same functionality, the clinician can select whether a specific alert condition will result in an audible device alert, an inaudible CareLink® monitor alert, or both.

In subjects randomized to the access arm, the **OptiVol® alert will be programmed "ON", but not audible to the subject.** This will result in only a CareAlert® to the physician through the CareLink® Network. The CareAlert® notifies the clinician each time the OptiVol® fluid index crosses the OptiVol® threshold.

In addition to the system and device performance conditions, the Medtronic CareAlert® monitoring feature in Virtuoso™ or Concerto™ devices (or subsequent market released devices) is designed to alert the clinician of heart rhythm conditions associated with atrial tachyarrhythmia (AT) and atrial fibrillation (AF) ("AT/AF alerts"). The AT/AF alerts are intended to monitor and convey heart rate and characteristics of AT and AF, similar to the data provided by an external event monitor. **In subjects randomized to the access arm as well as to the control arm the AT/AF alerts will be programmed "OFF".**

When data is transmitted using the CareLink® Network or when the device is interrogated, all alert conditions will be included. The device stores CareAlert® events as log entries. To avoid redundant log entries, an entry is recorded only the first time each CareAlert® condition is met. Each log entry includes the date and time of the alert event, a description of the alert event, and the programmable threshold that was exceeded. The log is also annotated with the date of the last session.

Once the alert criteria for enabled monitor alert conditions are satisfied, the device will immediately attempt to notify the Medtronic CareLink® monitor via wireless telemetry. The Medtronic CareLink®

monitor will communicate back to the device once the transfer of the information is successful. The device will attempt to communicate with the monitor every 3 hours, until successful transfer of the information, for a maximum of 72 hours. If the transfer of information was unsuccessful within 72 hours, the device will emit an audible high urgency alert at the designated device alarm time for that condition.

Table 1: Available alerts in study device Virtuoso™ ICD and Concerto™ CRT-D and alert programming according to randomization

ALERT TYPE VIRTUOSO™ ICD / CONCERTO™ CRT-D	PROGRAMMING			
	ACCESS ARM		CONTROL ARM	
		AUDIBLE Y/N		AUDIBLE Y/N
Clinical Management Alerts				
OptiVol® Fluid Index Threshold Crossing	**ON**	N	**OFF**	N
AT/AF-Burden at Rate Settings	OFF	N	OFF	N
Number of ICD-Shocks Delivered in an Episode	ON	Y	ON	Y
All Therapies in a Zone Exhausted for an Episode	ON	Y	ON	Y
Lead / Device Integrity Alerts	**Per discretion, however it is recommended that alerts are programmed "ON"**			
Lead impedance out of range – A / RV Pacing Impedance	ON	Y	ON	Y
Lead impedance out of range RV / SVC Defibrillation Impedance	ON	Y	ON	Y
Lead impedance out of range LV Pacing Impedance (CRT-D only)	ON	Y	ON	Y
Low Battery Voltage RRT (Recommended Replacement Time)	ON	Y	ON	Y
Excessive Charge Time	ON	Y	ON	Y
VF Detection Off, VT / FVT Therapies Off	ON	Y	ON	Y
Non-Programmable Alerts				
Electrical Reset	ON	Y	ON	Y
Pacing Mode DOO, VOO	ON	Y	ON	Y
Active Can Off without SVC	ON	Y	ON	Y
Charge Circuit Timeout	ON	Y	ON	Y

The OptiVol® alert can only be programmed "OFF (Observation Only)" in access arm subjects in the event of one or more of the following:

- System modification, resulting in dysfunction of the OptiVol® system,
- Study exit.

Study center personnel will document that the OptiVol® alert was programmed to "OFF (Observation Only)" and provide rationale. Study center personnel will reprogram the OptiVol® alert "ON" as outlined per type of system modification in section 4.13.

The OptiVol® alert must be turned "ON" within 2 business days after randomization of a subject to the access arm. OptiVol® reference impedance adjustment can be used anytime after the point of randomization in the access arm. Criteria outlined in section 2.3.3 should be taken into account when such an adjustment is planned.

2.3.7 HF Management Report and Cardiac Compass® Trends

Medtronic Virtuoso™ ICD and Concerto™ CRT-D system (or subsequent market released devices providing at least the same functionality) provide a range of diagnostic tools, including HF-Management Report and Cardiac Compass® Trends. Both are also accessible through a subset of observations on the Quick Look™ Screen and Quick Look™ Report.

Clinicians involved in the medical management of subjects in the control arm should be advised not to use this information through the Medtronic programmer.

The components of the Cardiac Compass® Report include the following:

- OptiVol® Fluid Trends,
- VT/VF episodes per day,
- One or more shocks per day,
- Ventricular rate during VT, FVT and VF,
- AT/AF total (hours) per day,
- Ventricular rate during AT/AF,
- Percent pacing per day,
- Average ventricular rate (day and night),
- Subject activity,
- Heart rate variability,

- Non-sustained VT/VF episodes per day,
- Percent pacing per day.

The Heart Failure Management Report includes the following additional components:

- OptiVol® thoracic impedance and index.

Observations provided by Quick Look™ are based on an analysis of interrogated data and programmed parameters. Four types of observations are provided: parameter, device status, episode data and clinical trends. For observations provided on the Quick Look™ screen and the Quick Look™ Report refer to Table 2.

Table 2: Observations which are accessible through Virtuoso ICD and Concerto™ CRT-D Quick Look™ Screen on the programmer

OBSERVATION	NOTE
Possible fluid accumulation: exceeded OptiVol® threshold <Date fluid index crossed above threshold> <Ongoing> if fluid index is still above threshold at time of interrogation. <Date fluid index crossed below threshold>	**Access arm:** This condition will be associated with an alert and the proceeding text "Alert" will be visible. **Control arm:** **Although OptiVol® is programmed "OFF" these observations will be visible on the Quick Look™ screen. To exclude "Soft-Cross-Over"** by awareness of this information, it is mandatory that the physician in charge of managing subjects of this study does not get this information for subjects of the control arm.
Atrial Tachycardia / Atrial Flutter-Information <Number of days> with more than <Number of hours> of AT / AF **Average Ventricular Rate during AT / AF** <Beats per minute> for <Number of hours> during AT / AF	**Access and control arm:** Even if AT/AF alerts are programmed "OFF" these observations will be visible on the Quick Look™ screen as well as on the CareLink® web page. This may lead in both study arms to interventional action; i.e. cardioversion of VF. The intervention must be documented on the ICD / CRT-D-Safety and Integrity Form (ICD / CRT-D-SIF), or AEF in case that a hospitalization is caused but is not considered to represent a cardiovascular hospitalization as defined in section 4.19.
Subject activity less than 1 hour / day <Number of weeks>	Available information for **access and control arm** This may lead in both study arms to interventional action. This must be documented on the ICD / CRT-D-SIF, or AEF in case that a hospitalization is caused.
Night heart rate over 85 beats per minute for 7 days	Available information for **access and control arm** This may lead in both study arms to interventional action. This must be documented on the ICD / CRT-D-SIF, or AEF in case that a hospitalization is caused.

ICD / CRT-D-SIF: Safety and Integrity Form; AEF: Adverse Event Form

2.3.8 Review of HF Management Report and Cardiac Compass® Trends (Access Arm only)

Whenever review of HF-Management Report and Cardiac Compass® Trends is required, it must include both (i.e. cannot just review the subset of observations on the Quick Look™ Screen or Quick Look™ Report). Data are accessible through the following components:

- HF-Management Report,
- Cardiac Compass® Report,
- Cardiac Compass® Trends on the Quick Look™ Report (Virtuoso™ Concerto™ CRT-D devices or subsequent market released devices providing at least the same functionality),
- A subset of observations on the Quick Look™ Screen and Quick Look™ Report (refer to Table 2),
- Event logs for CareAlert® information.

2.3.9 CareLink® Monitor Distribution

Study center personnel will initiate distribution of the Medtronic CareLink® monitor to subjects by enrolling the subject through the Medtronic CareLink® Network website (if the subject is not already enrolled in the CareLink® Network). Subjects should receive the Medtronic CareLink® monitor approximately two weeks after enrollment on the Medtronic CareLink® website. Study center personnel will provide training and/or demonstrate use of the Medtronic CareLink® monitor to the subject.

2.3.10 Shipment, Storage, Handling and Use

All the devices are commercially available in Europe and will be used within the intended indication. Therefore, no specific procedures to manage the distribution, shipment, storage and handling are required.

3 METHODOLOGY

3.1 Study Design and Rationale

The OptiLink HF study is a prospective, unblinded, randomized, and controlled study performed in multiple centers. It is planned to include 1000 subjects (500 per study arm) and to conduct the study in 20-30 centers specialized in ICD / CRT-D-implantation, and about 100 active satellite HF-management centers with access to Medtronic CareLink® Network. The study is designed with a control group to compare event-triggered HF-disease management through Medtronic's OptiVol® fluid status monitoring with automatically generated wireless CareAlert® notification of the clinician via the Medtronic CareLink® Network (access arm) to standard clinical assessment alone (control arm) in subjects eligible for ICD / CRT-D therapy suffering from heart failure.

The study is randomized to achieve structurally comparable sequence groups concerning known and unknown influence of confounding factors. Unblinded character results from the study design.

Figure 5 presents subject flow. Subjects will undergo screening to ensure they meet all of the inclusion and none of the exclusion criteria. Medical Ethics Committee (MEC) approval of the OptiLink HF clinical investigation plan and informed consent must be obtained prior to enrolling subjects in the OptiLink HF study. Subjects are considered enrolled upon signing the approved informed consent. Enrollment of the subject **can occur 3 days (72 hours) up to 21 days post-implant** while the OptiVol® algorithm activates 34 days after the implant (the period between implant and day 34 is used to build up the impedance reference value). **Subjects will be randomized directly after enrollment and after completion of KCCQ and EQ-5D questionnaires.** The time between randomization and activation of the OptiVol® system is used to organize the individual care link device. Eligible enrolled subjects will be randomized in a 1:1 fashion to the access arm or the control arm. Randomization will be stratified by risk, for details refer to section 4.4.2. Randomization requirements are summarized in appendix O.

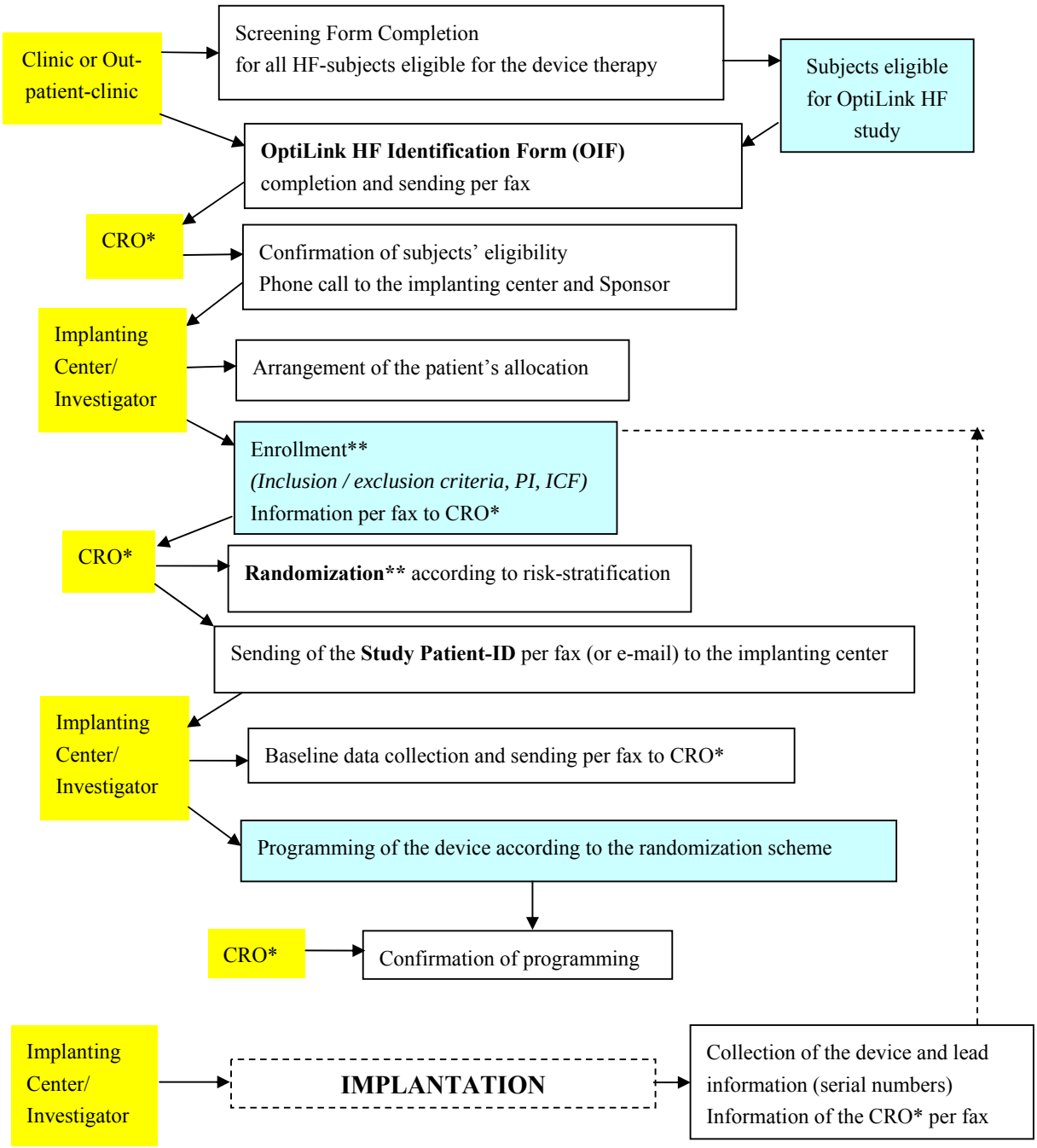
Enrolled subjects who fail to meet final eligibility criteria will not be randomized into the study. The subject will be withdrawn from the study and a study exit form (SEF) will be completed.

Clinical data are required to be collected at baseline/enrollment, randomization, and scheduled follow-up visits at 6 months and every 6 months thereafter until study closure or subject death/exit. Follow-up visit windows are listed in Table 4, section 4.6 and are based on days post-randomization.

Data collected at follow-up visits conducted outside the window will be considered non-compliant to the window, but will be included in the final analysis based on intention-to-treat analysis. Data collection requirements are summarized in Table 3, section 4.1.

The study center personnel must report all adverse events and changes in status of these adverse events from time of enrollment until a subject exits the study.

Figure 5: Subject flow



*CRO = Contract Research Organization = IFE Institute for Research and Development
**Enrollment is possible 3 up to 21 days after implantation while the randomization will be performed directly after enrollment
PI = Patient Information. ICF = Informed Consent Form

The study was designed with a control arm in order to adequately investigate the effect of early intervention triggered by CareAlert® notification and evaluation using HF-Management and Cardiac Compass® Report with OptiVol® fluid status monitoring.

Variables that differ between the access arm and the control arm include the following: access to CareLink®, the combination of Medtronic's OptiVol® fluid status monitoring with automatically generated wireless CareAlerts® via the Medtronic CareLink® Network, access to HF-Management-Report and Cardiac Compass® Trends.

In the event the investigator or subject does not comply with the randomization assigned, a deviation must be reported to Medtronic. The subject will continue to be followed on an intent-to-treat principle and should remain within the arm they were initially randomized.

3.2 Study Objectives

Primary objective:
The primary objective of the study is to establish whether the use of "OptiLink" decreases the **incidence rate of the combined endpoint of all-cause mortality or cardiovascular hospitalization** over an 18 months follow-up in subjects with HF and ICD or CRT-D treatment. All causes of death and unplanned admissions to hospital for cardiovascular reasons from randomization until 18-months follow-up visit are assessed.

Hospitalization is defined as an overnight stay or longer in a hospital environment or similar facility including admission to a day care facility.

Cardiovascular hospitalizations are defined as hospitalizations for:

- Heart failure (first or subsequent),
- Acute myocardial infarction,
- Unstable angina pectoris,
- Symptom-driven hospitalization for cardiac arrhythmia (atrial fibrillation, atrial flutter, supraventricular arrhythmias or ventricular arrhythmias),
- Stroke/cerebral vascular accidents.

Hospitalizations for elective CV procedures do not qualify as CV endpoint, this included planned admission for elective cardioversion of atrial fibrillation.

The following secondary objectives and endpoints will be analyzed:

1) Number of HF-related hospitalizations during follow-up;
2) HF-related hospitalization;
3) Sum of follow-up days minus days alive and out of the hospital;
4) All-cause mortality;

5) Cardiovascular mortality;
6) HF-related hospitalization and all-cause mortality;
7) Quality of Life (QOL);
8) Health Economics.

Exploratory endpoint:
Number of all-cause hospitalizations during 18 months follow-up.

3.3 Study Scope

Only subjects implanted with a single- or dual-chamber ICD or CRT-D device will be included in this study. The sample size was estimated using the experience from previous studies (CHARM). The results showed that event rates (i.e. proportion of subjects with at least one event) of 28% in 18 months for the combined event all-cause death or cardiovascular related hospitalization will be a reasonable estimator for the control arm. The assumption of a 30% improvement in the access arm, which results in a difference of 8.4% between the treatment arms, is the basis for the sample size calculation (see 5.6).

3.4 Claims and Intended Performance

The OptiLink HF study intends to establish whether the use of event-triggered HF-disease-management = Medtronic's OptiVol® fluid status monitoring with automatically generated wireless CareAlert® notification of the clinician via the Medtronic CareLink® Network can reduce the number of cardiovascular hospitalizations in a subject population with HF and ICD / CRT-D treatment by using the diagnostic tools available in the commercially released Medtronic ICD / CRT-D devices in combination with CareLink®. It is not the purpose of the OptiLink HF study to support labeling changes, instructions for use or promotional material claims for these devices.

3.5 Applicable Regulations

The study will be conducted in compliance with ISO 14155 part 1 & 2 and will use ICH-GCP as guidance. The study will comply with the Declaration of Helsinki concerning medical research, CFR part 11 and 54, and in accordance with the laws and regulations in the countries in which it is conducted. A Medical Ethics Committee (MEC) written approval or an investigator approval of a presented opinion from a MEC is required before center participation in this study.
All devices used in this investigation have the CE mark. The devices are manufactured in accordance with the provision of the Active Implantable Medical Device Directive (90/385/EEC) and comply

with all relevant legal requirements. The used devices and leads are market released and used within labeling. Please refer to appendix N for the CE declaration of conformity of the used devices.

3.6 Inclusion and Exclusion Criteria

Subjects of both genders who comply with all inclusion and none of the exclusion criteria are eligible for this clinical study.

Inclusion Criteria:

- Subjects have a Medtronic Virtuoso™ single- **or** dual-chamber ICD **or** Concerto™-CRT-D **or** subsequently market released Medtronic device providing at least the same functionality implanted, including device replacement. Subjects with CRT-D must fulfill CRT-indication as described in the ESC guidelines for cardiac pacing and cardiac resynchronization therapy 2007: EF ≤ 35% and NYHA III, and LVEDD> 55 mm, and QRS ≥ 120 ms, and optimized therapy,
- Subjects with stable chronic heart failure (CHF) in New York Heart Association (NYHA) class II or III for at least 30 days and left ventricular ejection fraction of no more than 35% (most recent measurement within 6 months prior to randomization by echocardiography or contrast ventriculography, magnetic resonance or nuclear imaging, based on local practice), on optimal target or maximal tolerated dose of ACE-inhibitors or angiotensin receptor blockers, ß-blockers and diuretics if clinically indicated to reduce fluid retention and one of the following criteria:
  At least one hospitalization due to the heart failure within the last 12 months before enrollment or one course of ambulatory IV- or oral diuretic treatment or a BNP value of > 400 pg/ml or a NT-proBNP values > 450 pg/ml in subjects < 50 years, > 900 pg/ml (50-75 years) and > 1800 pg/ml in subjects of > 75 years old within 30 days of enrollment,
- Written informed consent by the subject for study participation prior to clinical investigation plan specific procedures,
- The subject must be able and willing to comply with the clinical investigation plan and willing to remain available for follow-up visits to the study closure,

- Subjects or the subject's caregiver must be willing and able to use the Medtronic CareLink® monitor as instructed and to perform the required duties.

Exclusion Criteria:

- Subjects with chronic renal failure needing renal dialysis,
- Subjects with serum creatinine > 2.5 mg/dl, measured within 14 days prior to enrollment,
- Subjects with severe to very severe Chronic Obstructive Pulmonary Disease (COPD) as determined by physician and documented in medical records (Stage III or Stage IV),

  Subjects with suspected or confirmed COPD require a current test of lung function (not more than 12 months before inclusion). If the "forced expiratory volume" is < 1.0 L/sec, the subject may not participate in the study.

- Subjects on the heart transplantation list or subjects with transplanted hearts,
- Subjects listed for valve replacement or interventional valve therapy,
- Subjects with myocardial infarction within the last 40 days before ICD / CRT-D-implant. MI is defined by typical changes in biochemical markers including troponin levels > 3 times the upper limits of normal and creatinine kinase < 2 times of upper limit, or with CKMB greater than the upper limit of normal, combined (for all enzymes) with at least one of the following ischemic symptoms, ECG changes consistent of diagnostic ST-T wave changes or pathologic Q waves or new LBBB,
- Subjects with stroke within 40 days prior randomization,
- Subjects who have had a percutaneous coronary intervention within 3 months prior to randomization,
- Subjects with cardiac surgery within 90 days of randomization,
- Subjects with complex and uncorrected Congenital Heart Disease,
- Subject's life expectancy is less than 18 months in the opinion of the physician,
- Subjects in situations that would limit participation, not eligible to receive a CareLink® monitor (e.g. hearing or speech impaired with no family member or caregiver available to assist, or those who spend extended periods abroad, or those who intend to enroll in a study that would preclude use of the monitor),
- Subject is participating in a concurrent intervention study,
- Subject or the subject's caregiver is unwilling to give consent for the release of information for the evaluation or to give additional consent

for the release of subject medical and privacy data for CareLink® subjects,

- Subjects with exclusion criteria required by local law (age < 18, women who are pregnant or breastfeeding).

The enrolling physician will be responsible for identifying subjects who might participate in the evaluation and discussing participation with them.

