

# Fluid status monitoring with a wireless network to reduce cardiovascular-related hospitalizations and mortality in heart failure: rationale and design of the OptiLink HF Study (Optimization of Heart Failure Management using OptiVol Fluid Status Monitoring and CareLink)

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Received 13 December 2010; revised 1 February 2011; accepted 4 February 2011; online publish-ahead-of-print 8 May 2011

## Aims

The Optimization of Heart Failure Management using OptiVol Fluid Status Monitoring and CareLink (OptiLink HF) study is designed to investigate whether OptiVol fluid status monitoring with an automatically generated wireless CareAlert notification via the CareLink Network can reduce all-cause death and cardiovascular hospitalizations in an HF population, compared with standard clinical assessment.

## Methods

Patients with newly implanted or replacement cardioverter-defibrillator devices with or without cardiac resynchronization therapy, who have chronic HF in New York Heart Association class II or III and a left ventricular ejection fraction  $\leq 35\%$  will be eligible to participate. Following device implantation, patients are randomized to either OptiVol fluid status monitoring through CareAlert notification or regular care (OptiLink 'on' vs. 'off'). The primary endpoint is a composite of all-cause death or cardiovascular hospitalization. It is estimated that 1000 patients will be required to demonstrate superiority of the intervention group to reduce the primary outcome by 30% with 80% power.

## Conclusion

The OptiLink HF study is designed to investigate whether early detection of congestion reduces mortality and cardiovascular hospitalization in patients with chronic HF. The study is expected to close recruitment in September 2012 and to report first results in May 2014.

ClinicalTrials.gov Identifier: NCT00769457

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† In memoriam.

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**Keywords**

Chronic heart failure • Disease management • Telemedicine • Cardiac resynchronization therapy • Implantable defibrillator • Bioimpedance

**Introduction**

In patients with advanced heart failure (HF), hospital admissions are frequently associated with poor survival and are often preceded by pulmonary congestion, due to pulmonary fluid accumulation.<sup>1,2</sup> The use of implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy (CRT) systems has been shown to reduce hospitalizations and mortality, and to improve cardiac function, exercise tolerance and quality of life (QoL) in HF patients.<sup>3–6</sup>

Chronic HF remains a large medical and epidemiological problem.<sup>7</sup> Despite significant improvements in pharmacological treatment, morbidity and mortality are still high,<sup>8</sup> and in recent years, relatively few new approaches have proven beneficial. Device therapy, in particular ICD and the biventricular pacemaker (generally referred to as CRT), used either alone or in combination (CRT defibrillator or CRT-D), has gained increasing acceptance and is now implemented on a large scale. The first ICD study, which included patients with mild-to-moderate HF, was the SCD-HeFT (Sudden Cardiac Death in Heart Failure) Trial;<sup>4</sup> it showed that implantation of an ICD caused a 23% reduction in all-cause mortality, the primary endpoint of the study. Previous and current guidelines<sup>7,9</sup> regarding the place of ICD therapy in chronic HF are for an important part based on this study. For the place of CRT in HF, two other studies are of primary importance: the COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) trial<sup>5</sup> and the CARE-HF (Cardiac Resynchronization-Heart Failure) trial.<sup>10</sup> Implantation rates of devices for HF, particularly ICD and CRT-D, increased significantly between 2004 and 2008 in Europe, but there remain major differences between countries.<sup>11</sup>

A new generation of modern ICD- and CRT-D-systems allows the evaluation of pulmonary fluid status by measuring intrathoracic impedance. The OptiVol fluid status monitoring algorithm (Medtronic Inc, Minneapolis, MN, USA) detects changes in thoracic impedance resulting from accumulation of intrathoracic fluid as early signs of cardiac decompensation. Equipped with this dedicated algorithm, patients are automatically and audibly alerted if intrathoracic impedance drops below a certain threshold.<sup>12,13</sup>