3.7 Intended Blinding to HF-Management Report and Cardiac Compass® Trends

Study center personnel involved in the medical management of subjects in the control arm will be asked not to view HF-Management Report and Cardiac Compass® Trends for subjects in the control arm in order to adequately study the effect of review on the rate of hospitalizations and mortality. All efforts will be made to maintain this advice for subjects in the control arm.

3.8 General Center Requirements

A center may be included in the investigation if the center complies with the following requirements:

- Physician with expertise in subject therapy management,
- Absence of simultaneous competing clinical protocols that may interfere with this trial's subject enrollment and study compliance,
- Appropriate supplies, resources and equipment as required by the clinical investigation plan (e.g. Internet access, Medtronic CareLink® Network access, Medtronic 2090 or 2090W Programmer, required for implanting center, optional for active study center),
- Sufficient staff to carry out the clinical investigation plan requirements in a timely fashion and maintain compliance to the clinical investigation plan,
- Investigator with no known history of misconduct resulting in withdrawal of investigator's privileges / responsibilities by MEC or regulatory authorities,
- Acknowledgement of and agreement to comply with local regulatory requirements as well as with the clinical investigation plan and MEC requirements,
- Investigator permits monitoring and auditing by Medtronic or the CRO and inspection by regulatory authorities.

3.9 Investigator Agreement

A clinical trial agreement must be signed by each center and returned to IFE prior to the commencement of any study activities.

The investigator is indicating his/her approval of the clinical investigation plan and subsequent amendments, by signing and dating the agreement. Recent dated and signed curriculum vitae that reflect the investigator's current position and title will be required from each investigator participating in this study.

3.10 Medical Ethics Committee

MEC approval of the study and clinical investigation plan must be received and the contents of the approval letter accepted by Medtronic or the CRO before commencement of the study at a clinical site.

The MEC approval letter must contain the following elements:

- Name of study,
- Name of MEC and MEC composition / letter of compliance,
- Date of approval,
- Sufficient identification of version/date of clinical investigation plan, version/date of amendments (if applicable), version/date of center-specific subject information and informed consent form (see appendix A for the template version), and version/date of any other study specific documents approved by the MEC,
- If the investigator or any other member of the study team at the site is a member of the MEC, Medtronic shall be provided with written documentation that he/she did not participate in the voting approval process for this study.

3.11 Access to Center and Study Material

The principal investigator(s), his/her delegate(s) and the study coordinator(s) shall be accessible to the Medtronic field clinical support, the CRO-personnel and the study manager. This accessibility is of particular importance for reviewing data in the Case Report Forms (CRFs). For the study monitors, direct access to the subject records for source data verification will need to be granted and prepared prior to any monitoring visits.

3.12 Study Training

Center personnel (investigators, coordinators, other clinical staff) participating in the OptiLink HF clinical study will be trained in study activities relevant to their role prior to conducting any OptiLink HF study activities. Investigators and study coordinators will be trained on their responsibilities, investigational product usage and handling, ISO-14.155, obtaining informed consent, and the clinical investigation plan. Training on worksheet completion and CRF completion, will also be provided. Investigator and/or study coordinator meeting(s) or conference call(s) may be held to discuss the study, clinical investigation plan, training, study results, etc. Interim meetings or telephone conference calls may be organized to discuss relevant study issues. The investigator will agree to attend investigator meetings and/or conference calls or send a co-investigator if they are unable to attend, whenever possible.

The coordinator will agree to attend all coordinator meetings and/or conference calls, whenever possible.

3.13 Bias Reduction

The following methods were incorporated into the study to minimize bias:

- Subject demographics will be assessed by collecting information on possible differences that may affect the outcome. Information will be gathered on the subject's gender, ethnicity, medical background, diagnosis, and indications for ICD / CRT-D device therapy at time of implant,
- Subjects are assigned to the access arm or control arm by a randomization procedure, which is stratified by risk. This ensures statistical validity as well as a high probability of balanced confounding influences, refer to section 4.4.2,
- All centers will use the same version of the OptiLink HF clinical investigation plan,
- An independent committee of physicians will regularly assess, review and classify all hospitalizations, ED visits, urgent and non-urgent unscheduled office visits.
- To ensure a widespread distribution of data, the number of enrollments per center should not exceed 100 subjects,
- Data will be collected using standardized CRFs,

- Only subjects in the access arm are required to be enrolled on the Medtronic CareLink® Network,
- All study center personnel and Medtronic personnel will be trained on their respective aspects of the study using standardized training materials,
- Regular monitoring visits will be conducted for adherence to the clinical investigation plan and source data verification, refer to section 8,
- A Data Safety Monitoring Board (DSMB) will provide oversight of the study, refer to section 11.4,

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

3.14 Early Termination or Suspension

Suspension of a clinical investigator or a clinical center may occur for the following reasons:

- Non compliance to the inclusion/exclusion criteria,
- Failure to follow through with MEC/authority for approval or compliance to MEC conditions or continuation of the clinical study,
- Failure to follow subjects per scheduled follow-ups,
- Failure to submit data in a timely manner,
- Failure to follow-up with findings on monitoring reports,
- Failure to comply with adverse event reporting requirements.

4 STUDY PROCEDURES

4.1 Data Collection Overview

Clinical data is required to be collected at baseline/enrollment, randomization, and scheduled follow-up visits at 6 months and every 6 months thereafter until study closure or subject death/exit. Follow-up visit windows are listed in Table 4 and are based on days post-randomization.
Data collected at follow-up visits conducted outside the window will be considered non-compliant to the window but will be included in the final analysis based on intention-to-treat analysis.

Scheduled follow-up visits can be performed either by the study EP/implanting clinician or out-patient-clinic. The actual dates and windows for each follow-up will be obtained from the external CRO (IFE) performing monitoring. It is recommended that the study center personnel file the follow-

up schedule in the subject binder. If a follow-up visit falls outside the window, the original follow-up schedule will be maintained for subsequent visits. If a scheduled visit is missed, does not occur within the defined follow-up visit window, or the visits are more than ten days apart, a study deviation form (DEF) will be required with a justification.

Requirements for data collection during the follow-up visit:

- NYHA class,
- Current HF symptoms,
- Cardiovascular medication,
- Arrhythmia-episode review,
- ICD- / CRT-D-Device Therapy Safety and Integrity Information,
- Adverse events (AEs),
- Study deviation,
- Health Care Utilization (HCU),
- Programming check,
- Save-to-disk (control arm, access arm until save-to-disk equivalent data-files for analyses can be retrieved from the CareLink® Network).

Explicit elements for access arm (not for the control arm):

- Review of HF-Management Report and Cardiac Compass® Trends.

Clinical data will be collected via standard Case Report Form (CRFs), device interrogation and save-to-disk storage (control arm). In the access arm device interrogation and save-to-disk storage will be substitute by automatically transferred data-transmission to the CareLink® Network. The sponsor might decide to collect save-to-disk files also on the access arm in case equivalent data can not be retrieved from the CareLink® Network in order to secure the availability of data. Otherwise, only in case of in-office, hospital-visits, combined with reprogramming of the device a save-to-disk storage may be required, unless manual data-upload to the CareLink® website after reprogramming can not be performed within 3-4 days after visit. Medtronic and IFE will have read-only access to all CRF-data and to individual CareLink® Network accounts for all study centers upon completion of study-specific training.

CRFs will be entered by the trained, delegated and authorized study site personnel. Once data has been entered and submitted, there may be discrepancies that require clarification. Data clarifications are generated by queries and sent to the center.

The study site personnel are responsible for timely review and resolution of all queries. Investigators will be required to sign off on data as communicated by the study team.

Data collection requirements are summarized in Table 3.

Table 3: Data Collection Requirements

CRF or CareLink-Session or Visit	Baseline (BLF)	Randomi-zation (RRF)	Scheduled/ Unscheduled visit (ICD /CRT-D-SIF)	Tel. Contact by OptiVol® Alert (CAEF)	Hospitali-zation or AE (AEF)	Study Exit/ Subject Death (SEF)	Deviation (DEF)
Requirements	**A: Access Arm; C: Control Arm**						
Inclusion criteria	X						
NYHA class	II or III		X C: during office visit		X	X	
LVEF measurement	≤ 35%						
1. HF-related hospitalization within last 12 months	Yes, only one of these 3 items						
2. IV- or oral diuretics							
3. BNP value of > 400 pg/ml or a NT-proBNP values > 450 in subjects < 50 years, > 900 (50-75 years) and > 1800 in subjects of > 75 years old within 30 days of enrollment							
Exclusion criteria	X						
Informed consent signed	X						
Demographic data	X						
Medical history	X						
Weight and/or changes	X			X	X		
Medication and/or changes	X		C: during office visit A: via telephone contact	X	X	X	X
HF symptom status (or death information),	X			X	X	X	X
Continuous hospitalization check							
Blood sample	X		X[1] (Optionally at 6-month follow-up)		X[1] (Optionally)	X	

CRF or CareLink-Session or Visit	Baseline (BLF)	Randomi-zation (RRF)	Scheduled/ Unscheduled visit (ICD /CRT-D-SIF)	Tel. Contact by OptiVol® Alert (CAEF)	Hospitali-zation or AE (AEF)	Study Exit/ Subject Death (SEF)	Deviation (DEF)
Requirements	**A: Access Arm; C: Control Arm**						
Kansas City Cardiomyopathy Questionnaire (KCCQ) and EQ-5D	X		X[2] (Only at 6-month follow-up)			X	
Randomization assignment; handover of subject ID card to subject		X					
CareLink® enrollment		Only A					
Assign subject to CareLink® satellite		Only A					
ICD / CRT-D-therapy assessment		X	C: during office visit A: via CareLink®		X	X	X
Review Cardiac Compass® Trends and HF Management Report			C: should be limited A: via CareLink®	X	X	X	C: Review is unavoida-ble
Device interrogation StD	Only C		Only C A: via CareLink®		A and C	Only C A: via Care Link®	Only C A: via Care Link®
Intervention algorithm				Only A	A and C		
Health Care Unit Documentation				A and C	A and C		

[1] Optionally a blood sample will be collected at 6-month follow-up in-office visit or in the case of hospitalization after CareAlert®.
[2] Questionnaires will be filled in at 6-month. Subjects from the control arm will fill in the questionnaires at follow up visit, whereas subjects from the access arm will received questionnaires per post and fill them in at home.
[3] After randomization.

4.2 Implant/Pre-hospital Discharge

The surgical procedure for ICD / CRT-D implantation in the implanting center will be at the discretion of the implanting physician. Device information obtained from the implantation until hospital discharge will be documented on the Baseline Form (BLF) after enrollment.

The following device programming is required after randomization for the subjects in the access arm:

- OptiVol® is programmed "ON", but not audible to the subject,
- CareAlert® through CareLink® Network is programmed "ON".

4.3 Subject Informed Consents

Subject Informed Consent:

The study informed consent process is under the responsibility of the implanting center.
A MEC-approved subject information and informed consent form (see appendix A) shall be used for the informed consent procedure.

An initial review of a subject's medical record shall be performed by the center prior to approaching the subject with intent to present this study. If the subject appears to meet study inclusion and exclusion criteria, the trial should be presented to the subject. Since no procedures are necessary for the sole purpose of screening the subject for enrollment into the study, no subject informed consent shall be signed and dated prior to carrying out any study related procedures (e.g. randomization).

The informed consent process has to be conducted by a member of the investigator's team qualified and authorized to conduct this procedure. The completed form shall include the dated signatures of both subject and the investigator / co-investigator acknowledging that participation in the study is voluntary. The complete and original signed subject information and informed consent form shall be kept in the hospital/clinic with the subject's medical files or with the study documentation. These are available to Medtronic or CRO study personnel upon request during site visits. A copy of the complete signed and dated subject information and informed consent form will be provided to the subject.

In the event the subject cannot read and/or write, an informed consent procedure witnessed by an impartial third party will be allowed. Such a procedure requires detailed documentation in the subject's medical record as well as signature of the witness on the informed consent document.

The process of informed consent shall:

- Avoid any coercion of or undue influence of subjects to participate,
- Not waive or appear to waive subject's legal rights,
- Use language that is non-technical and understandable to the subject or his/her legal representative,
- Provide ample time for the subject to consider participation.

Subjects shall be required to provide written informed consent for enrollment.

When a subject signs an informed consent form for this clinical study, he/she is considered enrolled in the study. If, at any time, the subject does not wish to continue participation in the study, a study exit CRF shall be completed.

CareLink® Privacy Principles Statement:

Subjects randomized to the access arm are required to be enrolled in CareLink® Network. For this all eligible subjects need to be informed about the requirement to provide written informed consent for the data collection and handling given with CareLink® Network service prior to enrollment in the study. This information will be combined with the subject informed consent form (see appendix A). The information about CareLink® Privacy Principles Statement before enrollment as well as the sign off process following randomization for the access arm is under the responsibility of the implanting center.

Revisions in Subject Information and Informed Consent Forms:

Medtronic shall update the subject information and informed consent whenever relevant new information becomes available. This revised document shall be sent to the investigator for approval by their MEC. Once the MEC and Medtronic approve the informed consent, a copy of this information shall be provided to the participating subjects. If the new information is related to increased subject risk, all previously enrolled subjects shall be approached for their re-consent for participation in the study.
The investigator or his designee shall inform the subject in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the investigation. The investigator shall document the communication of this information in the subject file at the hospital.

Informed Consent in Emergency Situations:

All devices used in the study are market-released. Therefore guidelines related to emergency use of investigational devices are not applicable.

4.4 Baseline/Enrollment

A subject is enrolled in the OptiLink HF study when the subject has signed the informed consent form. Baseline/enrollment data will be collected for subjects meeting all eligibility requirements. If a consented subject fails to meet final eligibility criteria, the center will enter the screening information and reason for eligibility failure in a study exit form. Additionally, if a subject is enrolled but not

randomized, a study exit CRF will be completed. If the subject did not meet eligibility requirements and was randomized, a study deviation will be completed but the subject will remain in the study.

The following information is required as part of a subject's baseline evaluation for the OptiLink HF study and must be recorded on the CRFs within the baseline/enrollment visit:

Eligibility Criteria

Verify and document that the subject met the eligibility criteria for the study.

Serum creatinine measurement

The subject's serum creatinine measurement will be reported on the baseline/enrollment CRF.

This blood test is intended to provide evidence of adequate renal function as required by inclusion criteria. It is acceptable to report lab results drawn within the 14 days prior to enrollment. In the case several creatinine measurements are available, the worst result must be taken into consideration.

Other baseline testing/procedures must not be performed until it has been confirmed that the subject met the creatinine eligibility requirement. If the center fails to obtain a serum creatinine measurement within 14 days prior to enrollment or at baseline, a study exit form for not meeting eligibility criteria must be completed.

Informed consent

Record the date the informed consent was signed by the subject or subject's legally authorized representative.

Blood sample

After the informed consent procedure a blood sample (10 ml serum Monovette® and 10 ml EDTA-Monovette®) will be collected to detect a level of different biomarkers, like NT-proBNP in subject's blood. No further processing of the sample, i.e. no centrifugation or cooling of the sample is required. The sample will be subsequently sent to the Central Laboratory (CoreLab of the Hannover Medical School; MHH, for the contact information refer to Section 12) and the biomarkers will be detected using a commercial diagnostic kit. The samples should be labeled with the subject no., time of sampling („Randomization"), and date on the serum or EDTA-Monovette®.

Subject demographics and medical history

Information will be collected on the subject's date of birth, gender, and ethnicity. The subject's medical history will include information on the subject's heart failure etiology, cardiovascular history, cardiovascular surgical history, respiratory-related history, pulmonary-related history, vascular-related history, arrhythmia history and renal/endocrine-related history.

Intrinsic QRS duration and LVEF measurements

Study center personnel will record the subject's most recent intrinsic QRS duration and LVEF measurement within the last 6 months prior to randomization obtained prior to enrollment (see Section 3.6, inclusion criteria). The clinical investigation plan does not require that new measurements be obtained at baseline/enrollment.

Implant information

The following information will be collected:
a) Date of device implant,
b) NYHA classification (most recent prior to or at implant),
c) Primary indication for implant.

Weight and its changes and other HF signs or symptoms

Kansas City Cardiomyopathy Questionnaire (KCCQ)[o, p, q, r] and EQ-5D Questionnaire

Health status of subjects will be additionally assessed using the Kansas City Cardiomyopathy Questionnaire and the EQ-5D Questionnaire. Subjects should fill in the questionnaires after signing the informed consent form, but necessary before the randomization.

Device interrogation StD (only for subjects from the control arm).

Medication collection (cf. below, section 4.4.1).

4.4.1 Medication Collection

All cardiovascular medications will be collected. Study center personnel will verify the status of all cardiovascular medications at baseline/randomization, follow-up, telephone contact, in case of hospitalization or an AE, and study exit. Advised changes of medication during visits, adverse event

[o] Spertus J, Peterson E, Conard MW *et al.* Monitoring clinical changes in patients with heart failure: A comparison of methods. *American Heart Journal* 2005, 150 (4): 708-715.

[p] Soto GE, Jones P, Weintraub WS *et al.* Prognostic Value of Health Status in Patients With Heart Failure After Acute Myocardial Infarction. *Circulation.* 2004; 110: 546-551.

[q] Heidenreich PA, Spertus JA, Jones PG *et al.* for the Cardiovascular Outcomes Research Consortium. Health Status Identifies Heart Failure Outpatients at Risk for Hospitalization or Death. Journal of the American College of Cardiology. 2006; 47 (4): 752–6.

[r] Green CP, Porter CB, Bresnahan DR *et al*. Development and Evaluation of the Kansas City Cardiomyopathy Questionnaire: A New Health Status Measure. Journal of the American College of Cardiology. 2000; 35 (5): 1245–55.

situations or hospitalization must be recorded on the CRF. It is not necessary to report non-cardiovascular oral medications.

4.4.2 Randomization

After center confirmation that inclusion/exclusion study criteria have been fulfilled, and informed consent and baseline data have been obtained, subjects will be randomized. Enrollment of subjects is possible **3 days up to 21 days** after Virtuoso™ ICD or Concerto™ CRT-D (or subsequent market released devices providing at least the same functionality) implant. Eligible enrolled subjects will be randomized in a 1:1 fashion to the access arm or the control arm. **Subject will be randomized directly after enrollment and completion of KCCQ and EQ-5D questionnaires.** Randomization will be risk-stratified: by NYHA class II/III (40% NYHA class II / 60% NYHA class III), ischemic/non-ischemic cardiovascular disease, atrial fibrillation and occurred VT/VF episodes before implant.

<u>Access Arm:</u>

- Medtronic Virtuoso™ ICD or Concerto™ CRT-D system or subsequently market released system providing fluid status monitoring OptiVol® and with CareLink® access (OptiVol® "ON" and CareAlert® "ON"),

<u>Control Arm:</u>

- Medtronic Virtuoso™ ICD or Concerto™ CRT-D system or subsequently market released system without CareLink® access (OptiVol® "OFF").

Randomization requirements are summarized in appendix O.

A statistician from the involved Contract Research Organization (CRO), IFE will create a randomization schedule. Randomization will be performed centrally through the responsible CRO through a randomization request form, which will be submitted via fax to CRO, IFE to receive a randomization result.

Study center notifies CRO (IFE) per fax about subject enrollment by sending the Randomization Request Form (RRF). Randomization is performed by IFE by sending of the study subject-ID per fax (or optionally per e-mail) to the study center (Randomization Result Form, RRF). Randomization result of the subject will be recorded on the Baseline Form (BLF).

To ensure a widespread distribution of data, the maximum number of enrollments per center is 100 subjects. To attempt to ensure adequate numbers in each group, centers will be ranked by the number of subjects enrolled, and the top 25% of centers will be considered "high" enrolling centers. The high enrolling centers will be compared to the remaining 75% of "low" enrolling centers.

In the event the investigator or subject does not comply with the randomization assignment, a deviation must be reported to the sponsor.

Cross-over

Study participants are required to remain in the randomized arm to which they are assigned. Crossover is prohibited unless deemed clinically necessary by the investigator and approved by a designated member of the OptiLink HF steering committee who will review rationale for crossovers. To achieve approval the investigator must inform the CRO upfront about intended cross-over.

An approved crossover is defined as any instance when the study center personnel make a permanent, deliberate, medically intended decision to use Cardiac Compass® Trends and/or HF-Management Report to manage a subject in the control arm.

In the event the study center personnel do not comply with the randomization assigned, a deviation must be reported to the sponsor.

Refer to section 11.2 for the contact information of the steering committee members.

- In the event of a system modification when a study device is removed and not replaced with another study device, subjects initially randomized to the access arm will be crossed over to the control arm, but analyzed in the access arm (intention-to-treat). Prior approval by a designated member of the steering committee will not be required, however study center personnel must contact Medtronic and a study deviation must be recorded on the deviation form (DEF).

4.5 Subject Enrollment in CareLink® Network

Enrollment in CareLink® Network of subjects randomized to the access arm is under the responsibility of the study center. Enrollment in CareLink® Network is required to be done after enrollment into the study and randomization of the subject, up to 25 days after implantation. Information needed for enrollment in the CareLink® Network is based on the baseline form (BLF) completion for all subjects.

In order to ensure CareLink® functionality, subjects in the access arm will be trained on the usage of the CareLink® monitor conducted by a member of the investigator's team qualified to conduct this procedure. Moreover the following additional documentation is required for the access arm:

- CareLink® enrollment,
- CareLink® training,
- OptiLink HF programming.

4.6 Follow-up Visits

After enrollment of the subject into the study, subjects will be monitored via follow-up visits or contacts. Regular follow-ups are necessary to monitor the condition of the ICD / CRT-D therapy system and subject status. The follow-ups are required at six months, and every six months thereafter post-randomization, until study closure, or subject exit due to death or other cause.

The required follow-up or contact windows for this study are described in Table 4.

Visits to the clinician can be conducted remotely via CareLink®. The ICD / CRT-D programming will allow automatic routine data interrogation and transmission into the CareLink® Network every 6 months for subjects from the access arm.

Table 4: Follow-up Schedule/Visit Windows

Follow-up Visit (Months)	Window Start* (Days)	Target Day*	Window end (Days)
6	150	180	210
12	330	360	390
18	510	540	570

*Days post-randomization

The following information is required as part of every 6 months follow-up and must be recorded:

- Follow-up information,
- HF symptom status changes, if applicable,
- ICD / CRT-D-Device-Therapy Safety & Integrity Information,
- Changes in cardiovascular medication, if applicable,
- HCU information: hospital, emergency department, unscheduled clinic/office, urgent care or remote visits, if applicable
- Study deviations,
- Adverse events,
- Subject questionnaires (KCCQ and EQ-5D) as part of 6-month follow-up.