In HF patients, intrathoracic impedance measurement has been shown as a useful tool for monitoring pulmonary fluid status, detecting HF deterioration, and predicting cardiac decompensation before it becomes symptomatic.<sup>14–16</sup> When combined with modern data-transmitting technology, information can be monitored and transmitted immediately to caregivers who can then react quickly to prevent worsening of symptoms and subsequent hospitalization.<sup>17,18</sup> The CareLink Network (Medtronic Inc, Minneapolis, MN, USA) data-transmitting technology system is suitable for OptiVol-generated signals. CareLink device data can either be transmitted automatically via wireless Conexus Telemetry (Medtronic Inc, Minneapolis, MN, USA) or manually. Transmitted data

can either lead to the patient having an unscheduled in-office follow-up visit or can be used to reassure the physician that an in-office follow-up visit is not required.

The Optimization of Heart Failure Management using OptiVol Fluid Status Monitoring and CareLink (OptiLink HF) study is designed to evaluate whether the combination of OptiVol Fluid Status Monitoring and automatically generated CareAlerts through the CareLink Network can reduce mortality and cardiovascular hospitalizations. This article presents the rationale and the design of the OptiLink HF trial.

**Study design****Treatment**

The OptiLink HF trial is a prospective, multi-centre, unblinded, randomized study that aims to compare early detection of fluid overload by OptiVol monitoring linked to automatically generated wireless CareAlert notification of the clinician via the CareLink Network, with standard clinical assessment. Thirty-seven German centres with high experience in implantation and follow-up treatment of ICD and CRT-D systems and 85 out-patient clinics with access to the CareLink Network are participating in the trial.

Patients with stable chronic HF, implanted with single- or dual-chamber ICD devices (Virtuoso, Medtronic Inc, Minneapolis, MN, USA), or CRT systems with ICD function (CRT-D, Concerto, Medtronic Inc, Minneapolis, MN, USA) or any subsequently released devices that provide at least the same functionality, can be included in the study. After inclusion, patients will be randomized in a 1:1 fashion between CareLink access with CareAlert in case of OptiVol fluid index threshold crossing (access arm) and standard treatment without CareLink access and no CareAlert in case of OptiVol fluid index threshold crossing (control group). Neither group will have any audible OptiVol patient alerts.

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 HF hospitalization) vs. pre-clinical events and/or premature alerts/too early alerts. Increasing the threshold will reduce the number of alerts, but may also delay or prevent some clinically relevant alerts. Conversely, reducing the threshold will increase the number of alerts, but a larger portion may be clinically less meaningful.

Through CareLink the responsible clinician can also be alerted about heart rhythm conditions associated with atrial tachyarrhythmia (AT) and atrial fibrillation (AF) ('AT/AF alerts'). These AT/AF alerts, intended to monitor and convey heart rate and characteristics of AT and AF, will be programmed 'OFF' during the study.

**Patients**

Eligible patients can be of either sex, with a newly implanted or replacement Virtuoso single-, dual-chamber ICD, or Concerto

**Table 1 Inclusion and exclusion criteria****Inclusion criteria**

- Patients implanted with a new or replacement with Virtuoso single-, dual-chamber ICD or Concerto CRT-D or subsequently market-released Medtronic device providing at least the same functionality
- Subjects with CRT-D must fulfil CRT-indication (as described in ESC guidelines for cardiac pacing and cardiac resynchronization therapy<sup>19</sup>): EF  $\leq$  35% and NYHA III, and LVEDD  $>$ 55 mm, and QRS  $\geq$  120 ms, and optimized therapy
- Stable chronic HF NYHA class II or III for at least 30 days and LVEF  $\leq$  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,  $\beta$ -blockers and diuretics if clinically indicated to reduce fluid retention and one of the following criteria:
  - at least one hospitalization due to the HF within the last 12 months before enrolment
  - or one course of ambulatory intravenous diuretic treatment
  - or a BNP value  $>$ 400 pg/mL
  - or a NT-proBNP value  $>$ 450 pg/mL (in subject  $<$ 50 years),  $>$ 900 pg/mL (50–75 years) and  $>$ 1800 pg/mL (in subject aged  $>$ 75 years) within 30 days of enrolment

**Exclusion criteria**

- Chronic renal failure requiring dialysis
- Serum creatinine  $>$ 2.5 mg/dL, measured within 14 days prior to enrolment
- Severe COPD as determined by physician and documented in medical records (Stage III and Stage IV), suspected or confirmed COPD should have 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
- Listing for heart transplantation or subjects with transplanted hearts
- Planned valve replacement or interventional valve therapy
- MI within the last 40 days before implantation. MI is defined by typical changes in biochemical markers including troponin levels  $>$ 3 times the upper limits of normal and creatine 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 ischaemic symptoms, ECG changes consistent of diagnostic ST–T wave changes or pathological Q waves or new LBBB
- Stroke within 40 days prior to randomization
- Percutaneous coronary intervention within 3 months prior to randomization
- Cardiac surgery within 90 days of randomization
- Complex and uncorrected congenital heart disease
- Life expectancy less than 18 months in the opinion of the physician
- Situations limiting 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 enrol in a study that would preclude use of the monitor)

ACE, angiotensin-converting enzyme; BNP, brain natriuretic peptide; CKMB, creatine kinase isoenzyme MB; COPD, chronic obstructive pulmonary disease; CRT(-D), cardiac resynchronization treatment (-defibrillator); ECG, electrocardiogram; EF, ejection fraction; ESC, European Society of Cardiology; HF, heart failure; ICD, implantable cardioverter defibrillator; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association.

CRT-D device or other subsequently market-released Medtronic device. Heart failure should be New York Heart Association (NYHA) class II or III and left ventricular ejection fraction (LVEF)  $\leq$ 35%. Detailed inclusion and exclusion criteria are listed in *Table 1*.

The study aims to recruit 60% subjects with NYHA class III and 40% with NYHA class II.

## Study endpoints

The primary endpoint of the OptiLink HF trial is the occurrence of all-cause death or an unplanned admission to hospital for a cardiovascular reason, from the day of enrolment for device implantation until the 18-month follow-up visit.

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 (supraventricular or ventricular arrhythmias);
- stroke or cerebral vascular accident.

Hospitalizations for elective cardiovascular procedures do not qualify as endpoints; this includes planned admission for elective cardioversion of AF.

Secondary endpoints of the OptiLink HF study include:

- (1) all-cause mortality;
- (2) heart failure-related hospitalization;
- (3) cardiovascular mortality;
- (4) sum of follow-up days minus days alive and out of the hospital;
- (5) all-cause hospitalization during follow-up;
- (6) heart failure-related hospitalization and all-cause mortality;
- (7) quality of life;
- (8) health economics.

## Enrolment and randomization

Enrolment is performed 3–21 days after ICD/CRT-D device implantation or replacement. Enrolled subjects who fail to meet the eligibility criteria will not be randomized. If a failure to meet eligibility the criteria is discovered after randomization, the subject will remain in the study according to the intention-to-treat (ITT) principle.

Subjects are randomized directly after enrolment. Randomization is risk stratified by NYHA class II/III (40% NYHA class II/60% NYHA class III), ischaemic/non-ischaemic cardiovascular disease, AF and the occurrence of ventricular tachycardia (VT)/ventricular fibrillation (VF) episodes before implantation.

Subjects randomized to the access arm will be enrolled in the CareLink Network within 25 days after implantation. In order to ensure CareLink functionality, subjects will be trained on usage of the CareLink monitor.

## Study procedures

Clinical data are collected at baseline/enrolment, randomization, and scheduled follow-up visits at 6 months and every 6 months thereafter until study closure or subject death/exit. Data collection will be performed via standard case report forms (CRFs), device interrogation, and save-to-disk storage (control arm). In the access arm, device interrogation and save-to-disk storage will be replaced by data transmission to the CareLink Network.

Study centre personnel will verify the status of all cardiovascular medications at baseline/randomization, each follow-up visit, each telephone contact, in case of hospitalization or an adverse event (AE) and at study exit. Recommended changes to medication during visits, AE situations or hospitalization will be recorded on the CRF.