Optionally (control arm):

- Programming check,

- New York Heart Association (NYHA) classification,

Final ICD / CRT-D interrogation (all) to save-to-disk, if ICD / CRT-D interrogation performed in-office, and if CareLink® transmission not performed.

Additionally for all subjects a blood sample will be collected during the **in-office follow-up visit at 18 months** (10 ml serum Monovette® and 10 ml EDTA-Monovette®). No further processing of the sample, i.e. no centrifugation or cooling of the sample is required. The sample will be sent to the Central Laboratory (CoreLab of the Hannover Medical School; MHH, for the contact information refer to Section 12) and the biomarkers will be detected using a commercial diagnostic kit. The samples should be labeled with the subject no., time of sampling („18 months") and date on the serum or EDTA-Monovette®.

Optionally

A blood sample (10 ml serum Monovette® and 10 ml EDTA-Monovette®, compare above) for examination of a level of biomarkers should also be collected during the in-office follow-up visit at 6 months and in the case of a hospitalization (as a result of CareAlert®). The samples should be labeled with the subject no., time of sampling („6 months" or „Hospitalization") and date on the serum or EDTA-Monovette®.

4.7 Scheduled Follow-up Contacts

In case of a scheduled CareLink® remote visit, the subject must be contacted within 7 days to complete the follow-up contact related questions.
The following information is required as part of all follow-up contacts for both access arm and control arm and **the following that have occurred since the last scheduled contact must be recorded:**

- Contact information,
- HF symptom status changes, if applicable,
- ICD / CRT-D-Device-Therapy Safety & Integrity Information,
- Changes in cardiovascular medication, if applicable
- HCU information: hospital, emergency department, unscheduled clinic/office, urgent care or remote visits, if applicable,
- HF-related intervention, if applicable,
- Study deviations,
- Adverse events,

- Final ICD / CRT-D interrogation (all) to save-to-disk, if ICD / CRT-D interrogation performed in-office, and if CareLink® transmission not performed.

The following additional documentation as part of the follow-up contact documentation is required for the access arm:

- Review and classification of HF-Management and Cardiac Compass® Trends OptiVol® or CareAlert® reprogramming, if applicable.

4.8 Unscheduled Visits

Any interim/additional subject's contacts are at the discretion of the center schedule and may include follow-ups both for the technical ICD / CRT-D device testing and/or for heart failure management. Additional data will be collected at urgent and non-urgent unscheduled office visits, emergency department visits, hospitalizations, data associated with an intervention algorithm, telephone contacts, system modifications, adverse events, study deviations, and study exit/death.
The study center personnel must report all adverse events and a change in status of these adverse events from time of enrollment until a subject exits the study.
A **CareAlert® Evaluation Form (CAEF)** must be completed whenever a study personnel-initiated therapeutic action based on the **CareAlert®** is taken, or HF-Management Report and/or Cardiac Compass® is reviewed and treatment decisions are made (**access arm**).

An **Adverse Event Form (AEF)** must be completed whenever a study personnel-initiated therapeutic actions based on new or worsening signs and/or symptoms of cardiovascular decompensation occur, which are not notified through the CareLink® Network, and treatment decisions are made (**access and control arm**).

4.9 Health Care Utilization

Health Care Utilization will be measured by data received from the completion of an Adverse Event Form (AEF) or CareAlert® Evaluation Form (CAEF) in the following situations:

- Hospitalizations,
- Emergency Department (ED) visit,
- Unscheduled office visit (a visit to an out-patient clinic that is not a study scheduled follow-up but fulfills one or more of the following criteria):

a) OptiVol® alert and/or subject notified of possible fluid accumulation (access arm only).

b) Subject has new or worsening signs or symptoms of cardiovascular decompensation (including fluid overload or dehydration) and/or weight gain and the subject comes into the office.

c) In-office visits in conjunction with an intervention algorithm.

An unscheduled office visit will be defined as **"urgent"** if the visit occurs within 24 hours from when the subject communicates distress.

An unscheduled office visit will be defined as **"non-urgent"** if it is a visit to an out-patient clinic more than 24 hours from when the subject communicates distress.

The following information is required to be recorded on the AEF: date, type, name of facility, and primary reason of visit.

4.10 Intervention Algorithm

An intervention algorithm is required to be performed and documented when the subject currently meets the criteria:

- the OptiVol® fluid index exceeding the OptiVol® threshold (access arm),
- new or worsening signs and/or symptoms of cardiovascular decompensation (access and control arm).

Table 5: Intervention Algorithm Requirements – Access Arm with CareLink® vs. Control Arm

Access Arm	Control Arm
CareAlert® notification via SMS and/or e-mail of responsible study personnel based on OptiVol® fluid index exceeding OptiVol® threshold **Cardiac Compass® and HF-Management Report Review** **Signs and Symptoms Assessment** via telephone contact of the subject **Manual data transmission advice** to subject, **Follow-up of data transmissions**	**CareAlert® notification due to OptiVol® threshold-crossing is not possible** **HF-Management Report Review must be avoided, but it could happen. If it happens through programmer this must be documented** **(no protocol deviation)**
Up to the investigator, depending what is the best for the subject (both arms)	Up to the investigator, depending what is the best for the subject (both arms)

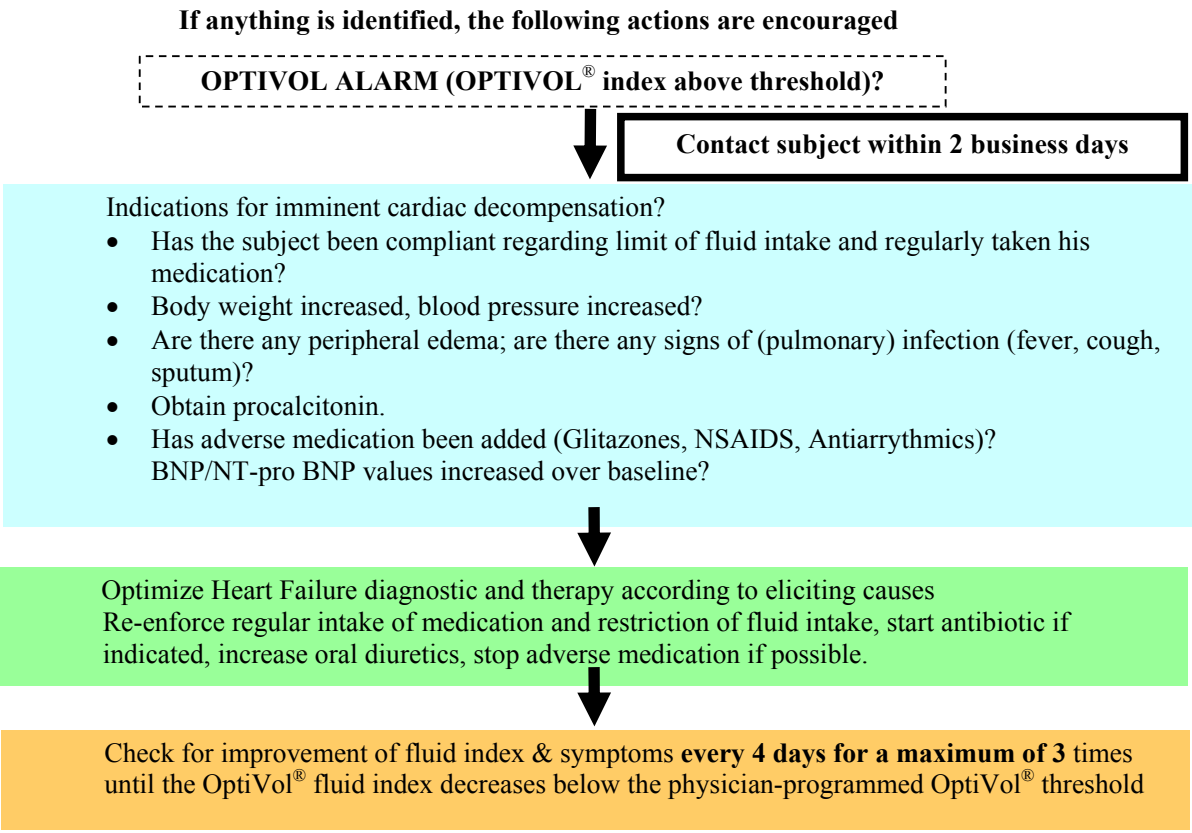
Access Arm:

If the subject contact occurs over the phone, study center personnel must instruct the subject to transmit data via CareLink®. Study center personnel will review the data received via CareLink® within 2 business days of receiving the transmission.

Once OptiVol® alert has been occurred, study center personnel (either the implanting center or the referring cardiologist) is notified on the OptiVol® alert condition. The HF-Management-Report and Cardiac Compass® Trends must be reviewed in association with **contacting subject within 2 business days** to evaluate the subject's condition and heart failure status.

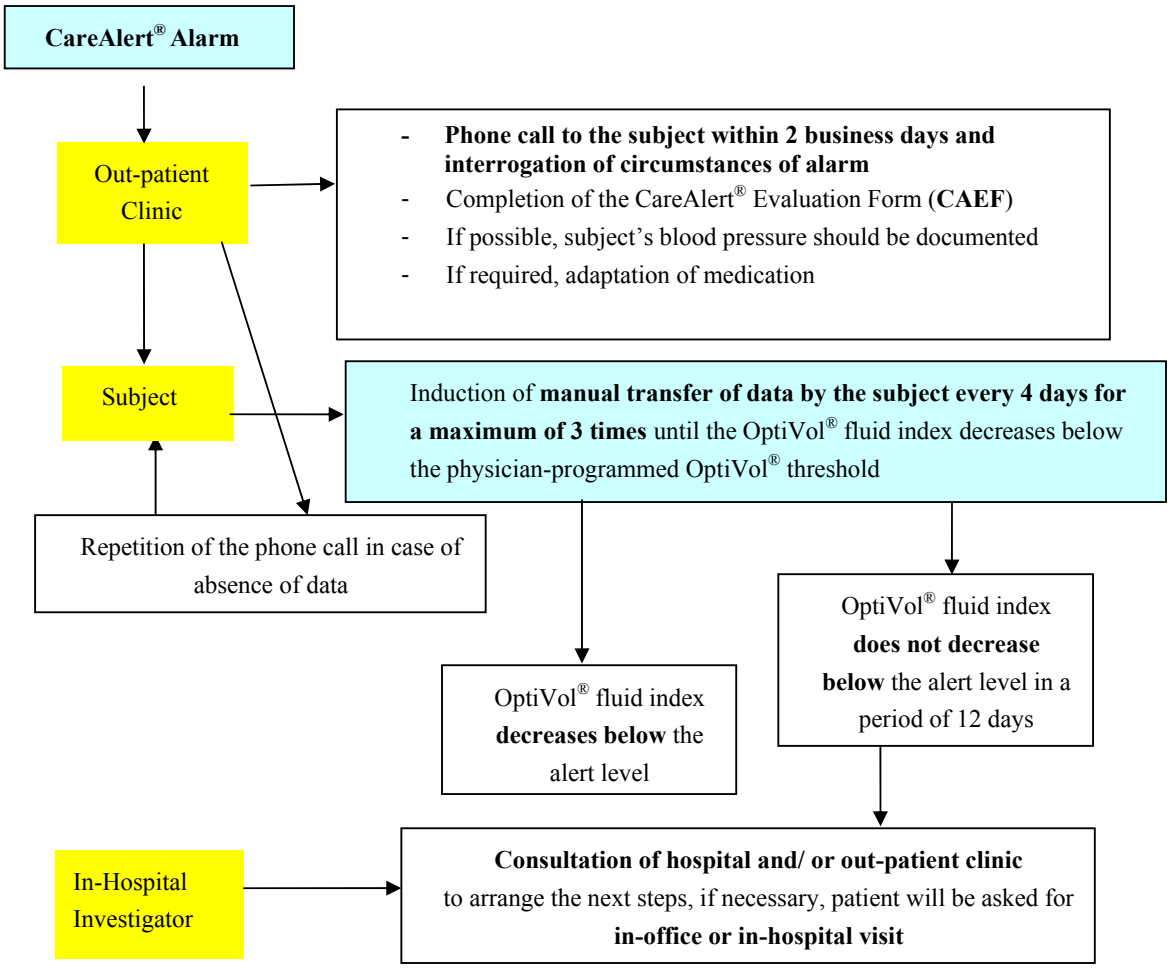
When the subject is initially contacted additional CareLink® remote visits are required to be scheduled with the subject who will be asked to interrogate and send ICD / CRT-D data via CareLink® Network **every 4 days for a maximum of 3 times** until the OptiVol® fluid index decreases below the physician-programmed OptiVol® threshold. Again the study center personnel is required to review HF-Management Report and Cardiac Compass® Trends and to **contact subject at least within 2 business days** to evaluate the subject's condition and heart failure status. This intervention algorithm must be followed until the OptiVol® fluid index decreases below the physician-programmed OptiVol® threshold. The following algorithm is encouraged to be followed: as outlined in Figure 6.

Figure 6: Intervention algorithm



A scheme of the intervention is presented in Figure 7.

Figure 7: Intervention (CareLink® Access Arm) notice



If, at any point in the intervention algorithm determination, the clinician identifies an audible alert other than the OptiVol® alert, the EP/implanting clinician (if different) must be notified and the subject will be managed per routine practice.

Study center personnel will document rationale if no action is taken upon initial notification of OptiVol® threshold crossing and/or new or worsening signs/symptoms of cardiovascular decompensation.

If the active peripheral HF-management center is completing the intervention algorithm, the clinician must notify the EP/implanting clinician (if different) and vice versa.

Control Arm:

An intervention is an action required and documented as an AE in the AEF in case of clinical deterioration either notified by the subject or recognized by a study physician.

4.11 Device Interrogation and Save-to-Disk

Save-to-disk (StD) data will be obtained using the Medtronic CareLink® Model 2090 and 2090W programmers. Data will be saved on a 3.5-inch computer diskette that is IBM compatible having capacity of either 720 Kb (DS, DD) or 1.44 Mb (DS, HD). Diskettes will be provided with attached labels. The Medtronic CareLink® model 2090 and 2090W programmers will automatically assign a unique name to each file and hence will not overwrite any existing session export file or memory report file. To indicate which file was saved for a particular session, the diskette file directory will automatically list the date and time each file was created.

Save-to-disk data with final programming are always required for subjects from the control arm, whenever a device reprogramming is performed.

If device reprogramming is performed for subjects from the access arm, the save-to-disk requirement is substituted by manual data transmission to CareLink® Network within a 2 days window after the in-office-/hospital visit. Save-to-disk data can also be required for subjects of the access arm, depending on the availability of data from the CareLink® Network for analysis.

Every save-to-disk must be sent to external CRO (IFE) and copy retained in the subject binder.

Table 6: Device Interrogation and Save-to-Disk-Requirements

Time	Type of Interrogation and Save-to-Disk (StD)
Baseline	**C:** If not yet received during implant then initial and final interrogation and StD with final programming
Scheduled follow-up visits and study exit	**Only C:** Initial and final interrogation and StD with final programming **A:** Verification of automatically transferred interrogation with unchanged programming
Unscheduled follow-up visits	**C:** Initial and final interrogation and StD with final programming **A – in case of office visit:** Save-to-disk is substituted by manual data transmission of device data to CareLink® Network
System modification	**A & C:** Final interrogation and StD with final programming of revised system / explanted device Final interrogation and StD with final programming of new implanted device

A: Access Arm
C: Control Arm

4.12 Study Exit

All consented subjects will be documented in the database. Enrolled subjects who fail to meet final eligibility criteria will not be randomized. The subject will be withdrawn from the study and a study exit CRF will be completed. If failure to meet eligibility criteria is discovered after randomization, the patient will stay in the study.

A study exit will be documented for any of the following:

- Subject death,
- Study closure,
- Subject withdrawal/investigator withdrawal of subject/lost to follow-up. In case withdrawal is considered, it is preferred to stop only those study procedures that are problematic and to continue the procedures that are still feasible. In particular, data collection on the primary endpoint should continue whenever possible.

The investigator shall complete the study exit form (SEF). The following information will be collected (if applicable):

- NYHA class,
- Medication and/or changes,
- HF symptom status (or death information),
- KCCQ and EQ-5D,
- ICD / CRT-D-therapy assessment,
- Review of Cardiac Compass® Trends and HF Management Report,
- Device interrogation, StD.

4.12.1 Subject Death

If the death occurs at a center remote from the investigational center, it is the investigative center's responsibility to make every attempt to retrieve all subject's information related to the subject's death and submit the investigator's summary of the known events surrounding the death.

In the event of a subject death, the following information related to the death will be documented on the study exit form (SEF) and reported to the CRO:

- Date of death,
- Date study center became aware of death,
- Description of death (see section 4.15),
- Primary cause of death,
- Location of death,
- Time of death (if known),
- Any adverse events leading up to the death,
- Investigator death relatedness classification (i.e. cardiac related, procedure related, system related),
- Death summary/autopsy report/death certificate, if available,
- Save-to-disk, if available,
- Whether or not the device and leads, if explanted, were sent to the sponsor.

If a physician's death summary report is available or an autopsy is performed, submit a copy of the autopsy report to the OptiLink HF study clinical trial leader. If the death occurs at a center remote from the investigational center, it is the study center's investigator responsibility to make every attempt to retrieve all pertinent information related to the subject's death and submit the investigator's summary of the known events surrounding the death.

4.12.2 Study Closure

Study closure is defined as a specific date that is determined when the clinical investigation plan requirements and/or regulatory requirements have been satisfied.

4.12.3 Subject Withdrawal/Investigator Withdrawal/Lost to Follow-Up

Any subject withdrawn from the study before the scheduled completion will be considered an early withdrawal, regardless of the reason for the withdrawal. The subject is free to withdraw from the study for any reason and at any time without giving any explanation for doing so and without penalty or loss of future medical care. The investigational center should indicate if the withdrawal was related to the investigational system.

The investigator is also free to terminate a subject's involvement in the study at any time if it would be to the subject's detriment to continue. It is also possible that the sponsor or the competent authorities request termination of the study, if there are concerns about conduct or safety. In particular cases the study may be terminated at a single investigational site, if the sponsor has relevant reasons (e.g. no compliance with the Good Clinical Practice or clinical investigation plan). In such cases subject's participation in the study can be terminated and the subject's consent is not needed.

A subject may withdraw from the study after enrollment, if he failed to meet eligibility criteria, but only before randomization. Once randomized, patients should be followed up according to the study protocol.

All data available at the time of withdrawal or last visit will be used for analysis. There will be no future required study-related follow-up visit for this subject.

The written documentation shall be provided stating the reason why the subject was withdrawn:

- To the sponsor and subject, if the investigator withdraw a subject from the study,
- To the investigator with the request to inform the subject, if the sponsor decides to withdraw a subject from the study,

- The investigator shall complete the study exit form (SEF).

The study investigator or Medtronic may terminate the subject's participation in the study without the subject's consent if two consecutive follow-up visits are missed, if subject routinely fails to complete required procedures, and/or if the investigator feels it is medically necessary. If the subject fails to comply with follow-up visits, the study center must make repeated attempts to contact the subject. At least three documented attempts must be made to contact the subject, documenting the method used (e.g. telephone contacts, registered letters). At least one attempt must be made in writing.

It is important to distinguish between withdrawal and stopping following study required procedures. If study procedures cannot be followed any more, it is preferable to continue data collection and to not completely withdraw the patient.

4.13 System Modification

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

In the event of a system modification, including removal and/or modification of the entire or a portion of the implantable system, the follow-up schedule for the subject will remain unchanged (i.e. the subject should continue to be followed and scheduled follow-up CRFs should be completed based on the original follow-up schedule). Study center personnel will report the adverse event as described in section 4.15 to document the underlying cause or events related to the system modification.

a) Explanted Devices

- Prior to device explant, interrogate the study device and perform a save-to-disk. An "Interrogate all" must be performed at the initial interrogation to collect all data from the device before it is reprogrammed as described below.
- Disable all VT/VF detection capabilities prior to removal to avoid inadvertent shock delivery. Whenever possible, disable the OptiVol® alert prior to device or RV lead explant.

For information on how to return an explanted device the local Medtronic representative should be contacted.

If the device is explanted and a replacement "study" device is not immediately re-implanted, continue to collect any adverse events, health care utilizations, telephone contacts, study deviations, and scheduled follow-up visit data through the time period where subject is without a study device. If the device is explanted and a replacement device will not be implanted, complete a study deviation and continue to follow the subject. If the subject was initially randomized to the access arm, the subject will be crossed over to the control arm and prior approval by a designated member of the steering committee will not be required, however study center personnel must contact Medtronic or the CRO. Not obtaining prior approval by a designated member of the steering committee for this purpose will not result in an additional study deviation. If the subject was initially randomized to the control arm, the subject will remain in the control arm.

b) Replaced Devices:

- Interrogate the replacement study device and perform a save-to-disk, unless the subject's replacement device is a non-study device,
- Enroll the subject in CareLink® under the new device serial number, unless the subject's replacement device is a non-study device (access arm only),

- If the subject's replacement device is a non-study device, complete a study deviation form. The subject will not be withdrawn but will be followed per their original follow-up schedule. If the subject was initially randomized to the access arm, the subject will be crossed over to the control arm and prior approval by a designated member of the steering committee will not be required. Not obtaining prior approval by a designated member of the steering committee for this purpose will not result in a study deviation. If the subject was initially randomized to the control arm, the subject will remain in the control arm. Note that primary and secondary objectives will be analyzed using the intent to treat principle.

c) Lead replaced / repositioned / capped / explanted or the subject had a pocket revision:

- Perform an initial interrogation and save to disk prior to the revision. The initial interrogation must be "Interrogate all",
- If the lead or pocket is modified and the subject is randomized to the access arm, consider programming the OptiVol® alert to "OFF (Observation only)" for a minimum of 30 days or until the time of the subject's post-operative visit, but no more than 60 days post-system modification. Consider adjusting the reference impedance once the subject's pulmonary fluid status is stable, the OptiVol® trends show the subject's daily thoracic impedance is stable, and if the reference impedance has not adjusted to the subject's daily impedance,
- Perform a final interrogation and save-to-disk with final programming after the revision.

In addition to the requirements outlined above, the system modification is required to be recorded on the study deviation form CRF.

4.14 Study Deviation

A study deviation is defined as an event within a study that does not occur according to the clinical investigation plan or the Clinical Trial Agreement.