The health status of subjects will be assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ)<sup>20</sup> and the EQ-5D questionnaire (standardized measure of health status developed by the EuroQoL Group).<sup>21</sup> Patients will complete the questionnaires after signing the informed consent form, but before randomization, and during specified follow-up visits.

## Health economics

A payer perspective covering the major cost drivers of hospitalization, emergency department visits, medication, and 'out-patient' visits will be used. Healthcare utilization based on emergency department visits, hospitalizations, out-patient visits, and all further utilization of healthcare resources will be collected based on discharge summaries (if applicable) and CRF-based information. Utilization of medication will be based on information recorded on the CRF at follow-up visits or during any other patient contacts. Life expectancy will be derived from mortality data collected within the trial.

## Follow-up

During follow-up, patients are monitored by personal visits to the clinic and via other contacts. Follow-up is required at 6 months, and then every 6 months post-randomization, until study closure, or subject exit due to death or other causes. The follow-up schedule is shown in *Figure 1*. During these follow-up visits,

interrogation of the device allows monitoring of the condition of the therapy system and of the patient's clinical status. In addition, QoL questionnaires (KCCQ and EQ-5D) are collected at the 6-month routine follow-up visit and at the 18-month routine follow-up/study exit visit.

Any interim/additional contacts with the patient are at the discretion of the individual centre and may include follow-up both for technical ICD/CRT-D device testing and/or for HF management. Additional data will be collected during unscheduled office visits, emergency department visits, hospitalizations, data associated with an intervention algorithm, telephone contacts, system modifications, AEs, study deviations and study exit/death.

In order to assure a reliable function of data transmission via CareLink for subjects in the access arm, study personnel are strongly advised to use the calendar on the CareLink clinician website to schedule automatically transferred CareLink transmissions through Conexus.

## Adverse events and hospitalizations

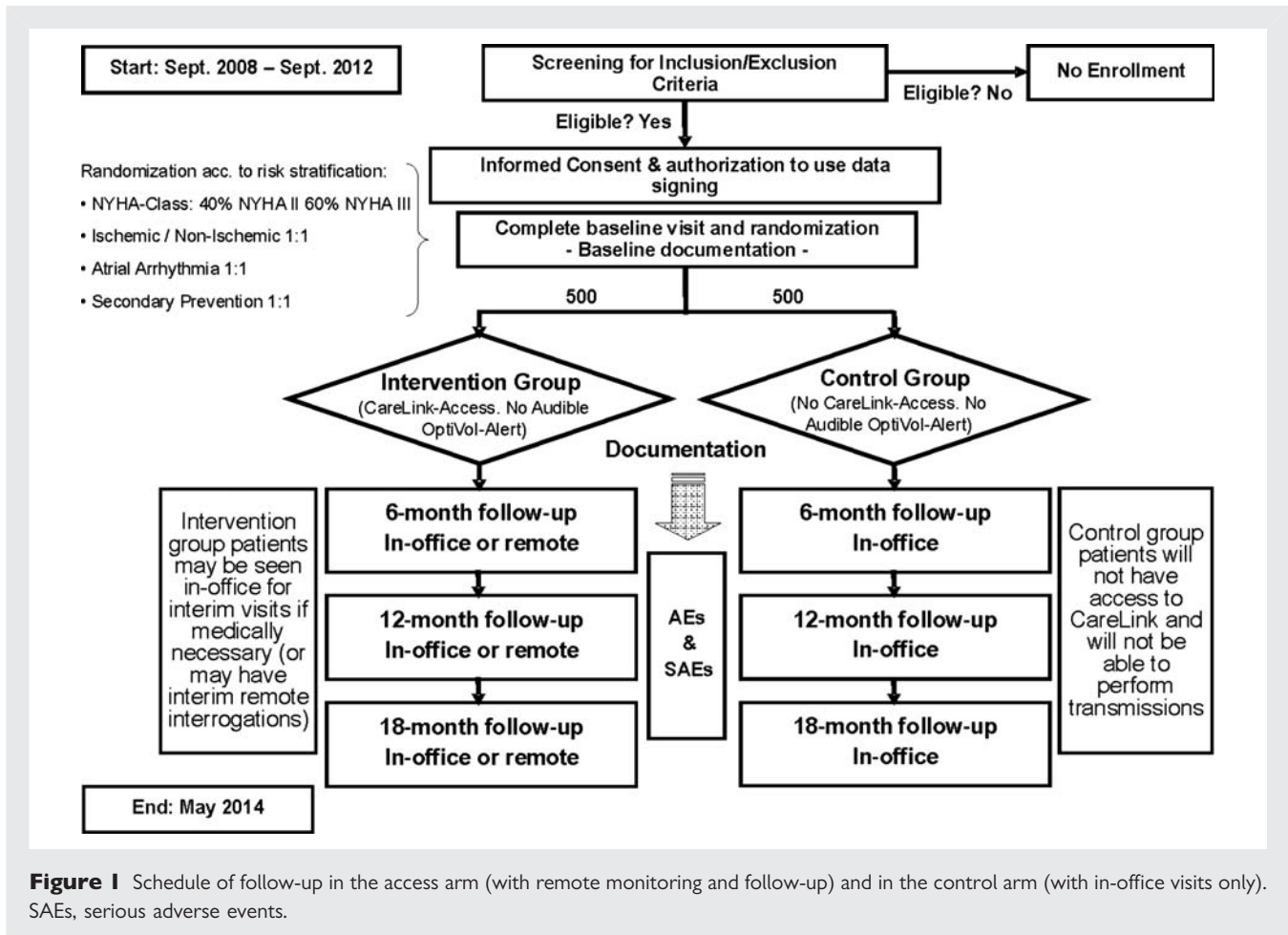
All new and/or worsening AE information will be collected from the time of enrolment until the event is resolved or the study ends. All AEs regardless of relatedness or outcome must be reported. This includes a description of the event, the diagnosis, the date of event onset, the relationship of the event to any procedure or to the device system, the outcome of the event, and the date on which the event was first noticed by the investigator. Additionally, actions that were taken as a result of the event have to be documented.

The Medical Dictionary for Regulatory Activities (MedDRA) will be used 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 event committee (see *Appendix*). The event committee will also regularly assess, review and classify all AEs including hospitalizations, emergency department visits, urgent and non-urgent unscheduled office visits. Additionally, the event 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.

Healthcare utilization will be measured by data received from the completion of an Adverse Event Form or CareAlert Evaluation Form in case of hospitalizations or an Emergency Department visit.

## Crossover and patient withdrawal

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 Executive Committee who will review the rationale for crossovers. In order to achieve approval the investigator must inform the sponsor upfront about intended crossover. An approved crossover is defined as any instance when the study centre personnel makes a permanent, deliberate, medically intended decision to use Cardiac Compass Trends and/or HF-Management Report to optimize patient care in the control arm.



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

## Device programming and system modification

Device programming and programming of the level of CareLink-based data transmission are at the centre's own discretion.

In the event of a system modification, such as removal of a study device without replacement with a single- or dual-chamber Virtuoso ICD system or Concerto CRT-D or successor models, subjects initially randomized to the access arm will be crossed-over to the control arm, but analysed in the access arm (ITT principle).

## Intervention algorithm

An intervention algorithm will be performed and documented if:

- CareAlert due to OptiVol fluid index exceeding the OptiVol threshold (access arm only);
- new or worsening signs and/or symptoms of cardiovascular decompensation appear (access and control arm).

The detailed intervention algorithm is shown in *Figure 2*.

## Study exit

A study exit will be documented for any of the following: subject death, study closure, subject withdrawal, investigator withdrawal, or subject lost to follow-up.