Prior approval by the Study Management 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 life or physical well being of a subject in an emergency. Prior approval is not expected in situations where unforeseen circumstances are beyond the investigator's control (e.g. subject failure to attend scheduled follow-up visits, inadvertent errors, equipment failure, or inability to perform required procedures due to subject illness). Refer for study Sponsor contact information to section 12.

All study deviations must be reported to IFE. In the case that the deviation involves a failure to obtain subject informed consent or is made to protect the life or physical well being of a subject in an

emergency, the deviation must be reported immediately to IFE. Reporting of all other study deviations should be completed as soon as possible and should comply with MEC policies and/or local laws. All deviations must be reported to IFE on the study deviation form (DEF).

Record any deviation together with an explanation for the deviation and corrective action. Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions. Medtronic will review study deviations and assess the need to amend the clinical investigation plan, conduct additional training, or to terminate the investigation. When relevant, deviations will be reported to the MEC or appropriate regulatory body. A center-specific report of study deviations will be provided to the investigator on regular basis (approximately every six months).

4.15 Adverse Events and Deaths

The following adverse event information will be collected throughout the study and reported to IFE on an adverse event form as described below:

Adverse Event

An adverse event is defined as any untoward medical occurrence in a subject. (ISO 14.155)
NOTE 1: This definition does not imply that there is a relationship between the adverse event and the device under investigation.

Adverse Device Effect (ADE)

Any untoward and unintended response to a medical device. (ISO 14.155)
NOTE 1: This definition includes any event resulting from insufficiencies or inadequacies.
NOTE 2: This definition includes any event that is a result of a user error.

Serious Adverse Event (SAE) (ISO 14.155)

An adverse event that

a) led to death

b) led to a serious deterioration in the health of a subject that

1) resulted in a life-threatening illness or injury,

2) resulted in a permanent impairment of a body structure or a body function,

3) required in-patient hospitalization or prolongation of existing hospitalization, or

4) resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function

c) led to fetal distress, fetal death or a congenital abnormality or birth defect.

An adverse event is considered "serious" if condition 1, 2, 3, or 4 apply in combination with a serious deterioration in health e.g. a planned hospitalization for a pre-existing condition, without a serious deterioration in health is not considered to be a SAE.

Serious Adverse Device Effect (SADE)

An ADE that has resulted in any of the consequences characteristic of a Serious Adverse Event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

Unavoidable Adverse Event - An adverse event inherent to a surgical procedure that is expected to occur in all subjects for a projected duration according to the investigator's opinion, including, but not limited to the unavoidable adverse events listed in Table 7. **The implantation is not a part of the study thus the list below should be considered as additional information.**

Table 7: Unavoidable Adverse Events

EVENTS DESCRIPTION	TIME FRAME (HOURS) FROM THE SURGICAL PROCEDURE
Anesthesia related nausea / vomiting	24
Low grade fever (100°F or 37.8°C)	48
Pocket site / incisional pain	72
Mild to moderate bruising / ecchymosis (at pocket site)	72
Sleep problems (insomnia)	72
Back pain related to laying on table	72

Relatedness

System Related Adverse Event

An adverse event that results from the presence or performance of the system. In this study, the system includes the Medtronic Virtuoso™ ICD or Concerto™ CRT-D (or subsequently market released devices providing at least the same functionality), pace/sense leads and cardioversion/defibrillation leads, and the Medtronic CareLink® 2090 or 2090W programmer and its market released software.

Non-System Related Adverse Event

An adverse event that does not result from the presence or performance of the system.

Death Reporting

All subject deaths will be collected from time of enrollment until the subject is withdrawn from the study or study closure. The investigator will report deaths using the study exit form (SEF) as soon as possible upon notification and classify the event based on the following categories:

- Cardiac (Y/N),

If cardiac, sudden vs. non-sudden

- Relatedness,
- Cause of death.

Death Review and Classification

An independent events committee will assess, review and classify all deaths. The committee will regularly review and adjudicate reported deaths.

All reported deaths will be reviewed and classified by the events committee based on the following categories:

- Cardiac (Y/N),

If cardiac, sudden vs. non-sudden:

- Witnessed vs. not witnessed,
- Relatedness,
- Cause of death.

Death Definitions

All reported deaths will be reviewed and classified by the events committee based on the following definitions:

Cardiac

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

Sudden Cardiac Death (SCD)

Natural death due to cardiac causes, heralded 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

A death not classified as a cardiac death.

Witnessed

The death is considered witnessed if someone was able to give a firsthand account of the death by either having seen or heard the subject at the time of death. In addition, the event will be considered witnessed if the subject was hospitalized and being monitored at the time of death.

Non-Witnessed

All deaths not classified as witnessed will be considered non-witnessed

System Related

A death will be considered system related if it results from the presence or performance of any component of the implantable system, investigational software, CareLink® monitor or the programmer and its market released software. The "system" includes the ICD / CRT-D device, CareLink® monitor (access arm only), pace/sense leads, and cardioversion/defibrillation leads.

Non-System Related

A death that does not meet the definition of "system related".

4.16 Recording and Reporting of Adverse Events

All new and/or worsening adverse event (AE) information, except for unavoidable adverse events, will be collected from time of enrollment until the event is resolved, the subject exits the study, or study closure. The investigator will report adverse events to the CRO using the adverse event form (AEF) as soon as possible. All adverse events, regardless of relatedness or outcome must be reported.

Investigators are provided with a list of previously reported adverse events for the subject population identified for the study in appendix K. For any changes in status of an adverse event (i.e. change in action, change in outcome), an adverse event update CRF will be completed until the adverse event is resolved, the subject exits the study, or until study closure, whichever occurs first.

Information reported on the adverse event form will include a description of the event, the diagnosis, the date of event onset, the relatedness of the event to the procedure, the relationship of the event to the device/system, actions taken as a result of the event and the outcome of the event and the date the event was first noticed by the investigator.

In case the investigator requires information from the sponsor in an emergency situation, the investigator can contact the sponsor. Contact details are given in section 12.

The investigator shall report serious adverse device effects and serious adverse events immediately after learning of the effect.

Medtronic shall report the serious adverse events and device effect to MEC and relevant competent authorities based on regulatory requirements in addition to reporting events through the standard vigilance reporting system, as required.

The adverse events need to be reported according to Table 8.

Table 8: Adverse event reporting requirements

Serious Adverse Events (SAE) and Serious Adverse Device Effects (SADE)	
Investigator submit to:	
IFE	Immediately via fax after the investigator first learns of the event.
MEC	Submit to MEC per local MEC requirement.
Sponsor submit to:	
Regulatory Authorities	Reporting timeframe as per local requirement.
MEC	Submit to MEC per local reporting requirement.

The following information shall be collected on the AE CRF:

- Subject ID and center address
- Date of report
- Date of event onset
- Date study center became aware of event
- Description of the event
- Primary diagnosis best representing the event
- Seriousness
- Device and procedure relatedness shall be assessed
- Action(s) taken
- The outcome of the event.

The sponsor will review all AEs. This review will include the determination whether the adverse event meets regulatory reporting requirements. The sponsor will ensure timely adverse event reporting to meet global regulatory requirements.

4.17 Event Review

MedDRA, the Medical Dictionary for Regulatory Activities, will be utilized to assign a key term for each event based on the information provided by the investigator. The key term will be reviewed and adjudicated by an independent events committee. The committee will regularly assess, review and classify all adverse events including hospitalizations, emergency department visits, urgent and non-urgent unscheduled office visits. The committee will **consist of a minimum of three and a maximum of nine physicians** including a chairperson appointed either by Medtronic or the events committee. The chairperson must either be present at each meeting or provide their input for the meeting attendees to discuss.

At least three committee members must review at a minimum all deaths, serious and system adverse events. At least one physician member of the committee will review all other adverse events. The committee will regularly review and adjudicate reported adverse events.

All reported adverse events will be reviewed and classified by the events committee based on the following categories:

- Relatedness to system/procedure (Y/N),
- Serious vs. not serious,
- Is the safety composite event definition met? (see below for definition),
- Is the Clinically Relevant Thoracic Event definition met? (see below for definition).

Additionally, an arrhythmia committee will review and classify device-detected sustained VT/VF episodes to determine which episodes were appropriately detected sustained VT/VF episodes for the safety composite event definition.

4.18 Emergency Contact Details in Case of Serious Adverse Event

In case of an immediately reportable adverse event the investigator should contact:

Dr. Michael Berghahn
IFE Europe GmbH
Zeche Katharina 6
D-45307 Essen, Germany
Phone: +49(0) 201/8990-123
Fax: +49(0) 201 8990-251
safety@ife-europe.com

4.19 Study Specific Definitions

A) HF Event

Heart Failure Hospitalization

A therapeutic, in-patient hospitalization extending over a calendar date change where admission occurs after consent for worsening heart failure associated with signs and symptoms of:

- congestion treated with administration of diuretic and/or vasodilators and/or inotropes and/or other parenteral therapy

OR

- low cardiac output due to heart failure indicated by organ compromise treated with IV therapy

B) Safety Composite Event

A safety composite event is an event that includes one or more of the following:

- Syncope,
- Worsening renal function resulting in IV therapy, ultrafiltration, or dialysis,
- Hypotension and/or hypovolemia resulting in the administration of fluids,
- Clinically significant electrolyte abnormalities resulting in IV replacement or ER/hospitalization for correction,
- Appropriately detected sustained VT/VF episode,
- Death.

C) Cardiovascular related hospitalization

A hospitalization extending over a calendar date change that is due to causes including, but not limited to, the following: heart failure, myocardial infarction, coronary insufficiency, acute coronary syndrome/unstable angina, non-ischemic atrial or ventricular dysrhythmias, symptomatic bradycardia/heart block, syncope, cardiac procedures (percutaneous or surgical), peripheral vascular disease or resulting complications, pulmonary or vascular emboli, aortic aneurysm / dissection, stroke, TIA, vascular surgery/procedure, or heart transplant.

D) Clinically Relevant Thoracic Event

An event that may impact thoracic impedance including but not limited to:

- Acute dialysis
- Pulmonary edema

- Pericardial effusion
- Pneumonia
- Pleural effusion
- Ultrafiltration for HF management
- Protocol required scheduled follow-up visits, ED, hospitalization, urgent or non-urgent unscheduled office visit with evidence of congestion.

4.20 Post Market Surveillance

All devices used in this study are marked released. Therefore Post Market Surveillance is applicable. It is the responsibility of the investigator to report all product complaints and malfunctions immediately via the regular channels for CE marked products.

The reporting of product complaints and malfunctions is not part of the clinical study and should be done in addition to the adverse event reporting requirements. The investigator must report issues with non-Medtronic leads to its manufacturer, not to Medtronic.

Product Complaint:

Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a device after it is released for distribution.

Malfunction:

Failure of a device to perform as claimed by the manufacturer. This includes all performance specifications and all claims made in the instruction for the device.

Medtronic will notify the Competent Authority of the following incidents immediately on 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 subject, 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 impairment of a body function or permanent damage to a body structure.

4.21 Health Economics

Cost Effectiveness:
A payer perspective is used, covering the major cost drivers of hospitalization, emergency department visits, medication and "out-patients" visits.

Data Collection:
Healthcare utilization of emergency department visits, hospitalization, out-patient and all further utilization of healthcare will be collected based upon discharge summaries (if applicable) and CRF based information. Utilization of medication will be based on CRF information assessed at follow-up visits or any other subject contacts, e.g. phone contact, by the implanting center and HF management center over time. Life expectancy will be derived from the mortality data collected within the trial. HRQOL data will be assessed by questionnaire leading to determination of QALY's and ICER's.

5 STATISTICAL METHODS AND DATA ANALYSIS

This chapter describes the statistical analysis as it is foreseen at the time of planning the study. Any major deviations from this plan, the reasons for such deviations, and all alternative or additional statistical analyses that may be performed will be mentioned in the **Statistical Analysis Plan (SAP)**, which gives a detailed technical description of all statistical analyses. All deviations and/or alterations will be summarized in the clinical study report (CSR).

Because of the unpredictability of potential problems, it may be necessary to decide about the manner of dealing with irregularities in a data review meeting.

5.1 Study Populations

Analyses will be based on the following sets: total population, safety population, intention-to-treat-population, and per protocol population. The definitions of the analysis sets follow those given in the ICH E9 guideline.

5.2 Total Population

The total population consists of all subjects enrolled including subjects withdrawn from the study.

5.3 Safety Population

The safety population includes all enrolled subjects after implantation.

5.4 Intention-to-treat Population

The intention to treat (ITT) population consists of all randomized subjects. Under strict conditions, subjects who have no post-baseline data available, or subjects who fail to satisfy major entry criteria may be excluded (details see ICH E9 guideline).

5.5 Per Protocol Population

The per protocol (PP) population consists of all subjects of the ITT population who completed the study without major protocol violations or who terminated the study prematurely due to an adverse event with at least likely relation to the study device or due to lack of efficacy. Decisions on protocol violations will be made individually in the data review meeting.

5.6 Statistical Analysis of Primary Objective

The primary objective of the OptiLink HF study is to demonstrate that the "OptiLink" functionality causes a clinically relevant decrease in the incidence rate of all-cause death or cardiovascular related hospitalization within 18 months. The primary objective will look at time to first event and the analysis will use survival analysis methods.

The following hypothesis will be investigated:

$$H_0: \; S_{control} = S_{alert} \qquad \text{vs} \qquad H_1: \; S_{control} \neq S_{alert}$$

where $S_{control}$ and S_{alert} denote the survival functions for freedom from all-cause death or cardiovascular related hospitalization within 18 months for the control arm and the access arm,

respectively. For example, $S_{alert}(1)$ is the proportion of patients in the access arm that is alive and free from cardiovascular hospitalizations at 1 year after implant.
Group comparison will be performed with an α-level of 5% using a two-sided log-rank test. The ITT population will be used for the primary analysis. Additionally, the confidence interval will be calculated for the hazard ratio using Cox regression.

Sample Size Calculation

The calculation of the sample size for the present study is based on available study data using the experience from previous studies (see 3.3). Only ICD / CRT-D subjects will be included in this study.

For sample size calculation the following assumptions are made:

- type I error $\alpha = 0.05$
- power = 0.80
- control arm proportion event-free at 18 months = 72.0%
- difference between treatment arms = 30% of control arm → 8.4%
- access arm proportion event-free at 18 months = 80.4%
- all subjects are followed for 1.5 years

The method for analysis of the primary criterion is the two-sided log-rank test. Based on these assumptions the total sample size of 798 subjects will have 80% power to detect a difference between the rates of all-cause death or cardiovascular related hospitalization of the two treatment arms. This is based on the method from Lakatos (1988)[s] and Cantor (1997)[t], setting accrual time to 0 to model subject exit after 18 months (SAS Power and Sample Size module, version 3.1). Taking into account early study termination and treatment non-compliance including cross-over, 1000 subjects will be enrolled in the study. This increase in sample size will ensure that power is maintained when 5.0% of subjects crosse over (based on simulation, with cross-over equally distributed over arms, assuming full compliance on other elements of the protocol). Then, the expected number of events is 238 (simulation).

Interim analysis:
Two interim analyses are planned when 33% and 67% of the 238 expected primary endpoints has been accrued. At the interim analyses, minimally the primary endpoint and the secondary mortality endpoint will be analyzed. The DSMB will review the results and will advise the Study Executive Committee about continuation of the study. The DSMB will consider to stop for success if the

s Lakatos, E. (1988), "Sample Sizes Based on the Log-Rank Statistic in Complex Clinical Trials," Biometrics, 44, 229–241
t Cantor, A. B. (1997), Extending SAS Survival Analysis Techniques for Medical Research, Cary, NC: SAS Institute Inc.

primary endpoint occurs significantly more often in the control arm with $p < 0.0001$ for the first and $p < 0.001$ for the second interim analysis. The DSMB will consider to stop for harm if the primary endpoint occurs significantly more often in the access arm with $p < 0.01$ or if mortality is significantly higher in the access arm with $p < 0.05$. The final analysis will use a modified alpha to compensate for the interim analyses, maintaining total type I error at 0.05.

5.7 Secondary Objectives

All secondary variables will be analyzed by descriptive statistical methods. For discrete variables frequencies and percentages will be determined, for continuous variables parameters for location and dispersion will be calculated. Shift-tables and pre-post differences can be determined, if applicable.

In general hospitalizations or deaths will be classified according to the following causes:

1) Cardiovascular related,
2) Heart failure related,
3) Related to other causes,
4) All causes,
5) Sudden cardiac death*

*only death.

The following secondary objectives will be tested on an α of 5% each. P-values will only be interpreted in an exploratory sense.

The number of hospitalizations per patient according to the above-mentioned causes will be compared for both study arms by means of Wilcoxon rank-sum test two-sided. The corresponding rates of first hospitalization will be compared using log-rank test.

The number of days in hospital and the number of days alive out of hospital according to the above-mentioned causes will be compared using Wilcoxon rank-sum test two-sided.

Mortality rates according to the above mentioned causes will be determined and compared by means of a log-rank test. Furthermore mortality rates as well as HF-related mortality rates after the first HF-related hospitalization and after the first decompensation will be determined.

Time to event analyses will be performed for the time to first all-cause hospitalization or death, the time to first all-cause hospitalization, time to first HF-related hospitalization, time to first cardiovascular related hospitalization, time to first hospitalization because of decompensation, time to first HF-related death, time to cardiovascular related death and time to first death because of decompensation. The time to event analyses will be carried out using Kaplan-Meier method and log-rank tests will be performed to compare the risk for both access arms.

Where appropriate, repeat-events survival analysis methods may be used to analyze recurring events, including adverse events, HF-related events and cardiovascular related events.

The quality of life assessed by means of the Kansas City Cardiomyopathy Questionnaire (KCCQ) and EQ-5D questionnaire will be compared by means of Wilcoxon rank-sum test.

Additionally all demographic data, medical history, previous and concomitant diseases and medication, vital signs and results from physical examination will be analyzed descriptively.

5.8 Subgroup Analyses

Subgroup analyses will be carried out for ischemic and non-ischemic cardiovascular diseases, subjects with or without atrial fibrillation and subjects with or without VT/VF episodes before implant.

5.9 Adverse Events

The recorded adverse events will be coded according to MedDRA. The adverse events will be summarized by treatment, System Organ Class, preferred-term and intensity.
Nature, incidence and intensity, as well as the investigator's and the sponsor's causality assessment will be reported for each treatment-emergent adverse event. Descriptive summary statistics, e.g. with regard to the incidence of symptoms and the causality assessment, will be presented for the study period.

5.10 Handling of Missing Values

Procedures will be in place to ensure complete reporting of subject visits and events. The statistical analysis will be based on available data. For primary objective, subjects will be censored at their last documented visit.

5.11 Data Entry and Validation

Data management procedures will be specified in the data management plan (e.g. double data entry, plausibility checks).

6 RISK ANALYSIS AND RISK ASSESSMENT

6.1 General Potential Risk associated with ICD or CRT-D Systems and CareLink®

The safety and clinical performance of the Medtronic market-released ICD or CRT-D systems have been demonstrated through previous pre-clinical testing and previous clinical studies. Model C154DWK / C174AWK Concerto™ CRT-D and D164AWC Virtuoso™ DR / D164VWC Virtuoso™ VR or subsequent devices providing at least the same functionality used in this study are market-released. Should subsequently market released devices be used within the study, their safety and clinical performance will have been assessed equally through clinical studies before market release.
Therefore, it is not anticipated that subjects implanted with these devices enrolled in this study will be exposed to any risks beyond those normally associated with ICD or CRT-D and transvenous lead systems.

Medtronic has attempted to minimize the risk of implanting Medtronic ICD or CRT-D systems through careful design and pre-clinical testing. Pre-clinical testing includes bench testing to verify

performance, software validation testing, biocompatibility tests, destructive analysis and shock tests and packaging qualifications.

6.2 Risk Minimization

Medtronic has attempted to minimize risk to subjects by requiring routine, scheduled follow-ups, training of study center personnel and Medtronic personnel, and implementing a Data Safety Monitoring Board to review safety issues as part of the study.

6.3 Potential Benefits

Literature has supported that subject outcomes improve during the course of participating in a clinical study. This may be a result of study subjects having increased interaction with study center personnel. Consequently, the clinician may evaluate their HF status more frequently.

The information gained from this study may help clinicians understand how to better manage HF in the future. The implementation of this study may provide insight into how subjects can be better served by reinforcing the interaction between HF and EP clinicians. Additionally, information collected from this study may assist in the design of new product(s)/therapy(ies) and/or instructions for use.

7 WARRANTY AND INSURANCE

7.1 Warranty

Warranty information is provided in the product packaging for the commercially released Concerto™, Virtuoso™, and subsequently market released devices and the Medtronic leads used in this study. Warranty information will be provided in the product packaging for any future CE-approved Medtronic devices with OptiVol® fluid status monitoring. This study does not affect the warranty.

7.2 Insurance

The following statement of the provisions made for subject compensation and of insurance to cover liability:

Medtronic GmbH 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 MEC.

8 MONITORING AND AUDIT

8.1 Monitoring

It is the responsibility of the study sponsor, Medtronic GmbH, to ensure that proper monitoring of the study is conducted and that MEC review and approval of the investigation is obtained. Trained Medtronic personnel or delegates from the CRO appointed by the study sponsor will conduct monitoring activities in order to ensure that the investigation is conducted, recorded and reported in accordance with the clinical investigation plan, signed clinical trial agreement, and applicable regulatory requirements of the local law. The following factors will be taken into account when determining the frequency of the monitoring visit:

- Subject enrollment rate at each center,
- Total number of subjects enrolled at each center,
- Clinical investigation plan compliance at each center,
- Any suspected inconsistency in data that requires investigation.

Monitors shall require direct access to subject medical records, study management documents, regulatory documents, and subject informed consent documents, as well as other potential applicable records not listed here. Monitors may ensure the clinical investigator have and continue to have staff and facilities to conduct the clinical investigation safely and effectively.