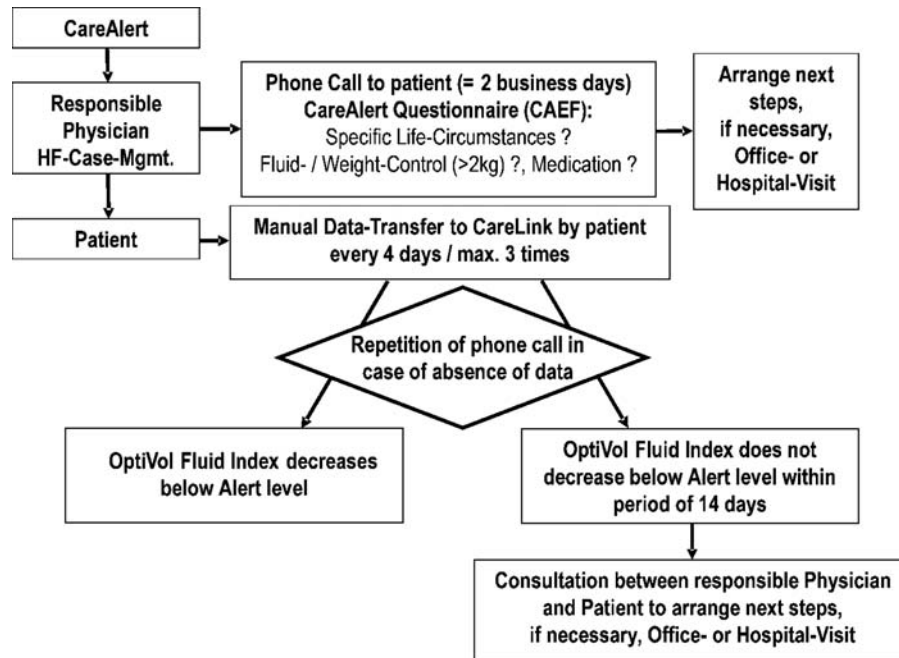
## Ethical conduct and data management

The OptiLink HF study is registered on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) with the registration number NCT00769457. The study will be conducted in compliance with ISO-14155, guided by Good Clinical Practice and in accordance with the Declaration of Helsinki and the laws and regulations of the Federal Republic of Germany. All centres must provide written approval from the local Medical Ethics Committee. All patients will be required to provide written informed consent to participate in the study.

OptiLink HF is sponsored by Medtronic Inc. (Minneapolis, MN, USA). The sponsor is responsible for training of personnel involved into the study. All devices are market released and are used according to licensed indications. Study data management is performed by the Contract Research Organization Pierrrel Research GmbH Essen, Germany.

## Statistical analysis

The OptiLink HF trial is designed to show the superiority of OptiVol fluid status monitoring with automatically generated



**Figure 2** Intervention algorithm.

wireless CareAlert notification via the Medtronic CareLink Network, compared with standard clinical assessment. This should be reflected by a relevant decrease in the rate of all-cause death or cardiovascular related hospitalization during the follow-up period.

The following hypothesis will be investigated:

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

with  $S_{\text{control}}$  and  $S_{\text{access}}$  denoting the survival functions for freedom from all-cause death or unplanned cardiovascular-related hospitalization within 18 months for the control arm and access arms, respectively. Group comparison will be performed on  $\alpha$ -level of 5% using a two-sided log-rank test. The ITT population will be used for the primary analysis.

The study is sized to have 80% power to detect a 30% reduction in the percentage of patients who experience a primary event in the first 18 months after randomization. For sample size calculation, the following assumptions are made: type I error  $\alpha = 0.05$ , control arm proportion event-free at 18 months of 72.0%, difference between treatment arms of 30%, which means an 8.4% absolute risk reduction; access arm proportion event-free at 18 months of 80.4%, all subjects are followed for 1.5 years.

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 in the two treatment arms. This is based on the method from Lakatos<sup>22</sup> and Cantor,<sup>23</sup> 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.

Missing values for the primary endpoint will be avoided to the extent possible. Patients for whom the randomized treatment is discontinued will be followed continuously. The ITT analysis will include these patients in the arm to which they were randomized. In case of study exit, attempts will be made to obtain at least vital status and dates of unplanned cardiovascular hospitalizations. Any remaining missing values will be taken into account in the primary analysis by censoring the patient at the last available visit.

Two interim analyses are planned when 33 and 67% of the 238 expected primary endpoints have been accrued. At the interim analyses, the primary endpoint and the secondary mortality endpoint will be analysed. The Data Safety Monitoring Board (DSMB) will review the results and will advise the Study Executive Committee about continuation of the study. The DSMB will consider stopping 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. However, it will consider stopping 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.

All secondary variables will be analysed 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.

Subgroup analyses will be carried out for the presence of ischaemic and non-ischaemic cardiovascular disease, subjects with or

without AF and subjects with or without VT/VF episodes before implantation (primary vs. secondary prevention).

## Timelines

The first OptiLink HF patient was enrolled in September 2008. At the time of manuscript submission, almost 500 patients have been included in the study and study recruitment is expected to be completed in September 2012. Thus, the last subject visit should occur by the end of March 2014 and the first results on the primary objective should be available by the end of 2014.

## Discussion

The OptiLink HF trial is designed to evaluate whether OptiVol fluid status monitoring with an automatically generated wireless CareAlert notification via the CareLink Network reduces all-cause death and cardiovascular hospitalizations in a HF population, compared with standard clinical assessment.

Modern and device associated HF disease management uses, besides CRT, two new strategies. The first new strategy involves the measurement and continuous monitoring of intrathoracic impedance as a surrogate parameter of changes in pulmonary fluid status. Preliminary data showed that the OptiVol algorithm for intrathoracic impedance measurement allowed the detection of clinical HF with a sensitivity of 60% and a positive predictive value of 60% in 373 patients over a follow-up period of 4.2 months.<sup>15</sup> These data were confirmed by Ypenburg *et al.*,<sup>14</sup> who reported a sensitivity of 60% and a specificity of 73% for the assessment of HF, depending on the selected threshold for the OptiVol alert, in 115 patients over a follow-up period of  $9 \pm 5$  months.

Ongoing trials are currently trying to evaluate the sensitivity of the fluid detection algorithm for predicting HF-related hospitalizations,<sup>24</sup> and to investigate whether the clinical outcome of patients with an implanted HF device can be improved by using information from intrathoracic impedance monitoring.<sup>25</sup> However, none of these trials are designed to analyse whether fluid status monitoring reduces all-cause death and cardiovascular hospitalizations in HF patients as the OptiLink HF trial does.

The second new strategy is the use of telemonitoring for device-based data transmission. The TEN-HMS (Trans-European Network-Home-care Management System) trial was one of the first to show that mean duration of hospital admissions was reduced by 6 days and mortality was reduced significantly with home telemonitoring as compared with usual care in 426 HF patients.<sup>26</sup> However, although TEN-HMS measured weight, blood pressure, heart rate, and rhythm, it was not capable of measuring implantable device-based parameters. Using CareLink for the first time in 67 patients, remote monitoring was seen as a potential tool to improve the clinical management of patients with CRT-D devices.<sup>17</sup> Especially in HF patients, CareLink was shown to reduce in hospital visits in 70% of patients with intrathoracic impedance alerts.<sup>18</sup>

Remote patient management by direct transmission of data related to patient's health status is a promising strategy for improving HF outcomes. The efficacy of telemonitoring using a telephone-based interactive voice-response system that collects daily information regarding symptoms and weight was recently tested in a

large-cohort multi-centre clinical trial conducted by Chaudhry *et al.*<sup>27</sup> Although patients randomized to the intervention group reported their general health- and HF-related symptoms on a daily basis, the investigators did not observe a correlation between the reduction in hospital re-admission or death risk and the use of telemonitoring when compared with usual care.