Monitors may conduct the following monitoring activities throughout the study:

- Verification that the current MEC-approved informed consent was signed and dated by each subject prior to participating in study required procedures,
- Verification of documentation in the subject's record that informed consent was signed prior to initiation of study procedures,
- Comparison of CRFs against source documentation for accuracy and completeness of information,
- Verification that subjects met study enrollment criteria,
- Confirmation that the study is being conducted according to the clinical investigation plan and applicable regulations,
- Verification that study deviations are documented and reported,

- Verification that the procedures for recording and reporting adverse events to the sponsor are followed,
- Ensuring proper error correction,
- Reviewing subject documentation with regard to subjects deemed lost to follow-up and subject drop-outs (to determine accuracy and ensure valid attempts to locate subject lost to follow-up),
- Verification of training documentation of all study personnel participating in study-related activities,
- Reviewing all correspondence and regulatory documents, including confirmation of MEC-approved clinical investigation plan or amendments,
- Resolution of outstanding issues and completion of assigned tasks will be documented by the monitors.
- Other monitoring items as they arise.

New and previous findings (ongoing or resolved) and recommended corrective/preventative actions (if applicable) will be communicated with the study staff during the visit and will also be addressed in a final letter that will be sent to the investigator after the visit. Items requiring resolution will be documented on an action item worksheet maintained by the sponsor.

Study closure visits (for definition refer to section 4.12.2) will be conducted at all enrolling clinical sites in order to review record retention requirements, device/software disposition requirements, etc., with site personnel. A telephone contact may take the place of a study closure visit if appropriate (e.g. low subject enrollment, recent monitoring visit, etc.). For contact information on the CRO performing study monitoring refer to administrative page. A separate monitoring plan will specify details on the monitoring process and source data verification

8.2 Auditing

All records and other information about subjects participating in this study will be treated as confidential. IFE will collect data and monitor study records. The sponsor or regulatory authority may audit the study center to evaluate the conduct of the study. The clinical investigator(s)/center(s) shall allow auditing of this study by providing direct access to source data/documentation. Participating subjects will not be identified by name in any published reports about this study.

9 RECORDS AND REPORTS

9.1 Investigator Records and Reports

The investigator is responsible for the completion (review and signature, if applicable) and retention of the records cited below. The following records are subject to inspection by the regulatory bodies and must be retained for a period of two years after the date on which the investigation is terminated or completed or according to local regulatory requirements, whichever is greater. Study closure is defined as a specific date that is determined when the clinical investigation plan requirements and/or regulatory requirements have been satisfied.

The investigator shall maintain the following accurate, complete and current records relating to the investigator's participation in this study:

- Relevant correspondence/documentation with another investigator, an MEC, competent authorities, Medtronic, monitors including required reports that relate to this study,
- Delegated tasks list,
- Subjects' case history records including:
  - Signed subject informed consent documents,
  - Medical history,
  - All CRFs and supporting data (source documents),
  - All relevant subject complaints,
  - Observations of adverse events.
- All clinical investigation plans and amendments,
- Final CRFs,
- Documentation of the dates and reasons for any deviation from the clinical investigation plan,
- Study center personnel training records,
- Investigator Agreement,
- Signed clinical trial agreements/Co-Investigator addenda including Financial Disclosure information,
- Current curriculum vitae for principal investigator and any co-investigators,
- MEC/authorities approvals, renewals, and correspondence,

- MEC approved Patient Informed Consent Form,
- Insurance statement/certificate.

IFE will supply required paper CRFs. The investigator is responsible for the accurate and correct preparation (review and signature) and submission to the sponsor of all CRFs, all deaths and reportable adverse events and any deviations from the clinical investigation plan. All reports are subject to inspection and to the retention requirements described above for investigator records. If an MEC takes any action related to this clinical study, copies of all pertinent documentation shall be forwarded to the sponsor.

Table 9: Investigator Reports

REPORT	SUBMIT TO	DESCRIPTION/CONSTRAINTS
Withdrawal of MEC Approval (either suspension or termination)	Sponsor	Report if required by local law.
Deviation from clinical investigation plan	Sponsor & MEC/authorities	Any deviation from the CIP shall be recorded together with an explanation for the deviation. (EN ISO 14155-2:2003(E)4.9) For MEC: deviations associated with emergency situations to protect the life and well being of the subject. Informed consent shall be obtained in writing and documented before a subject is enrolled into the clinical investigation. (EN ISO 14155-1:2003(E))

9.2 Sponsor Records and Reports

Records are subject to inspection by regulatory bodies. Medtronic will maintain (but is not limited to) the following records:

- Relevant correspondence (including correspondence with authorities and MEC, as applicable) which pertains to the investigation, including MEC approval letter,
- Signed clinical trial agreement, recent curriculum vitae of investigators (signed and dated), and confidential disclosure agreement,
- Study reportable adverse events, deaths,
- All CRFs submitted by investigator and center-specific samples of subject informed consents,

- Clinical investigation plan and any amendments,
- Training documentation of all IFE study personnel,
- Insurance statement / certificate,
- Name of principal investigator and institution in which the clinical investigation is conducted,
- Approvals of study documents,
- CIP deviations.

Table 10: Sponsor Reports

REPORT	SUBMIT TO	DESCRIPTION/CONSTRAINTS
Premature termination or suspension of the clinical investigation	Investigators, MECs/ competent authority	Medtronic will provide prompt notification of termination or suspension and reason(s).
Final Report	All MECs and competent authority	A final report will be submitted to the MECs after completion or termination of the study.

10 PUBLICATIONS

10.1 Publication Committee

The publication committee will be composed of members of the executive board, the steering committee, at least one member of the sponsor study team and physicians participating in the study and demonstrating a high scientific interest and subject contribution to the study. It will convene at or near the time of the first enrollment to further refine the publication strategy. Participating investigators, members of the executive board and members of steering committee, may submit publication ideas through the publication committee and may author publications. The publication committee is responsible for overseeing the development of case reports, manuscripts and abstracts according to the publication strategy, identifying and appointing the manuscript/abstract first author(s)/writer(s), and identifying Medtronic personnel responsible for assisting the first author. The publication committee will meet approximately every year to refine the publication strategy. The publication committee may refine the publication strategy during the course of the study if needed.

The publication committee reviews not only main publications, but also ancillary publications. If necessary, specified authorship criteria may be applied for ancillary publications. The committee may

decide that no case reports, publications or abstracts will be prepared prior to the end of the study. The timelines for submission are dependent upon the clinical study timelines.

10.2 Authorship Selection

Authorship is determined on the basis of the following, at a minimum:

1) Substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data,

2) Drafting the article or revising it critically for important intellectual content,

3) Final approval of the version to be published.

Authors must meet conditions 1, 2, and 3 (including Medtronic CRM clinical personnel).

Being a member of the publication committee does not guarantee authorship.

Once authorship is determined, the following criteria, at a minimum, will be considered in selecting co-authorship:

1) Demonstration of a high level of interest in the disease state, product and unique product feature(s) being studied,

2) The ability to write, review, edit, and present the publication within a reasonable time frame,

3) Author contributes to the high quality of study data for assessment of the study endpoint,

4) A demonstration of a good publication history.

Criteria for selecting first and subsequent authors will be determined and documented in a publication strategy. All investigators not listed as co-authors may be acknowledged as the "OptiLink HF clinical study investigators" and may be individually listed according to the guidelines of the scientific journal.

10.3 Ancillary Publications

Ancillary publications include those reporting on a subset of the subject population or reporting a specific aspect of the study that requires either Medtronic resources or data from the OptiLink HF clinical study. The publication committee must approve publication of ancillary requests and will need to ensure that requests do not present conflicts with other previously submitted requests. Requests for publications utilizing clinical study data will be evaluated for scientific validity and the ability of Medtronic to provide resources. If multiple geographies contribute data, co-authorship will be representative, using the guidelines for authorship selection described above.

11 ADDITIONAL COMMITTEES

11.1 Executive Committee

The executive committee consisting of 10 physicians from Germany, a member of the sponsor study team. It will be established to guide the development of the study. For detail list of the executive committee members refer to the appendix P.

11.2 Steering Committee

A steering committee consisting of physicians including also members of the executive committee and a member of the sponsor study team will be utilized to assist with planning, organizing and performance of the study. The steering committee members are listed below and may participate as investigators in the study. For detail list of the steering committee members refer to appendix R.

11.3 Events Committee

An events committee consisting of approximately nine physicians (minimum three, maximum nine) will assist in the following:

- Protocol development,
- Establishing committee guidelines and processes,
- Adjudicating events for study objectives,
- Documenting event classifications,
- Attending meetings as requested.

The events committee members are listed in appendix S and will **not be otherwise participating** in the study (i.e. no study center investigator will be involved) to assure that the transmission of information to the study center investigators about events triggering per study arm or per subject does not take place. Medtronic personnel may facilitate the events committee meeting (e.g. statistician, clinical trial leader), but they will not be voting members. The events committee will consist of two working groups (one for adjudication of HF-related events and the other for arrhythmia-related events).

The events committee will not be made aware of the randomization assignment of study subjects.

For detail list of the events committee members refer to appendix S.

11.4 Data Safety Monitoring Board

An independent, unblinded Data Safety Monitoring Board (DSMB) will be established by Medtronic to review the interim data analyses as well as to periodically review the total incidence of adverse events and deaths in this study. The DSMB for this study will consist of a minimum of three and up to seven members with study related backgrounds. Medtronic will appoint members of the DSMB and the chairperson. Up to two additional investigators participating in this study may participate in the open meetings to offer clarification of events, but will not be given voting privileges. Medtronic personnel may facilitate the DSMB meeting (e.g. clinical trial leader, statistician), but they will not be voting members.

A quorum of the committee will review the results of each interim analysis in which the results are analyzed against the primary objective. A summary of adverse events will be reviewed at this time also. Review and consensus by the entire committee is required to recommend that the study should be stopped.

All documentation will be de-identified of clinical center and subject identifiers.

Alleviating Pain · Restoring Health · Extending Life

OptiLink HF

Statistical Analysis Plan

Version 1
17 SEP 2014

Author:
Lou Sherfesee

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1 PURPOSE

This Statistical Analysis Plan has been designed to document, before data is analyzed in the final analysis, the rationale for the study design, and the planned analyses that will be included in final study report.

2 RATIONALE FOR STUDY DESIGN

The Statistical Analysis Plan was developed based on Clinical Investigational Plan Version 3.3 (October 2, 2009).

The OptiLink HF study is a prospective, unblinded, randomized, and controlled study performed in multiple centers. It is planned to include 1000 subjects (500 per study arm) and to conduct the study in 20-30 centers specialized in ICD / CRT-D-implantation, and about 100 active satellite HF management centers with access to Medtronic CareLink® Network. The study is designed with a control group to compare event-triggered HF-disease management through Medtronic's OptiVol® fluid status monitoring with automatically generated wireless CareAlert® notification of the clinician via the Medtronic CareLink® Network (access arm) to standard clinical assessment alone (control arm) in subjects eligible for ICD / CRT-D therapy suffering from heart failure.

The study is randomized to achieve structurally comparable sequence groups concerning known and unknown influence of confounding factors. The study was designed with a control arm in order to adequately investigate the effect of early intervention triggered by CareAlert® notification and evaluation using HF-Management and Cardiac Compass® Report with OptiVol® fluid status monitoring. Variables that differ between the access arm and the control arm include the following: access to CareLink®, the combination of Medtronic's OptiVol® fluid status monitoring with automatically generated wireless CareAlerts® via the Medtronic CareLink® Network, access to HF-Management-Report and Cardiac Compass® Trends.

Subjects will undergo screening to ensure they meet all of the inclusion and none of the exclusion criteria. Subjects must have an implanted study-compliant device prior to enrollment, and enrollment of the subject **can occur 3 days (72 hours) up to 21 days post-implant** while the OptiVol® algorithm activates 34 days after the implant (the period between implant and day 34 is used to build up the impedance reference value). **Subjects will be randomized directly after enrollment and after completion of KCCQ and EQ-5D questionnaires.** The time between randomization and activation of the OptiVol® system is used to organize the individual care link device. Eligible enrolled subjects will be randomized in a 1:1 fashion to the access arm or the control arm. Randomization will be stratified by risk (40% NYHA II, 60% NYHA III, as well as by ischemic/non-ischemic cardiovascular disease, atrial fibrillation and VT/VF episodes prior to implant).

Data collected at follow-up visits conducted outside the window will be considered non-compliant to the window, but will be included in the final analysis based on intention-to-treat analysis.

Because of the duration of the trial and nature of the outcomes endpoints, two interim analyses were planned to occur when 33% and 67% of the expected primary endpoints

had been accrued. At the interim analyses, minimally the primary endpoint and the secondary mortality endpoint would be analyzed. The DSMB would review the results and advise the Study Executive Committee about continuation of the study. The DSMB would consider to stop for success if the primary endpoint occurs significantly more often in the control arm with $p < 0.0001$ for the first and $p < 0.001$ for the second interim analysis. The DSMB would consider to stop for harm if the primary endpoint occurred significantly more often in the access arm with $p < 0.01$ or if mortality was significantly higher in the access arm with $p < 0.05$. The final analysis would use a modified alpha to compensate for the interim analyses, maintaining total type I error at 0.05 (see Section 3.2.1.3, Subsection B). As of the creation of Version 1 of the Statistical Analysis Plan, both interim analyses had taken place and the DSMB recommended continuation of the trial. Version 1 of the SAP was created by a statistician blinded to the interim analysis results.

3 DESCRIPTION OF ANALYSIS

3.1 General Summaries

3.1.1 Description of Baseline Variables

A number of characteristics will be recorded for each subject at baseline. These include gender, age, cardiovascular history, and spontaneous arrhythmia history. Tables and descriptive statistics will be used to summarize subject data with respect to these variables by arm. For quantitative variables such as age, the mean, minimum, maximum, and standard deviation will be given. For qualitative variables, percentages and counts will be given.

3.1.2 Special Considerations

Prior to the final analysis of the primary objective, poolability assessments will be performed regarding gender, device type, history of AF, history of VT/VF, and ischemic status. Each variable will have two levels (Male vs Female, NYHA II vs. III, CRT-D vs. ICD, Hx of AF vs. No Hx of AF, Hx of VT/VF vs. No Hx of VT/VF, Ischemic vs. Non-ischemic).

Each covariate of interest will be assessed for poolability separately using Cox proportional hazards models with randomization arm as a covariate. For the main analysis, it is assumed that the treatment/control arm hazard ratio for patients at one level of a covariate (e.g. CRT-D patients) is equivalent to that of patients at the other level of the covariate (e.g. ICD patients), so that the model has only one parameter to estimate: the overall hazard ratio among all (CRT-D & ICD) patients. To test this assumption, for each event type a two-sided 95% bootstrap confidence interval will be generated for the difference in subgroup hazard ratios (e.g. CRT-D hazard ratio – ICD hazard ratio). This will be done as follows:

1. For a particular covariate (e.g. device group), sample with replacement from the set of subjects in one level of the covariate (e.g. CRT-D subjects), and use all of the events from those sample subjects in the calculation of the treatment/control arm hazard ratio.
2. Do the same thing for the subjects in the other level of the covariate (e.g. ICD subjects), and then take the difference of these two hazard ratios.

3. Repeat this process a total of 10000 times, and determine the 2.5th and 97.5th percentile of these 10000 differences. This will be the 95% bootstrap confidence interval. If the interval contains 0, then it will be concluded that there is not sufficient evidence to reject the null hypotheses that the two hazard ratios are equivalent. If the confidence interval does not contain 0, then conclude that the two hazard ratios are not equivalent and analyze the subgroups separately.
4. Repeat this process for each covariate (gender, Hx of AF, Hx of VT/VF, ischemic status).

If the null hypothesis of equivalence across subgroups is rejected for a particular analysis, then the objective will be analyzed separately for each subgroup, unless it can be determined that it is still appropriate to pool the data across subgroups.

During the course of the trial the protocol was revised and follow-up was extended from the 18 month visit to the end of the trial (when all subjects had had the opportunity to have an 18 month visit). Subjects were given the option to re-consent for this extended follow-up, and for those who did follow-up data beyond 18 months will be available. Before incorporating this data into the analysis of objectives, the subjects in the primary objective analysis cohort who did re-consent and were followed beyond 18 months will be compared against those who survived to 18 months but did not re-consent and exited at the 18 month visit. These comparative analyses will be restricted to those subjects enrolled under the initial protocol. The subjects will be compared with respect to the same covariates for which poolability was assessed: gender, device type, history of AF, history of VT/VF, and ischemic status. Fisher's Exact tests will be used to compare the two subgroups with regard to each of these characteristics. While the analyses of objectives in this document specify that only data through 18 months will be used, if the p-value does not fall below 0.05 for any of the analyses, the post-18 month follow-up data will be included in the main analysis of each objective other than the Quality of Life objective. If the two subgroups (subjects followed beyond 18 months and subjects exited at 18 months) are found to significantly differ by one or more of the covariates, then the post-18 month data will be summarized separately.

3.1.3 Reports for which this Statistical Analysis Plan applies

The documents for which this SAP applies include the Final Report, and possibly publications to be created after the approval date for the Statistical Analysis Plan.

3.2 Primary Objective(s) or Main Objective(s)

In this study there are two randomized arms:

- OptiLink arm: ICD/CRT-D subjects managed with CareLink, with the Optivol CareAlerts programmed ON, and for whom clinicians have access to the Heart Failure Management Report and Cardiac Compass Report
- Control arm: ICD/CRT-D subjects followed without CareLink, with the Optivol CareAlerts programmed OFF, and for whom clinicians do not have access to the Heart Failure Management Report and Cardiac Compass Report

In this document the term "OptiLink" will be used to refer to the set of management tools and diagnostic programming that differentiates the OptiLink arm from the Control arm.

3.2.1 Primary Objective

The primary objective of the study is to establish whether the use of "OptiLink" decreases the incidence rate of the combined endpoint of all-cause mortality or cardiovascular hospitalization over an 18 months follow-up in subjects with HF and ICD or CRT-D treatment.

3.2.1.1 Hypotheses

Let $S_{Control}(t)$ denote the survival function for freedom from all-cause mortality or cardiovascular hospitalization among patients not receiving "OptiLink" (CareLink + Optivol CareAlerts + HF Management Report), and let $S_{Alert}(t)$ denote he corresponding survival function among patients whose treatment can be influenced by "OptiLink". The hypotheses for the primary objective are:

H_0: $S_{Control}(t) = S_{Alert}(t)$ for all $0 \le t \le 18$, and
H_A: $S_{Control}(t) \neq S_{Alert}(t)$ for some $0 \le t \le 18$

A. Rationale for Choice of Hypothesis
Because the Control arm is denied access to CareLink and because Cardiac Compass offers the clinician information beyond heart failure, the endpoint was a composite of all-cause mortality or cardiovascular hospitalization. Subjects initially consented to be followed for only 18 months and many did not re-consent to be followed beyond that point, and so the scope of the objective is restricted to the time frame from randomization to 18 months, as there may be bias in which subjects elected to re-consent for longer follow-up.

3.2.1.2 Endpoint Definition

The endpoint will be defined as the time from randomization until the minimum of death, first cardiovascular hospitalization, last point of contact prior to exit, and last point of contact on or prior to the 18 month visit. If a subject exits prior to the 18 month visit and the reason for exit is not that the subject was lost to follow-up, the date of exit will be considered the last point of contact. A cardiovascular hospitalization is defined as a therapeutic hospitalization that is due to causes including, but not limited to:

- Heart failure (first or subsequent),
- Acute myocardial infarction,
- Coronary insufficiency,
- Acute coronary syndrome/Unstable angina pectoris,
- Symptom-driven hospitalization for cardiac arrhythmia (atrial fibrillation, atrial flutter, supraventricular arrhythmias or ventricular arrhythmias),
- Stroke/cerebral vascular accidents.

Hospitalizations will be adjudicated by an events committee to determine if they satisfy the primary endpoint criteria. Hospitalizations for elective CV procedures, such as planned admissions for elective cardioversion of atrial fibrillation, do not qualify as a primary endpoint. If a subject does not experience a primary endpoint as of the endpoint date, the subject will be considered censored at that date.

3.2.1.3 Analysis Methods

A. Statistical Methodology

Under the proportional hazards assumption,

$$\lambda_{Alert}(t) = \theta\lambda_{Control}(t)\ (t) \text{ for all } t \geq 0$$

Where $\lambda_{Control}(t)$ represents the hazard rate for patients not receiving "OptiLink". The parameter of interest is the proportionality measure, θ, also known as the hazard ratio.

For comparing the time to death or first CV hospitalization between randomization arms, a two-sided stratified log-rank test will be used, with device groups (CRT-D vs. ICD), NYHA (II/III), Ischemic/Non-ischemic status, history of AF, and history of VT/VF serving as strata. The test will not assess the impact of stratum on hazard rates; it will simply allow the baseline rate ($\lambda_{Control}$) to differ by stratum but will assume that the "OptiLink" vs. No "OptiLink" hazard ratio (θ) is the same between the two strata. The test will be performed with α = 0.05. Kaplan-Meier curves will be generated for all four randomization arm/device group combinations.

B. Alpha Level for Final Analysis

A formal alpha-spending function was not pre-specified for the first two interim analyses. Alpha levels of 0.0001 and 0.001 were chosen for the first and second interim analysis, respectively, and now before the final analysis is performed the nominal alpha level for that analysis will be determined based on these previously used alpha levels and a projected 360 subjects with primary endpoints at the end of the trial. To determine what the alpha level should be for the final look based on the assumed final event rate, one must recognize how they are determined.

The observed number of subjects with events at the interim stages of the study were 79 at the first interim analysis, and 158 at the second. In February 2014 the number of randomized subjects who had met a primary endpoint within the first 18 months of follow-up was 342. It is projected that by the conclusion of the study, 360 subjects will have met a primary endpoint within 18 months of implant.

Table 1:Projected Alpha Spending with Nominal Alpha Levels at Interim Analyses

Interim/Final Analysis	# of Subjects with Events	Nominal Alpha Level Used	Corresponding two-sided Z Value	Cumulative alpha-level
#1	79	0.0001	3.8906	
#2	158	0.001	3.2905	?
#5	360 (projected)	?	?	?

Because there will be three analyses, there are three thresholds which the observed test statistics will be compared against.. Each of these thresholds will be derived using a standard normal Z statistic $Z_T = (Z_1, Z_2, Z_3)$ evaluated at the nominal alpha level for that interim analysis. For example, the nominal alpha level for the first interim analysis was 0.0001. The Z statistic for a two-sided test at that alpha level is 3.8906 (i.e. the area under the standard normal curve to the right of 3.8906 or left of -3.8906 is 0.0001). Thus, $Z_1 = 3.8906$. In similar fashion, $Z_2 = 3.2905$.

In the case of the primary objective analysis, at each analysis the corresponding threshold will be used and compared against a test statistic from a two-sided log-rank

test for the hazard ratio. The question that must be answered is what the nominal alpha levels should be at the final analysis to ensure an overall alpha level of 0.05. In other words, what is the value for Z_3.