The Telemedical Interventional Monitoring in Heart Failure (TIM-HF) study uses a remote monitoring system with the ability to monitor the electrocardiogram, blood pressure, and body weight of the patient via a mobile phone network connection. Telemedical Interventional Monitoring in Heart Failure aims to assess total mortality compared with standard health-care patients, and has already recruited 710 stable chronic HF patients. It is expected that TIM-HF will provide important data on the impact of telemedical management.<sup>28</sup> However, OptiLink HF is the first trial to use CareAlert notification via the CareLink Network for fluid status monitoring to assess all-cause death and cardiovascular hospitalizations in HF patients.

The occurrence of ventricular but also atrial arrhythmias is a strong predictor of outcome in patients with CRT. New onset AF is especially detrimental to CRT patients. Buck *et al.*<sup>29</sup> showed that failure of CRT was associated with new-onset AF. They studied 114 CRT patients with (49%) or without (51%) known AF, and used total atrial conduction time measurements to predict CRT response. They also found that the response rate was significantly higher when an improvement of one or more NYHA class was found during CRT. This is in accordance with other reports showing that the prevalence of AF increases with an increase in NYHA class.<sup>30</sup> Although the use of arrhythmia alerts would be helpful to guide therapy, participating study centres are not allowed to individually programme AT/AF alerts in OptiLink HF.

Two other aspects of the OptiLink HF study have not been previously addressed by any other study. One is the close collaboration and networking between the implanting hospitals and the out-patient clinics, based on the CareLink Network system. This allows remote patient and device management by the implanting centre using the CareLink data, for example, in case of problems regarding rhythm therapy programming, during patient visits to the out-patient clinic. Another aspect is that the use of the CareLink Network system might have an impact on health economics, the extent of which is unknown at present.

In summary, the OptiLink HF trial is designed to investigate whether OptiVol fluid status monitoring with an automatically generated wireless CareAlert notification using the CareLink Network can reduce all cause death and cardiovascular hospitalizations in HF patients implanted with ICD or CRT-D systems.

## Funding

The OptiLink HF Study is sponsored by Medtronic Inc (Minneapolis, MN, USA).

**Conflict of interest:** Authors J.B., M.B., K.R., G.K., C.B., H.K., R.S., J.S., C.I., and A-M.S. have all received grant support from the study sponsor. C.W.I. is a speakers bureau member for Medtronic Boston Scientific, Biotronic and St Jude Medical, an Advisory Board member for Medtronic and Sorin and is participating in studies sponsored by Medtronic, Biotronik, and Boston Scientific. The authors are solely responsible for the design and conduct of this study, the drafting and editing of

the paper and its final contents. Statistical support for the paper and for the study design was provided by B. Gerritse, Medtronic Bakken Research Center (BRC) Maastricht, Netherlands.

## Appendix

### Study Committees

**Executive Board:** The Executive Board consists of eight physicians and one member of the sponsor study team. Members: M. Böhm, J. Brachmann, K. Rybak, G. Klein, R. Bosch, C. Butter, H-P. Schultheiss, E. Erdmann.

### Event Adjudication Committee (EAC)

The Event Adjudication Committee consisting of three independent physicians will adjudicate events for study objectives and document event classifications. Members: M. Haass, W. Haverkamp, S. Stoerk.

The event committee members do not otherwise participate in the study (i.e. no study centre investigator is involved) to assure that the transmission of information to the study centre investigators about events triggering per study arm or per subject does not take place. Medtronic personnel may facilitate the EAC meeting (e.g. statistician, clinical trial leader), but they will not be voting members. The EAC will not be made aware of the randomization assignment of study subjects.

### Data Safety Monitoring Board (DSMB)

An independent Data Safety Monitoring Board is established to review the interim data analyses as well as to periodically review the total incidence of AEs and deaths in this study. The DSMB for this study consists of members with study related backgrounds. Members: S. Anker, K. Swedberg, H. Wellens, L. Tavazzi, S. Pocock.

Up to two additional investigators participating in this study may take part 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 AEs will also be reviewed at this time. Review and consensus by the entire committee is required to recommend that the study should be stopped. All documentation will be anonymized in terms of clinical centre and subject identifiers.

## References

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