Distribution of Z_T

Under the null hypothesis, the distribution of Z_T is asymptotically multivariate normal with mean vector $(0,0,0)^T$, and covariance matrix $\mathbf{\Sigma} = (\sigma_{lk})$ where

$$\sigma_{lk} = \text{cov}(Z_l, Z_k) = \sqrt{(i_l/i_k)} \quad i \le k$$

where i_l and i_k are the amount of information available at the ith and kth interim look. Since this is a survival analysis endpoint, this equals the number of subjects with events at the lth and kth interim analyses (column 2 in the table above). For example,

$$\sigma_{12} = \text{cov}(Z_1, Z_2) = \sqrt{(i_1/i_2)} = \sqrt{(79/158)} = 0.7071 = \sigma_{21}$$

Therefore, under the null hypothesis of this objective, the distribution of Z_T is approximately

$$Z_T \sim N\left(\begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}, \begin{bmatrix} 1 & 0.7071 & 0.4684 \\ 0.7071 & 1 & 0.6625 \\ 0.4684 & 0.6625 & 1 \end{bmatrix}\right)$$

O'Brien-Fleming Alpha Spending Function and Cumulative Alpha Spent

The O'Brien-Fleming Alpha Spending Function is a cumulative spending function. In other words, at time point t*, the function

$$\alpha(t^*) = 2 - 2\Phi(Z_{\alpha/2}/\sqrt{t^*})$$

represents the cumulative amount of α that has been spent at time t*. However, t* does not have to reflect time; it can also reflect proportion of information obtained. If *I* represents the total amount of information expected at the end of the study, then $t_1 = i_1/I$ would represent the proportion of information obtained at the first interim analysis.

In the case of a survival analysis endpoint, you can think of *I* as the total number of patients with events at the end of the study. Thus, t_1 can represent the proportion of patients with events that had been observed as of the first interim analysis. Therefore, by projecting the number of events at the future analysis, we can also project the cumulative alpha level at that time point using the O'Brien Fleming alpha spending function[1]. For the final analysis, it is projected that 360 patients with events will have been observed. Therefore,

$$t_3 = 360/360 = 1.$$

Therefore,

$$\alpha(t_3) = 2 - 2\Phi(Z_{\alpha/2}/\sqrt{t_3}) = 2 - 2\Phi(Z_{0.025}/\sqrt{1}) = 2 - 2\Phi(1.96) = 2 - 2(0.9864) = 0.05.$$

[1] DeMets D, Lan K. Interim Analysis: The Alpha Spending Function Approach. Statistics in Medicine. Vol. 13, 1341-1352 (1994).

The cumulative alpha level at the final analysis will be 0.05 by design.

Table 2: Cumulative Alpha Spending at Final Analyses

Interim/Final Analysis	# of Subjects with Events	Nominal Alpha Level	Corresponding Z Value	Cumulative alpha-level
#1	79	0.0001	3.8906	
#2	158	0.001	3.2905	?
#3	360 (projected)	?	?	**0.05**

Estimating Cumulative Alpha Spent as of Final Analysis

Given that for the first 2 interim analyses, the Z values were chosen without consideration for an alpha-spending function and the total number of endpoints is higher than projected for the trial, one cannot simply use the O'Brien-Fleming alpha-spending function to determine the cumulative alpha spent as of the second interim analysis. Instead, one must use the multivariate normal distribution of Z_T to determine the probability that at least one of the first two interim analyses yielded a positive result ($\acute{\alpha}(t_2)$). In other words, given that Z_1 and Z_2 were already chosen, calculate

$$\acute{\alpha}(t_2) = P(|Z_1| \geq 3.8906 \text{ or } |Z_2| \geq 3.2905)$$

To do this, generate some large number of values from a univariate standard normal distribution. Convert this vector to a 3 x N matrix, such that each column in this matrix will represent one random vector of Z_T. Now to convert this matrix to a matrix of vectors from a multivariate normal distribution with variance-covariance matrix equal to $\mathbf{\Sigma}$ on the previous page, take the Cholesky Decomposition of $\mathbf{\Sigma}$ (this can be done in R using the chol function). This will give you the matrix A such that $A^TA = \mathbf{\Sigma}$. Then multiply the transpose of this matrix by the 3 x N matrix of univariate normal values. The resulting matrix will be a 3 x N matrix in which each column is a vector from the multivariate normal distribution of Z_T, with mean vector (0,0,0) and variance-covariance matrix $\mathbf{\Sigma}$.

Now simply calculate the proportion of columns of this matrix in which the first element is ≥ 3.8906 or the second element is ≥ 3.2905. This will be the probability above, and will represent the cumulative alpha-level after the second interim analysis. Letting N = 2,000,000 vectors, this probability was estimated to be $\acute{\alpha}(t_2) = 0.00107$ Therefore, in the table below, the bolded value represents the cumulative alpha-level spent as of the third second analysis.

Table 3: Projected Alpha Spending with Cumulative Alpha Spending As of 2nd Interim Analysis

Interim/Final Analysis	# of Subjects with Events	Nominal Alpha Level	Corresponding Z Value	Cumulative alpha-level
#1	79	0.0001	3.8906	
#2	158	0.001	3.2905	**0.00107**
#3	360 (projected)	?	?	0.05

Estimating the Nominal Alpha Levels for Remaining Analysis

To determine the nominal alpha levels for the final analysis, one must first recall that, based on the O'Brien-Fleming cumulative alpha spending function, the cumulative pre-

specified alpha to be spent as of the final analysis is 0.05. Given that it has been determined that 0.00107 has already been spent as of the second interim analysis, the incremental alpha to be spent at the final analysis is 0.05 – 0.00107 = 0.04893. Therefore,

$0.05 = \alpha(t_3) = P_0$(A positive result in any of 3 analyses)

$= P_0(|Z_1| \geq 3.8906$ or $|Z_2| \geq 3.2905$ or $|Z_3| \geq C_3$ for some value $C_3)$

$= P_0($ A positive result in any of 1st 2 interim analyses) +
P_0(Positive result in final analysis & no positive result in interim analyses)

$= \acute{\alpha}(t_2) + P_0(|Z_1| < 3.8906$ and $|Z_2| < 3.2905$ and $|Z_3| \geq C_3)$

$= 0.00107 + 0.04893$

Therefore, one must determine the unknown value C_3 such that

$0.04893 = P(|Z_1| < 3.8906$ and $|Z_2| < 3.2905$ and $|Z_3| \geq C_3)$

Once again, one can find this through using the multivariate normal distribution of Z_T. Simply iteratively determine C_3 such that the proportion of columns of the matrix generated in a previous section that satisfy the criteria in the equation above is 0.04893. This value was determined, and $C_3 = 1.9634$. The corresponding alpha-level for this value is $2*(1 - \Phi(1.9634)) = 0.0496$.

Table 4: Projected Table of Alpha Spending with Nominal Alpha Levels at All Analyses

Interim/Final Analysis	# of Subjects with Events	Nominal Alpha Level	Corresponding Z Value	Cumulative alpha-level
#1	79	0.0001	3.8906	
#2	158	0.001	3.2905	0.00107
#3	360 (projected)	**0.0496**	**1.9634**	0.05

If the number of subjects with events is not approximately 360, then prior to final analysis the nominal alpha level will be recalculated based on the final observed number of subjects with events.

C. Determination of Patients/Data for Analysis

The analysis will be performed using the Intent to Treat principle, meaning that all post-randomization data for a subject will be used in the analysis and allocated to the arm the subject was randomized to. Hospitalizations adjudicated to be elective will be excluded from the analysis. Only data on or prior to the 18 month visit will be included, unless conditions are met as specified in section 3.2.1. Hospitalizations with admission dates equal to the 18 month visit will be included. All randomized subjects will be included in the analysis provided they are not documented to violate the following inclusion criteria/exclusion criteria at time of enrollment:

- Subjects with severe COPD exclusion criterion
- Subjects with chronic renal failure needing renal dialysis exclusion criterion
- Heart failure inclusion criterion:
  - o Subjects have stable NYHA II/III CHF for at least 30 days, AND
  - o most recent LVEF in the prior 6 months to randomization is at most 35%, AND

o they either have at least one HF hospitalization within the prior 12 months OR one course of ambulatory IV or oral diuretic treatment OR have a BNP value of > 400 pg/mL OR a NT-proBNP value exceeding the age-specific requirement

3.2.1.4 Sample Size Methods and Assumptions

The calculation of the sample size is based on available study data using the experience from the CHARM study (see 3.3 of the Clinical Investigational Plan Version 3.3). Only ICD / CRT-D subjects will be included in this study.

For sample size calculation the following assumptions are made:
o type I error α = 0.05
o power = 0.80
o control arm proportion event-free at 18 months = 72.0%
o difference between treatment arms = 30% of control arm → 8.4%
o access arm proportion event-free at 18 months = 80.4%
o all subjects are followed for 1.5 years

The method for analysis of the primary criterion is the two-sided log-rank test. Based on these assumptions the total sample size of 798 subjects will have 80% power to detect a difference between the rates of all-cause death or cardiovascular related hospitalization of the two treatment arms. This is based on the method from Lakatos (1988)[2] and Cantor (1997)[3], setting accrual time to 0 to model subject exit after 18 months (SAS Power and Sample Size module, version 3.1). Taking into account early study termination and treatment non-compliance including cross-over, 1000 subjects will be enrolled in the study. This increase in sample size will ensure that power is maintained when 5.0% of subjects cross over (based on simulation, with cross-over equally distributed over arms, assuming full compliance on other elements of the protocol). Then, the expected number of events is 238 (simulation).

3.3 Secondary or Ancillary Objectives

3.3.1 Secondary Objective #1: Number of HF-related Hospitalizations

3.3.1.1 Hypothesis

Let $\theta_{Control}$ denote the mean rate of HF hospitalizations per patient month through 18 months post-implant among study-eligible patients not receiving “OptiLink” (CareLink + Optivol CareAlerts + HF Management Report), and let $\theta_{Alert}(t)$ denote the corresponding mean rate among study-eligible patients whose treatment can be influenced by “OptiLink”. The hypotheses for this secondary objective are:

H_0: $\theta_{Control} = \theta_{Alert}$, and

[2] Lakatos, E. (1988), “Sample Sizes Based on the Log-Rank Statistic in Complex Clinical Trials,” Biometrics, 44, 229-241.
[3] Cantor, A. B. (1997), Extending SAS Survival Analysis Techniques for Medical Research, Cary, NC: SAS Institute Inc.

H_A: $\theta_{Control} \neq \theta_{Alert}$

A. Rationale for Choice of Hypothesis
Because subjects initially consented to be followed for only 18 months and many did not reconsent to be followed beyond that point, the scope of the objective is restricted to the time frame from randomization to 18 months, unless conditions are met as specified in section 3.2.1, as there may be bias in which subjects elected to reconsent for longer follow-up.

3.3.1.2 Endpoint Definition

The endpoint for each subject will be the number of HF hospitalizations experienced during the time from randomization to last point of contact on or prior to the 18 month visit. If a subject exits prior to the 18 month visit and the reason for exit is not that the subject was lost to follow-up, the date of exit will be considered the last point of contact.

A heart failure-related hospitalization is defined as a therapeutic, in-patient hospitalization extending over a calendar date change where admission occurs after consent into the trial where signs and symptoms of heart failure requiring the administration and/or adustments of heart failure therapy is present.

3.3.1.3 Analysis Methods

A. Statistical Methodology
For each randomized subject the number of post-randomization HF hospitalizations will be divided by the number of months of follow-up post-randomization (randomization to the minimum of the 18 month visit or last point of contact on or prior to exit). A two-sided Wilcoxon rank-sum test will be performed with α=0.05 to compare the rates for the two randomized arms.

This analysis differs from the protocol version 3.3, which indicates that rates will reflect HF hospitalizations per patient rather than per patient month. The reason for the difference is that such rates among subjects who exit early would likely be biased low.

B. Determination of Patients/Data for Analysis
The analysis will be performed using the Intent to Treat principle, meaning that all post-randomization data for a subject will be used in the analysis and allocated to the arm the subject was randomized to. Only data on or prior to the 18 month visit will be included. HF hospitalizations with admission dates equal to the 18 month visit will be included. All randomized subjects will be included in the analysis provided they are not documented to violate the following inclusion criteria/exclusion criteria:

- Subjects with severe COPD exclusion criterion
- Subjects with chronic renal failure needing renal dialysis exclusion criterion
- Heart failure inclusion criterion:
  - Subjects have stable NYHA II/III CHF for at least 30 days, AND
  - most recent LVEF in the prior 6 months to randomization is at most 35%, AND
  - they either have at least one HF hospitalization within the prior 12 months OR one course of ambulatory IV or oral diuretic treatment OR have a BNP value of > 400 pg/mL OR a NT-proBNP value exceeding the age-specific requirement

3.3.2 Secondary Objective #2: HF Hospitalizations

3.3.2.1 Hypothesis

Let $\lambda_{Control}(t)$ denote the hazard function for first HF hospitalization among study-eligible patients not receiving "OptiLink" (CareLink + Optivol CareAlerts + HF Management Report), and let $\lambda_{Alert}(t)$ denote he corresponding hazard function among study-eligible patients whose treatment can be influenced by "OptiLink". The hypotheses for this secondary objective are:

H_0: $\lambda_{Control}(t) = \lambda_{Alert}(t)$ for all $0 \le t \le 18$, and
H_A: $\lambda_{Control}(t) \neq \lambda_{Alert}(t)$ for some $0 \le t \le 18$

A. Rationale for Choice of Hypothesis
Because subjects initially consented to be followed for only 18 months and many did not reconsent to be followed beyond that point, the scope of the objective is restricted to the time frame from randomization to 18 months, unless conditions are met as specified in section 3.2.1, as there may be bias in which subjects elected to reconsent for longer follow-up.

3.3.2.2 Endpoint Definition

There are two endpoints for this objective. The first endpoint will be defined as the time from randomization until the minimum of first heart-failure-related hospitalization and last point of contact on or prior to the 18 month visit. If a subject exits prior to the 18 month visit and the reason for exit is not that the subject was lost to follow-up, the date of exit will be considered the last point of contact.

A heart failure-related hospitalization is defined in section 3.3.1.2.

Hospitalizations will be adjudicated by an events committee to determine if they satisfy these criteria. If a subject does not experience a HF hospitalization as of the endpoint date, the subject will be considered censored at that date.

The second endpoint will be an expansion of the first, and include the time between consecutive HF hospitalizations for those subjects who experience multiple HF hospitalizations within their first 18 months of follow-up. The time between successive events will be defined as time from discharge of the first event to admission date of the following event. Additionally, the time between the last HF hospitalization within the first 18 months of follow-up and the minimum of date of death and last contact on or prior to 18 month visit will be included in the analysis.

3.3.2.3 Analysis Methods

A. Statistical Methodology

Under the proportional hazards assumption,

$$\lambda_{Alert}(t) = \theta\lambda_{Control}(t) \text{ for all } t > 0$$

The parameter of interest is the proportionality measure, θ, also known as the hazard ratio.

For comparing the time to first HF hospitalization between randomization arms, a two-sided stratified log-rank test will be used, with device group (CRT-D vs. ICD), NYHA (II/III), Ischemic/Non-ischemic status, history of AF, and history of VT/VF serving as strata in case the hazard rate for time to first HF hospitalization differs by device group. The test will not assess the impact of device group on hazard rates; it will simply allow the baseline rate ($\lambda_{Control}$) to differ by device group but will assume that the "OptiLink" vs. No "OptiLink" hazard ratio (θ) is the same between the two device groups. The test will be performed with $\alpha = 0.05$. Kaplan-Meier curves will be generated for all four randomization arm/device group combinations.

To compare the randomization arms allowing for multiple HF hospitalizations per subject, a Prentice Williams Peterson (PWP) proportional hazards regression model[4] will be applied to test for a significant difference between the hazard rates of the two therapy arms, so as to allow for increased risk of events following initial HF hospitalizations. The model above will be stratified by device group (CRT-D vs. ICD), NYHA (II/III), Ischemic/Non-ischemic status, history of AF, and history of VT/VF and if the p-value for the coefficient, θ (the hazard ratio), is less than 0.05, then it will be concluded that the hazard rate for HF hospitalizations among study-eligible patients with "OptiLink" is different from that of the corresponding hazard rate for study-eligible patients without "OptiLink".

B. Determination of Patients/Data for Analysis

The analysis will be performed using the Intent to Treat principle, meaning that all post-randomization data for a subject will be used in the analysis and allocated to the arm the subject was randomized to. Only data on or prior to the 18 month visit will be included. Heart failure hospitalizations with admission dates equal to the 18 month visit will be included. All randomized subjects will be included in the analysis provided they are not documented to violate the following inclusion criteria:

- Subjects with severe COPD exclusion criterion
- Subjects with chronic renal failure needing renal dialysis exclusion criterion
- Heart failure inclusion criterion:
  - Subjects have stable NYHA II/III CHF for at least 30 days, AND
  - most recent LVEF in the prior 6 months to randomization is at most 35%, AND
  - they either have at least one HF hospitalization within the prior 12 months OR one course of ambulatory IV or oral diuretic treatment OR have a BNP value of > 400 pg/mL OR a NT-proBNP value exceeding the age-specific requirement

[4] R.L. Prenteice, B.J. WIllams, and A.V. Peterson. On the regression analysis of multivariate failure time data. *Biometrika*, 68:373-379, 1981. .

3.3.3 Secondary Objective #3: Expected FU Days Missed due to Death or CV Hospitalization

3.3.3.1 Hypothesis

Let μ_{ALERT} denote the mean days hospitalized for cardiovascular reasons per follow-up year for the first 18 months post-implant among study-eligible patients receiving "OptiLink" (CareLink + Optivol CareAlerts + HF Management Report). Let $\mu_{Control}$ denote the days hospitalized for cardiovascular reasons per follow-up year for the first 18 months post-implant for study-eligible patients not receiving "OptiLink". The hypotheses used to evaluate this metric are as follows:

H_0: $\mu_{ALERT} = \mu_{Control}$
H_A: $\mu_{ALERT} \neq \mu_{Control}$

A. Rationale for Choice of Hypothesis
Days alive and out of hospital" is an accepted endpoint in CV trials, however it picks up additional variability from between-patient differences in total follow-up time. In OptiLink HF the intention was to remove this variability by using the endpoint of maximal achievable follow-up duration minus days alive out of hospital. Because subjects initially consented to be followed for only 18 months and many did not re-consent to be followed beyond that point, the scope of the objective is restricted to the time frame from randomization to 18 months, unless conditions are met as specified in section 3.2.1, as there may be bias in which subjects elected to re-consent for longer follow-up.

3.3.3.2 Endpoint Definition

The endpoint will be defined as the sum of the days hospitalized for cardiovascular reasons (i.e. among all cardiovascular-related hospitalizations as adjudicated by the events committee, subtract the discharge date from the admission date, and add these differences for each subject; see definition of CV hospitalization in section 3.2.1.2) as well as the days from death to the expected 18 month visit if the subject died prior to their 18 month visit. Only hospitalizations involving an overnight stay and occurring on or before the subject's 18 month visit are included in the analysis. For each subject, divide this sum by the number of follow-up days (from randomization to the last point of contact on or before the subject's 18 month visit). If a subject exits prior to the 18 month visit and the reason for exit is not that the subject was lost to follow-up, the date of exit will be considered the last point of contact.

3.3.3.3 Analysis Methods

A. Statistical Methodology
At each visit, the clinician will record via in-office communication with the subject all hospitalizations the subject has experienced since their last visit, and an events committee will adjudicate each hospitalization to determine if it meets the criteria for a cardiovascular-related hospitalization.
A Wilcoxon Rank-Sum test will be performed using the subject proportions of expected days within the first 18 months missed due to either CV hospitalization or death. If the p-value is less than 0.05, it will be concluded the mean days missed due to either death or being hospitalized for CV reasons per patient year among study-eligible patients supported

by a device with “OptiLink” features is significantly different from that of patients followed through only in-office visits with the “OptiLink” features OFF.

B. Determination of Patients/Data for Analysis

The analysis will be performed using the Intent to Treat principle, meaning that all post-randomization data for a subject will be used in the analysis and allocated to the arm the subject was randomized to. Only data on or prior to the 18 month visit will be included, and hospitalizations that did not involve an overnight stay will be excluded from analyses. Hospitalizations with admission dates equal to the 18 month visit will be included. All randomized subjects will be included in the analysis provided they are not documented to violate the following inclusion criteria:

- Subjects with severe COPD exclusion criterion
- Subjects with chronic renal failure needing renal dialysis exclusion criterion
- Heart failure inclusion criterion:
  - Subjects have stable NYHA II/III CHF for at least 30 days, AND
  - most recent LVEF in the prior 6 months to randomization is at most 35%, AND
  - they either have at least one HF hospitalization within the prior 12 months OR one course of ambulatory IV or oral diuretic treatment OR have a BNP value of > 400 pg/mL OR a NT-proBNP value exceeding the age-specific requirement

3.3.4 Secondary Objective #4: All-cause Mortality

3.3.4.1 Hypothesis

Let $\lambda_{Alert}(t)$ denote the hazard rate function for all-cause mortality among study-eligible patients receiving "OptiLink" (CareLink + Optivol CareAlerts + HF Management Report), and let $\lambda_{Control}(t)$ denote he corresponding hazard rate function among study-eligible patients not receiving "OptiLink". The hypotheses for this secondary objective are:

H_0: $\lambda_{Control}(t) = \lambda_{Alert}(t)$ for all $0 \le t \le 18$, and
H_A: $\lambda_{Control}(t) \neq \lambda_{Alert}(t)$ for some $0 \le t \le 18$

A. Rationale for Choice of Hypothesis
Because subjects initially consented to be followed for only 18 months and many did not re-consent to be followed beyond that point, the scope of the objective is restricted to the time frame from randomization to 18 months, unless conditions are met as specified in section 3.2.1, as there may be bias in which subjects elected to re-consent for longer follow-up.

3.3.4.2 Endpoint Definition

The endpoint will be defined as the time from randomization until the minimum of death and the last point of contact (including CareLink transmissions and/or Save-to-Disk interrogation dates) on or prior to the 18 month visit. If a subject exits prior to the 18 month visit and the reason for exit is not that the subject was lost to follow-up, the date of exit will be considered the last point of contact. If the subject does not die as of this minimum date, the subject will be considered censored.

3.3.4.3 Analysis Methods

A. Statistical Methodology

Under the proportional hazards assumption,

$$\lambda_{Alert}(t) = \theta\lambda_{Control}(t)\ (t) \text{ for all } t > 0$$

The parameter of interest is the proportionality measure, θ, also known as the hazard ratio.

For comparing the time to death between randomization arms, a two-sided stratified log-rank test will be used, with device groups (CRT-D vs. ICD), NYHA (II/III), Ischemic/Non-ischemic status, history of AF, and history of VT/VF serving as strata in case the baseline hazard rate($\lambda_{Control}$) for time to death differs by device group. The test will not assess the impact of device group on hazard rates; it will simply allow the baseline rate ($\lambda_{Control}$) to differ by device group but will assume that the "OptiLink" vs. No "OptiLink" hazard ratio (θ) is the same between the two device groups. The test will be performed with $\alpha = 0.05$. Kaplan-Meier curves will be generated for all four randomization arm/device group combinations.

B. Determination of Patients/Data for Analysis

The analysis will be performed using the Intent to Treat principle, meaning all post-randomization data for a subject will be used in the analysis and allocated to the arm the subject was randomized to. All randomized subjects will be included in the analysis provided they are not documented to violate the following inclusion criteria:

- Subjects with severe COPD exclusion criterion
- Subjects with chronic renal failure needing renal dialysis exclusion criterion
- Heart failure inclusion criterion:
  - o Subjects have stable NYHA II/III CHF for at least 30 days, AND
  - o most recent LVEF in the prior 6 months to randomization is at most 35%, AND
  - o they either have at least one HF hospitalization within the prior 12 months OR one course of ambulatory IV or oral diuretic treatment OR have a BNP value of > 400 pg/mL OR a NT-proBNP value exceeding the age-specific requirement

3.3.5 Secondary Objective #5: CV Mortality

3.3.5.1 Hypothesis

Let $\lambda_{Alert}(t)$ denote the hazard rate function for cardiovascular mortality among study-eligible patients receiving "OptiLink" (CareLink + Optivol CareAlerts + HF Management Report), and let $\lambda_{Control}(t)$ denote the corresponding hazard rate function among study-eligible patients not receiving "OptiLink". The hypotheses for the primary objective are:

H_0: $\lambda_{Control}(t) = \lambda_{Alert}(t)$ for all $0 \le t \le 18$, and
H_A: $\lambda_{Control}(t) \neq \lambda_{Alert}(t)$ for some $0 \le t \le 18$

A. Rationale for Choice of Hypothesis
Because subjects initially consented to be followed for only 18 months and many did not re-consent to be followed beyond that point, the scope of the objective is restricted to the time frame from randomization to 18 months, unless conditions are met as specified in section 3.2.1, as there may be bias in which subjects elected to re-consent for longer follow-up.

3.3.5.2 Endpoint Definition

The endpoint will be defined as the time from randomization until the minimum of *cardiovascular-related* death (as determined by the events committee), the last point of contact (including CareLink transmissions and/or Save-to-Disk interrogation dates) prior to the exit, and the last point of contact on or prior to the 18 month visit. If a subject exits prior to the 18 month visit and the reason for exit is not that the subject was lost to follow-up, the date of exit will be considered the last point of contact. If the subject does not die as of this minimum date, the subject will be considered censored. If the subject dies as of the minimum date but the death is not adjudicated to be cardiovascular-related, the subject will be censored at the time of death.

3.3.5.3 Analysis Methods

A. Statistical Methodology

Under the proportional hazards assumption,

$$\lambda_{Alert}(t) = \theta\lambda_{Control}(t)\ (t) \text{ for all } t > 0$$

The parameter of interest is the proportionality measure, θ, also known as the hazard ratio.

For comparing the time to cardiovascular death between randomization arms, a two-sided stratified log-rank test will be used, with device groups (CRT-D vs. ICD), NYHA (II/III), Ischemic/Non-ischemic status, history of AF, and history of VT/VF serving as strata in case the baseline hazard rate($\lambda_{Control}$) for time to cardiovascular death differs by device group. The test will not assess the impact of device group on hazard rates; it will simply allow the baseline rate ($\lambda_{Control}$) to differ by device group but will assume that the "OptiLink" vs. No "OptiLink" hazard ratio (θ) is the same between the two device groups. The test will be performed with $\alpha = 0.05$. Kaplan-Meier curves will be generated for all four randomization arm/device group combinations.

B. Determination of Patients/Data for Analysis

The analysis will be performed using the Intent to Treat principle, meaning that all post-randomization data for a subject will be used in the analysis and allocated to the arm the subject was randomized to. Only data on or prior to the 18 month visit will be included. All randomized subjects will be included in the analysis provided they are not documented to violate the following inclusion criteria:

- Subjects with severe COPD exclusion criterion
- Subjects with chronic renal failure needing renal dialysis exclusion criterion
- Heart failure inclusion criterion:
  - Subjects have stable NYHA II/III CHF for at least 30 days, AND
  - most recent LVEF in the prior 6 months to randomization is at most 35%, AND
  - they either have at least one HF hospitalization within the prior 12 months OR one course of ambulatory IV or oral diuretic treatment OR have a BNP value of > 400 pg/mL OR a NT-proBNP value exceeding the age-specific requirement

3.3.6 Secondary Objective #6: HF Hospitalization/All-cause Mortality

3.3.6.1 Hypothesis

Let $\lambda_{Alert}(t)$ denote the hazard rate function for freedom from all-cause mortality and HF hospitalizations among study-eligible patients receiving "OptiLink" (CareLink + Optivol CareAlerts + HF Management Report), and let $\lambda_{Control}(t)$ denote the corresponding hazard rate function among study-eligible patients not receiving "OptiLink". The hypotheses for this secondary objective are:

H_0: $\lambda_{Control}(t) = \lambda_{Alert}(t)$ for all $0 \le t \le 18$, and
H_A: $\lambda_{Control}(t) \ne \lambda_{Alert}(t)$ for some $0 \le t \le 18$

A. Rationale for Choice of Hypothesis

Because subjects initially consented to be followed for only 18 months and many did not re-consent to be followed beyond that point, the scope of the objective is restricted to the time frame from randomization to 18 months, unless conditions are met as specified in section 3.2.1, as there may be bias in which subjects elected to re-consent for longer follow-up.

3.3.6.2 Endpoint Definition

The endpoint will be defined as the time from randomization until the minimum of death, first heart-failure-related hospitalization, last point of contact prior to exit, and last point of contact on or prior to the 18 month visit. If a subject exits prior to the 18 month visit and the reason for exit is not that the subject was lost to follow-up, the date of exit will be considered the last point of contact.

A heart failure-related hospitalization is defined in section 3.3.3.2.

Hospitalizations will be adjudicated by an events committee to determine if they satisfy these criteria. Subjects who either die or experienced a HF hospitalization will be considered to have met the endpoint. If a subject does not experience a HF hospitalization or expire as of the endpoint date, the subject will be considered censored at that date.

For subjects who experience a post-randomization HF hospitalization prior to an 18 month visit, the time from discharge of that first HF hospitalization to death or last contact on or prior to the 18 month visit will also be determined.

3.3.6.3 Analysis Methods

A. Statistical Methodology

Under the proportional hazards assumption,

$$\lambda_{\text{Alert}}(t) = \theta\lambda_{\text{Control}}(t)(t) \text{ for all } t > 0$$

The parameter of interest is the proportionality measure, θ, also known as the hazard ratio.

For comparing the time to death or first HF hospitalization between randomization arms, a two-sided stratified log-rank test will be used, with device groups (CRT-D vs. ICD), NYHA (II/III), Ischemic/Non-ischemic status, history of AF, and history of VT/VF serving as strata in case the baseline hazard rate(λ_{Control}) for time to death or HF hospitalization differs by device group. The test will not assess the impact of device group on hazard rates; it will simply allow the baseline rate (λ_{Control}) to differ by device group but will assume that the “OptiLink” vs. No “OptiLink” hazard ratio (θ) is the same between the two device groups. The test will be performed with $\alpha = 0.05$. Kaplan-Meier curves will be generated for all four randomization arm/device group combinations.

For subjects who experience at least one HF hospitalization between randomization and an 18 month visit, Kaplan-Meier curves will be generated for each randomization arm summarizing the time from discharge of the first HF hospitalization to death (endpoint) or last contact on or prior to the 18 month visit. This will also be done for time from discharge of the first HF hospitalization to HF death (endpoint) or last contact on or prior to the 18 month visit. This will also be done for time from discharge of the first HF decompensation to HF-related death (endpoint) or last contact on or prior to the 18 month visit.

B. Determination of Patients/Data for Analysis

The analysis will be performed using the Intent to Treat principle, meaning that all post-randomization data for a subject will be used in the analysis and allocated to the arm the subject was randomized to. Only data on or prior to the 18 month visit will be included. Heart Failure hospitalizations with admission dates equal to the 18 month visit will be included. All randomized subjects will be included in the analysis provided they are not documented to violate the following inclusion criteria:

- Subjects with severe COPD exclusion criterion
- Subjects with chronic renal failure needing renal dialysis exclusion criterion
- Heart failure inclusion criterion:
  - Subjects have stable NYHA II/III CHF for at least 30 days, AND
  - most recent LVEF in the prior 6 months to randomization is at most 35%, AND
  - they either have at least one HF hospitalization within the prior 12 months OR one course of ambulatory IV or oral diuretic treatment OR have a BNP value of > 400 pg/mL OR a NT-proBNP value exceeding the age-specific requirement

3.3.7 Secondary Objective #7: Quality of Life

3.3.7.1 Hypothesis

Let $\theta_{Control,6}$ denote the mean change in QOL score from baseline to 6 months among study-eligible patients not receiving "OptiLink" (CareLink + Optivol CareAlerts + HF Management Report), and let $\theta_{Alert,6}$ denote the corresponding mean change among study-eligible patients who are receiving "OptiLink". The hypotheses for the objective are:

H_0: $\theta_{Control,6} = \theta_{Alert,6}$ and
H_A: $\theta_{Control,6} \neq \theta_{Alert,6}$

Similarly, let $\theta_{Control,18}$ denote the mean change in QOL score from baseline to 18 months among study-eligible patients not receiving "OptiLink" (CareLink + Optivol CareAlerts + HF Management Report), and let $\theta_{Alert,18}$ denote the corresponding mean change among study-eligible patients who are receiving "OptiLink". The hypotheses for the objective are:

H_0: $\theta_{Control,18} = \theta_{Alert,18}$ and
H_A: $\theta_{Control,18} \neq \theta_{Alert,18}$

These hypotheses will apply to the EQ-5D QOL tool, as well as all 10 subscores of the Kansas City Cardiomyopathy Questionnaire.

3.3.7.2 Endpoint Definition

The endpoints for this objective will be the absolute difference between baseline and 6 months, as well as between baseline and 18 months for each KCCQ and EQ-5D.

The KCCQ is a validated, self-administered, 23-item questionnaire that quantifies 5 domains: physical limitations, symptoms, self-efficacy, social interference and quality of life[5]. The questionnaire is scored by assigning an ordinal score of 1-5, 1-6 or 1-7 (lowest to

[5] Green CP, Porter CB, Bresnahan DR, Bilven B, Spertus JA. The Kansas City Cardiomyopathy Questionnaire, a New Quality of Life Measure for Heart Failure is Reliable

highest level of functioning, depending on the question) to each item and the items are averaged within each domain. Normalized scoring is obtained for each domain and for three summary scores, functional and clinical status and total symptoms, resulting in 10 total scores. The EQ-5D questionnaire results in a single weighted score based on 5 questions.

3.3.7.3 Analysis Methods

A. Statistical Methodology

For both the 6 and 18 month visit, the subject's follow-up – baseline difference in each of the eight KCCQ subscale and two summary scores, as well as the corresponding difference for the EQ-5D Questionnaire composite score will be calculated. A Wilcoxon rank sum test will be applied to each of these eleven measures. If the p-value for the test corresponding to a particular subscale is less than 0.05, it will be concluded that, on average, patients followed with "OptiLink" have a significantly different average change in the subscale measure than patients managed without "OptiLink". If a poolability assessment demonstrates a significant difference between device groups regarding the mean difference, this will be done separately for subjects with CRT-D devices and subjects with ICD devices.

To control the overall alpha level at each time point (6 and 18 months), the 11 QOL test p-values (10 KCCQ and 1 EQ-5D) will be adjusted via the Holm Procedure. This will be done by ordering the 11 p-values from smallest to largest ($p_{(1)},\ldots, p_{(11)}$) and their corresponding null hypotheses ($H_{(1)}\ldots H_{(11)}$). Then let k be the minimal index such that $p_{(k)} > 0.05/(11 + 1 - k)$. Reject the null hypotheses $H_{(1)}\ldots H_{(k-1)}$ and do not reject $H_{(k)},\ldots,H_{(11)}$.

B. Determination of Patients/Data for Analysis

The analysis will be performed using the Intent to Treat principle, meaning that all post-randomization data for a subject will be used in the analysis and allocated to the arm the subject was randomized to. There will be no data imputation; for each time point (6 and 18 months), only subjects with paired data for the particular QOL subscore will be included in the analysis of that subscore at that time point. Because QOL is collected at exit rather than at the 18 month visit, only subjects who exit at their 18 month visit will be included in the analyses of the 18 month endpoints. Randomized subjects will be excluded from all the analyses if they are documented to violate any of the following inclusion criteria:

- Subjects with severe COPD exclusion criterion
- Subjects with chronic renal failure needing renal dialysis exclusion criterion
- Heart failure inclusion criterion:
  - Subjects have stable NYHA II/III CHF for at least 30 days, AND
  - most recent LVEF in the prior 6 months to randomization is at most 35%, AND
  - they either have at least one HF hospitalization within the prior 12 months OR one course of ambulatory IV or oral diuretic treatment OR have a BNP value of > 400 pg/mL OR a NT-proBNP value exceeding the age-specific requirement

and Responsive to Clinical Change [abstract]. *JACC*. February 1999;33(suppl 1):247A. Abstract 1077-116.

3.3.8 Secondary Objective #8: Health Economics

For a summary of specified analyses for this objective, refer to the OptiLink-HF-Health-Economics-Analysis Plan AlphaCare-30112008 document provided in the Appendix.

3.3.9 Ancillary Objective #1: All-cause Hospitalizations

3.3.9.1 Hypothesis

Let $\lambda_{Control}(t)$ denote the hazard function for first hospitalization among study-eligible patients not receiving "OptiLink" (CareLink + Optivol CareAlerts + HF Management Report), and let $\lambda_{Alert}(t)$ denote the corresponding hazard function among study-eligible patients whose treatment can be influenced by "OptiLink". The hypotheses for the primary objective are:

H_0: $\lambda_{Control}(t) = \lambda_{Alert}(t)$ for all $0 \le t \le 18$, and
H_A: $\lambda_{Control}(t) \neq \lambda_{Alert}(t)$ for some $0 \le t \le 18$

A. Rationale for Choice of Hypothesis
Because subjects initially consented to be followed for only 18 months and many did not reconsent to be followed beyond that point, the scope of the objective is restricted to the time frame from randomization to 18 months, unless conditions are met as specified in section 3.2.1, as there may be bias in which subjects elected to reconsent for longer follow-up.

3.3.9.2 Endpoint Definition

There are two endpoints for this objective. The first endpoint will be defined as the time from randomization until the minimum of first hospitalization and last point of contact on or prior to the 18 month visit. If a subject exits prior to the 18 month visit and the reason for exit is not that the subject was lost to follow-up, the date of exit will be considered the last point of contact.

A hospitalization is defined as a therapeutic, in-patient hospitalization extending over a calendar date change where admission occurs after consent. If a subject does not experience a hospitalization as of the endpoint date, the subject will be considered censored at that date.

The second endpoint will be an expansion of the first, and include the time between consecutive hospitalizations for those subjects who experience multiple hospitalizations within their first 18 months of follow-up. The time will be defined as time between discharge of one visit and admission of the next consecutive visit. Additionally, the time between the last hospitalization within the first 18 months of follow-up and the date of death or last contact on or prior to 18 month visit will be included in the analysis.

3.3.9.3 Analysis Methods

A. Statistical Methodology

Under the proportional hazards assumption,

$$\lambda_{\text{Alert}}(t) = \theta\lambda_{\text{Control}}(t) \text{ for all } t > 0$$

The parameter of interest is the proportionality measure, θ, also known as the hazard ratio.

For comparing the time to first hospitalization between randomization arms, a two-sided stratified log-rank test will be used, with device group (CRT-D vs. ICD), NYHA (II/III), Ischemic/Non-ischemic status, history of AF, and history of VT/VF serving as strata in case the hazard rate for time to first hospitalization differs by device group. The test will not assess the impact of device group on hazard rates; it will simply allow the baseline rate (λ_{Control}) to differ by device group but will assume that the "OptiLink" vs. No "OptiLink" hazard ratio (θ) is the same between the two device groups. The test will be performed with α = 0.05. Kaplan-Meier curves will be generated for all four randomization arm/device group combinations.

To compare the randomization arms allowing for multiple hospitalizations per subject, an Andersen-Gill proportional hazards regression model will be applied to test for a significant difference between the hazard rates of the two therapy arms. The model above will be stratified by device group (CRT-D vs. ICD), and if the p-value for the coefficient, θ (the hazard ratio), is less than 0.05, then it will be concluded that the hazard rate for hospitalizations among study-eligible patients with "OptiLink" is different from that of the corresponding hazard rate for study-eligible patients without "OptiLink".

B. Determination of Patients/Data for Analysis

The analysis will be performed using the Intent to Treat principle, meaning that all post-randomization data for a subject will be used in the analysis and allocated to the arm the subject was randomized to. Only data on or prior to the 18 month visit will be included. Hospitalizations with admission dates equal to the 18 month visit will be included. All randomized subjects will be included in the analysis provided they are not documented to violate the following inclusion criteria:

- Subjects with severe COPD exclusion criterion
- Subjects with chronic renal failure needing renal dialysis exclusion criterion
- Heart failure inclusion criterion:
  - Subjects have stable NYHA II/III CHF for at least 30 days, AND
  - most recent LVEF in the prior 6 months to randomization is at most 35%, AND
  - they either have at least one HF hospitalization within the prior 12 months OR one course of ambulatory IV or oral diuretic treatment OR have a BNP value of > 400 pg/mL OR a NT-proBNP value exceeding the age-specific requirement

3.3.10 Ancillary Objective #2: CV Hospitalizations

3.3.10.1 Hypothesis

Let $\lambda_{Control}(t)$ denote the hazard function for first CV hospitalization among study-eligible patients not receiving "OptiLink" (CareLink + Optivol CareAlerts + HF Management Report), and let $\lambda_{Alert}(t)$ denote he corresponding hazard function among study-eligible patients whose treatment can be influenced by "OptiLink". The hypotheses for the primary objective are:

H_0: $\lambda_{Control}(t) = \lambda_{Alert}(t)$ for all $0 \le t \le 18$, and
H_A: $\lambda_{Control}(t) \neq \lambda_{Alert}(t)$ for some $0 \le t \le 18$

A. Rationale for Choice of Hypothesis
Because subjects initially consented to be followed for only 18 months and many did not re-consent to be followed beyond that point, the scope of the objective is restricted to the time frame from randomization to 18 months, unless conditions are met as specified in section 3.2.1, as there may be bias in which subjects elected to re-consent for longer follow-up.

3.3.10.2 Endpoint Definition

There are two endpoints for this objective. The first endpoint will be defined as the time from randomization until the minimum of first CV hospitalization and last point of contact on or prior to the 18 month visit. If a subject exits prior to the 18 month visit and the reason for exit is not that the subject was lost to follow-up, the date of exit will be considered the last point of contact.

A cardiovascular hospitalization is defined in section 3.2.1.2.

Hospitalizations will be adjudicated by an events committee to determine if they satisfy these criteria. Hospitalizations for elective CV procedures, such as planned admissions for elective cardioversion of atrial fibrillation, do not qualify and will be excluded. If a subject does not experience a CV hospitalization endpoint as of the endpoint date, the subject will be considered censored at that date. Kaplan-Meier curves will be generated for all four randomization arm/device group combinations.

The second endpoint will be an expansion of the first, and include the time between consecutive CV hospitalizations for those subjects who experience multiple CV hospitalizations within their first 18 months of follow-up. The time will be defined as time between discharge of one visit and admission of the next consecutive visit. Additionally, the time between the last CV hospitalization within the first 18 months of follow-up and the date of death or last contact on or prior to 18 month visit will be included in the analysis.

3.3.10.3 Analysis Methods

A. Statistical Methodology

Under the proportional hazards assumption,

$$\lambda_{Alert}(t) = \theta\lambda_{Control}(t) \text{ for all } t > 0$$

The parameter of interest is the proportionality measure, θ, also known as the hazard ratio.

For comparing the time to first CV hospitalization between randomization arms, a two-sided stratified log-rank test will be used, with device group (CRT-D vs. ICD), NYHA (II/III), Ischemic/Non-ischemic status, history of AF, and history of VT/VF serving as strata in case the hazard rate for time to first CV hospitalization differs by device group. The test will not assess the impact of device group on hazard rates; it will simply allow the baseline rate ($\lambda_{Control}$) to differ by device group but will assume that the "OptiLink" vs. No "OptiLink" hazard ratio (θ) is the same between the two device groups. The test will be performed with $\alpha = 0.05$.

To compare the randomization arms allowing for multiple CV hospitalizations per subject, a Prentice Williams Peterson (PWP) proportional hazards regression model will be applied to test for a significant difference between the hazard rates of the two therapy arms. The model above will be stratified by device group (CRT-D vs. ICD), and if the p-value for the coefficient, θ (the hazard ratio), is less than 0.05, then it will be concluded that the hazard rate for CV hospitalizations among study-eligible patients with "OptiLink" is different from that of the corresponding hazard rate for study-eligible patients without "OptiLink".

B. Determination of Patients/Data for Analysis

The analysis will be performed using the Intent to Treat principle, meaning that all post-randomization data for a subject will be used in the analysis and allocated to the arm the subject was randomized to. Only data on or prior to the 18 month visit will be included. Cardiovascular hospitalizations with admission dates equal to the 18 month visit will be included. All randomized subjects will be included in the analysis provided they are not documented to violate the following inclusion criteria:

- Subjects with severe COPD exclusion criterion
- Subjects with chronic renal failure needing renal dialysis exclusion criterion
- Heart failure inclusion criterion:
  - Subjects have stable NYHA II/III CHF for at least 30 days, AND
  - most recent LVEF in the prior 6 months to randomization is at most 35%, AND
  - they either have at least one HF hospitalization within the prior 12 months OR one course of ambulatory IV or oral diuretic treatment OR have a BNP value of > 400 pg/mL OR a NT-proBNP value exceeding the age-specific requirement

3.3.11 Ancillary Objective #3: All-cause Hospitalization/All-cause Mortality

3.3.11.1 Hypothesis

Let $\lambda_{Alert}(t)$ denote the hazard rate function for freedom from all-cause mortality and hospitalizations among study-eligible patients receiving "OptiLink" (CareLink + Optivol CareAlerts + HF Management Report), and let $\lambda_{Control}(t)$ denote the corresponding hazard rate function among study-eligible patients not receiving "OptiLink". The hypotheses for the primary objective are:

H_0: $\lambda_{Control}(t) = \lambda_{Alert}(t)$ for all $0 \le t \le 18$, and

H_A: $\lambda_{Control}(t) \neq \lambda_{Alert}(t)$ for some $0 \leq t \leq 18$

A. Rationale for Choice of Hypothesis

Because subjects initially consented to be followed for only 18 months and many did not re-consent to be followed beyond that point, the scope of the objective is restricted to the time frame from randomization to 18 months, unless conditions are met as specified in section 3.2.1, as there may be bias in which subjects elected to re-consent for longer follow-up.

3.3.11.2 Endpoint Definition

The endpoint will be defined as the time from randomization until the minimum of death, first hospitalization, and last point of contact on or prior to the 18 month visit. If a subject exits prior to the 18 month visit and the reason for exit is not that the subject was lost to follow-up, the date of exit will be considered the last point of contact.

A hospitalization is defined as a therapeutic, in-patient hospitalization extending over a calendar date change where admission occurs after consent, and which is not considered elective. Hospitalizations for elective CV procedures, such as planned admissions for elective cardioversion of atrial fibrillation, do not qualify.

If a subject does not experience a hospitalization as of the endpoint date, the subject will be considered censored at that date.

3.3.11.3 Analysis Methods

A. Statistical Methodology

Under the proportional hazards assumption,

$$\lambda_{Alert}(t) = \theta\lambda_{Control}(t) \text{ for all } t > 0$$

The parameter of interest is the proportionality measure, θ, also known as the hazard ratio.

For comparing the time to death or first hospitalization between randomization arms, a two-sided stratified log-rank test will be used, with device groups (CRT-D vs. ICD), NYHA (II/III), Ischemic/Non-ischemic status, history of AF, and history of VT/VF serving as strata in case the baseline hazard rate($\lambda_{Control}$) for time to death or hospitalization differs by device group. The test will not assess the impact of device group on hazard rates; it will simply allow the baseline rate ($\lambda_{Control}$) to differ by device group but will assume that the "OptiLink" vs. No "OptiLink" hazard ratio (θ) is the same between the two device groups. The test will be performed with $\alpha = 0.05$. Kaplan-Meier curves will be generated for all four randomization arm/device group combinations.

B. Determination of Patients/Data for Analysis

The analysis will be performed using the Intent to Treat principle, meaning that all post-randomization data for a subject will be used in the analysis and allocated to the arm the subject was randomized to. Only data on or prior to the 18 month visit will be included. Hospitalizations with admission dates equal to the 18 month visit will be

included. All randomized subjects will be included in the analysis provided they are not documented to violate the following inclusion criteria:

- Subjects with severe COPD exclusion criterion
- Subjects with chronic renal failure needing renal dialysis exclusion criterion
- Heart failure inclusion criterion:
  - Subjects have stable NYHA II/III CHF for at least 30 days, AND
  - most recent LVEF in the prior 6 months to randomization is at most 35%, AND
  - they either have at least one HF hospitalization within the prior 12 months OR one course of ambulatory IV or oral diuretic treatment OR have a BNP value of > 400 pg/mL OR a NT-proBNP value exceeding the age-specific requirement

4 APPENDIX: HEALTH ECONOMIC ANALYSIS PLAN

Project managed by ***Alpha Care GmbH***

ALPHA CARE
HEALTHCARE RESEARCH AND CONSULTING

Client:	Medtronic
Project Title :	Health Economic Analysis of Optilink-HF Study
Project Number :	233
Issued by :	Dr. Bernd Brüggenjürgen
Submitted on :	30.11.08 Version 1st Draft

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Cover
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Project Title: Health Economic Analysis of Optilink-HF Study
Project No: 233

1. Background

The objective of the study is to establish whether the use of event-triggered HF-disease management through Medtronic's OptiVol® fluid status monitoring with an automatically generated wireless CareAlert® notification of the clinician via the Medtronic CareLink® Network can reduce cardiovascular related hospitalizations and the number of deaths in a subject population with HF and ICD / CRT-D treatment as compared to standard clinical assessment. As a measure for the reduction of hospitalizations and deaths the rate of all-cause deaths or cardiovascular related hospitalizations will be determined.

The health economic analysis will provide substantial input for assessing the value of the Optimization of Heart Failure Management using Medtronic OptiVol® Fluid Status Monitoring and Medtronic CareLink® Network in Germany. Despite being reimbursed in Germany economic data would be supportive for an appropriate use of the technology and potential future negotiation as well as adaptation in other markets. The major share of the major markets has established or is establishing cost-benefit assessments. Whilst in the UK cost-utility assessment with QALYs are well accepted, in France and Germany cost-effectiveness analyses are preferred with Germany being currently still in the early consideration or development phase of official mandatory guidelines for all health technologies. That is why different kinds of health economic approaches will be applied (see economic analyses).

2. Health economic perspective

The primary health economic perspective is a payer perspective including direct costs and patient burden.

3. Timeframe of health economic assessment

All study information for the 18 months period will be used for complementing the required economic data.

4. Sources of economic data

The economic data on unscheduled resource use and costs due to hospitalization and alert-related visits will be collected directly from the participating healthcare providers (who will supply data on treatment resources/costs, main diagnoses and procedures, if available ICD, OPS, or DRG) and the patients themselves (who will supply data on consultation resource

consumption behaviour, e.g. physician visits) using patient's questionnaires.

5. Resource Measurement

For cost determination of the economic evaluation, the bottom-up approach will be used (figure 1). The first step is the patient's individual resource measurement (see the attached questionnaires).

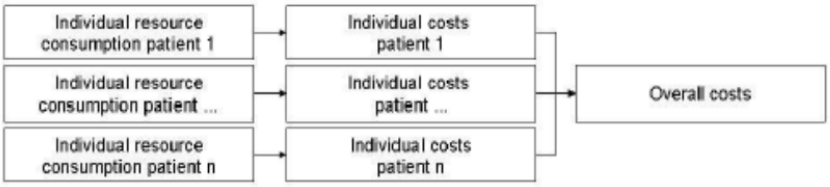

Figure 1. Bottom-up cost modelling

This resource measurement is focused on the following health care utilization:

Direct resource use:

- Hospital stays
- Rehabilitation inpatient/outpatient (from patient)
- Physician visits (from patient)
- Use of medication (to be derived from study information)
- Home or institutional care
- Adjuvant therapy, aids and remedies (to be derived from study information):

6. Resource separation into diagnose specific and overall resource use

The resource use will be mainly measured in an overall approach, regardless of the disease on which it is based upon. Additional a distinction will be made, whether a resource use is allocated to heart failure (or related with this disease), or the documented resource consumption is untouched by this condition.

7. Cost determination

After the measurement of resource consumption, it becomes necessary to include a monetary valuation (see figure 1). This valuation will take individual and (if adaption to other countries is planned) country specific cost characteristics into account.

Direct costs:

- Hospitalizations
  As far it will be possible from participating study centres to obtain the main ICD-codes and OPS-procedures to verify a DRG
  Number of hospital days outside the study centre or in a rehabilitation clinic will be multiplied with a fixed rate.

- Inpatient Rehabilitation
  Number of hospital days outside the study centre or in a rehabilitation clinic will be multiplied with a fixed rate.

- Physician visits
  The number of physician contacts will also be multiplied with a fixed monetary rate. This rate should represent the average cost incurred by one doctor's visit. For the German setting, such rates are available from statistics of the German Association of Statutory Health Insurance Physicians (Kassenärztliche Vereinigung).

- Use of medication
  Each day of medication use will be multiplied with costs of a daily-defined dosage (if no further detailed data are available). If these costs are not available, the medication intake recommendation of the country specific pharmacopoiea (e.g. Rote/Gelbe Liste in Germany) will be applied.
  For the German setting, the costs of a daily defined dose were available from the annual published pharmaceutical prescriptions report (Arzneiverordnungsreport).

- Adjuvant therapy and remedies
  For measurement of adjuvant therapies and remedies, a fixed cost rate will be used. The number of different adjuvant therapies and remedies will multiplied with this rate for calculating the occurred costs.

8. Economic analyses

The economic analysis will be based on a predefined analysis structure (see following figure).

Project Title: Health Economic Analysis of Optilink-HF Study
Project No: 233

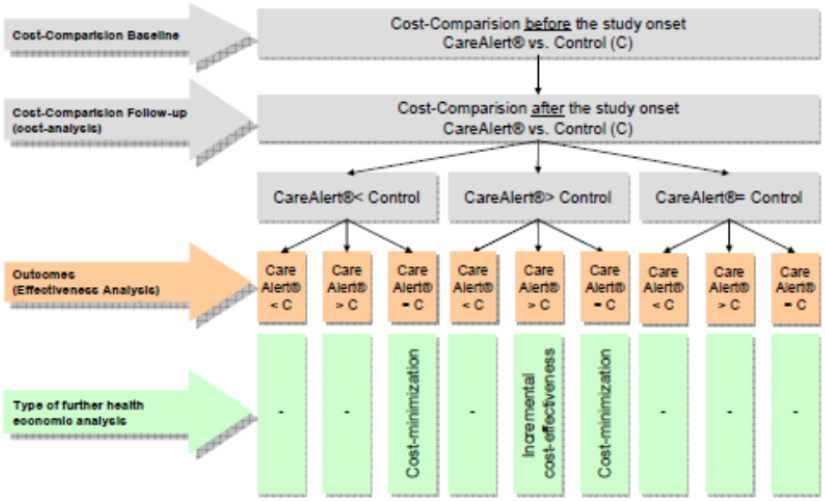

Figure 2. Health economic analyses flowchart

8.1 Cost-comparison analyses

The first step entails analysing costs at baseline to identify potential cost-differences between the groups prior to study onset. If any differences are observed, a statistical adjustment could be performed for the following analyses. The second step is the cost-evaluation, which will be performed at predefined follow-up dates and for the full study period.

8.2 Cost-effectiveness analyses

A direct comparison of outcomes and related costs will be performed as a next step. For this, the relation of costs and outcomes will be calculated using the following formula:

Cost-effectiveness relation = costs / outcomes

Both a cost-effectiveness-analysis (CEA based on the KCCQ) and a cost-utility-analysis (CUA based on the EQ-5D) will be performed. The effectiveness parameter is based on the secondary endpoints and will be translated into "gained time without hospitalization" or "number of hospitalizations avoided". As a further patient relevant outcome the quality of

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sleep could be chosen for the cost-effectiveness analysis. As an outcome-parameter for cost-utility analyses (which is a special kind of cost-effectiveness analyses), the quality-adjusted-life years (QALYs) derived from the EQ-5D will be used.

8.3 Incremental cost-effectiveness analyses

If the CareAlert® -treatment is both, more effective and more costly, additional incremental cost-effectiveness (based on KCCQ and EQ-5D) analyses will be performed. The differences in costs and effects will be compared between the two groups and the incremental cost-effectiveness ratio (ICER) will be calculated using the following relation(1):

ICER = [costs (CareAlert®) – costs (control)] / [effects (CareAlert®) – effects (control)]

The ICER shows the additional costs for one extra KCCQ score / QALY (quality adjusted life year) gained compared to control treatment. The ICER could be measured against a societal threshold value λ, which is often described as society's willingness to pay for one QALY gained. In the UK, a threshold of £30,000 to QALY has been found to be consistent with decisions for adopting new technologies by NICE (2). In Germany, a comparable threshold does not yet exist. As a benchmark, an arbitrary and hypothetical threshold of max. €50,000 per QALY could be used. If the ICER is below such a threshold value, the treatment can be regarded as cost-effective. Some further input are expected over the next year from the introduction period at the IQWiG

In addition, cost-effectiveness acceptability curves could be carried out by applying the net benefit approach (3; 4):

Net benefit = (threshold value λ * [effects (CareAlert®) – effects (control)])
- [costs (CareAlert®) – costs (control)]

For a given value of λ, an intervention can be considered cost-effective if its net benefit is greater than zero (i.e. the ICER is below λ). The results on costs and effectiveness will be bootstrapped (see statistical analyses) and transformed into net benefit values under varying threshold values. Subsequently, the results can be plotted in cost-effectiveness acceptability curves. Under a Bayesian framework, the cost-effectiveness acceptability curve shows the probability that the incremental cost-effectiveness will be below λ for a whole range of values of λ.

8.4 Cost minimization analysis

If the effectiveness of CareAlert®-treatment and the control treatment is similar, the less costly treatment will be recommended in terms of a cost-minimisation analysis approach.

8.5 Sensitivity analyses

Additional sensitivity analyses will be performed to assess the effect of realistic variations in important impact variables, thus improving the validity of our results. In this context, Monte-Carlo simulations are well established along health economic modelling and are useful for the present project. (5) For these purposes, important variables will be diversified simultaneously and randomly within their 95% confidence intervals.

9. Statistical analysis

An ANCOVA will be applied with age, gender, study centre, as well as cost-differences at baseline as covariates to estimate costs and cost differences between the groups during the follow up period.
To derive cost-effectiveness acceptability curves (see incremental cost effectiveness analyses) we will use non-parametric bootstrapping. (6) The original sample will be bootstrapped 1,000 times to obtain 1,000 means for cost and effect differences and the resulting ICERs. These bootstrap results can used to build the cost-effectiveness acceptability curves as described in the incremental cost effectiveness section above.
For inferential statistics, we will use SPSS©. Finally, we will use MS EXCEL© to model cost-effectiveness analyses for patient subgroups and to perform the additional sensitivity analyses. Furthermore, significance level of $p<0.05$ will be considered.

10. References

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Executive Board

The Executive Board consists of 7 physicians and 1 member of the sponsor study team.

Event Adjudication Committee (EAC)

The Event Adjudication Committee consisting of 3 independent physicians to adjudicate events for study objectives and document event classifications.

The event committee members did not otherwise participate in the study. Medtronic personnel did facilitate the EAC sessions (e.g. statistician, clinical trial leader), but they were not voting members. The EAC was not made aware of the randomization assignment of study subjects.

Data Safety Monitoring Board (DSMB)

An independent Data Safety Monitoring Board has reviewed the interim data analyses as well as periodically reviewed the total incidence of AEs and deaths in this study. The DSMB for this study consisted of members with study related backgrounds. Medtronic personnel facilitated the DSMB sessions (e.g. clinical trial leader, statistician), but they were not voting members.

Executive Board

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Data Safety Monitoring Board

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Participating German Centres and Investigators

Study Center	Investigator	Site-ID	Total Number of Enrollments
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Klinikum Coburg gGmbH **II. Medizinische Klinik** Ketschendorfer Str. 33 96450 Coburg	**Prof. Dr. med. Brachmann** **Vice-Priciple Investigator**	0201	71
Kardiologische Praxis Kochstedter Kreisstrasse 11 06847 Dessau	**Dr. med. Rybak**	0401	64
Evangelisches Krankenhaus Bielefeld Klinik für Innere Medizin - Kardiologie und Angiologie Burgsteig 13 33617 Bielefeld	**PD Dr. med. Israel**	5201	55
Klinikum Universität München - Großhadern Med. Klinik & Poliklinik IMarchioninistr. 15 81377 München	**PD Dr. med. Käab**	2301	54
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Marienhaus GmbH Neuwied Friedrich-Ebert-Str. 59 56564 Neuwied	**Dr. med. Huegl**	0701	40
Klinikum Dortmund gGmbH Medizinische Klinik Mitte – Kardiologie Beurhausstrasse 40 44137 Dortmund	**Prof. Dr. med. Heitzer**	3901	38
Segeberger Kliniken GmbH Herz-Kreislauf-Zentrum Am Kurpark 1 23795 Bad Segeberg	**Dr. med. Seivani**	0901	33
Kardiologische Praxis Asperger Strasse 48 71634 Ludwigsburg	**PD Dr. med. Bosch**	0501	32
Asklepios Kliniken Schwalm-Eder GmbH Klinikum Schwalmstadt-Ziegenhain Krankenhausstrasse 27 34613 Schwalmstadt	**Dr. med. Puplat**	2601	31

Study Center	Investigator	Site-ID	Total Number of Enrollments
Kardiologische Praxis Hoheneggerstrasse 9 76646 Bruchsal	**Dr. med. Ringwald**	2802	25
Universitätsklinikum Rostock - Kardiologie – Ernst-Heydemann-Strasse 6 18057 Rostock	**Prof. Dr. med. Bänsch**	4501	19
Universitätsklinikum des Saarlandes Innere Medizin III Kirrberger Strasse 66421 Homburg / Saar	**Prof. Dr. med. Böhm** **Principle Investigator**	2001	19
Herz- und Diabeteszentrum NRW - Klinik für Kardiologie Georgstrasse 11 32545 Bad Oeynhausen	**Dr. med. Heintze**	1001	19
Klinikum Ingolstadt GmbH Krumenauerstrasse 25 85049 Ingolstadt	**Prof. Dr. med. Seidl**	5701	18
Klinikum Lippe-Detmold GmbH Kardiologie und Angiologie Röntgenstrasse 18 32756 Detmold	**Prof Dr. med. Tebbe**	4901	18
Universitätsklinikum Aachen Med. Klinik I Pauwelsstrasse 30 52074 Aachen	**PD Dr. med. Mischke**	1601	18
St.-Marien-Hospital Lünen Altstadtstrasse 2 44534 Lünen	**PD Dr. med. Perings**	1501	18
Lukaskrankenhaus GmbH Medizinische Klinik I Preussenstrasse 84 41464 Neuss	**Prof. Dr. med. Haude**	0301	18
Kardiologische Praxis John-Brinckmann-Strasse 8-10 19370 Parchim	**Dr. med. Knapp**	3402	16
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Klinikum Fulda gAG Medizinischen Klinik I - Pacelliallee 4 36043 Fulda	**Prof. Dr. med. Schächinger**	4801	15
Universitätsklinikum Giessen Med. Klinik I Klinikstrasse 36 35385 Gießen	**Dr. med. Schmitt**	2901	15
Universitätsklinikum Hamburg-Eppendorf Universitäres Herzzentrum Martinistrasse 52 20246 Hamburg	**Prof. Dr. med. Willems**	5801	14

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Universitätsklinikum Essen Kardiologie Hufelandstrasse 55 45122 Essen	**Prof. Dr. med. Erbel**	5901	9
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Kardiologische Praxis Bahnhofstraße 18 ¼ 86150 Augsburg	**Dr. med. Nagel**	4602	6
Kardiologische Praxis Am Bahnhof 3 56841 Traben-Trarbach	**Dr. med. Fossmeyer**	0603	6
Kardiologische Praxis Kirchstraße 33 72622 Nuertingen	**Dr. med. Ruppert**	0512	6
Krankenhaus Buchholz Innere Medizin / Kardiologie Steinbecker Strasse 44 21244 Buchholz	**Dr. med. Raut**	3701	5
Klinikum Friedrichshafen GmbH Med. Klinik II Röntgenstrasse 2 88048 Friedrichshafen	**PD Dr. med. Jäger**	2201	5

Study Center	Investigator	Site-ID	Total Number of Enrollments
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Kardiologische Praxis Bahnhofsplatz 2 96450 Coburg	**Dr. med. Keller**	0202	4
Kardiologische Praxis Hauptstrasse 91 76571 Gaggenau	**Dr. med. Markert**	2803	4
Kardiologische Praxis Im Vogelsang 5-11 45527 Hattingen	**Dr. med. Jochheim**	1409	4
Kardiologische Praxis Donaustrasse 78 87700 Memmingen	**Dr. med. Jochham**	2206	4
Klinikum der Johannes Gutenberg-Universität Mainz 2. Medizinische Klinik & Poliklinik Langenbeckstrasse 1 55131 Mainz	**Prof. Dr. med. Muenzel**	0601	4
Klinikum Nürnberg Süd Med. Klinik 8 – Kardiologie Breslauer Strasse 201 90471 Nürnberg	**Dr. med. Göhl**	3501	3
Charité Campus Benjamin Franklin Klinik II - Kardiologie & Pneumologie Hindenburgdamm 30 12207 Berlin	**Prof. Dr. med. Schultheiss**	3401	3
Märkische Kliniken GmbH Kardiologie Paulmannshöher Strasse 14 58515 Lüdenscheid	**Prof. Dr. med. Lemke**	1701	3
Kardiologische Praxis Langenbeckplatz 2 65189 Wiesbaden	**Dr. med. Mahr**	0605	2
Städtisches Klinikum Lüneburg gGmbH Klinik für Kardiologie Bögelstrasse 1 21339 Lüneburg	**Prof. Dr. med. Weiss**	4701	2
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Study Center	Investigator	Site-ID	Total Number of Enrollments
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Kardiologische Praxis Uerdingerstrasse 62 47799 Krefeld	**Dr. med. Fahlenbrach**	0302	2
Städtisches Klinikum München – Schwabing Kardiologie Kölner Platz 1 80804 München	**Prof. Dr. med. Sack**	4301	1
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Berufsgenossenschaftliche Kliniken Bergmannsheil Kardiologie & Angiologie Burkle-de-la-Camp Platz 1 44789 Bochum	**Dr. med. Lawo**	1401	1
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Kardiologische Praxis Tiergartenstrasse 105 30559 Hannover	**Dr. med. Hartung**	0104	Only Follow-Up
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Study Center	Investigator	Site-ID	Total Number of Enrollments
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Kardiologische Praxis Ladeburger Strasse 20 16321 Bernau	**Dr. med. Gola**	0804	Only Follow-Up
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Kardiologische Praxis Hansastrasse 59 44137 Dortmund	**Dr. med. Landgraf**	3902	Only Follow-Up
Kardiologische Praxis Hansastrasse 59 44137 Dortmund	**Dr. med. Fadgyas**	3904	Only Follow-Up
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