Optimization of the Ambulatory Monitoring for Patients With Heart Failure by Tele-cardiology (OSICAT)

ClinicalTrials.gov ID: NCT02068118

STUDY PROTOCOL

Version n° 14.0 dated 27 JUL 2018 revised on 06 SEP 2018

ClinicalTrials.gov version prepared on 15 SEP 2021

Optimization of the Ambulatory Monitoring for Patients With Heart Failure by Tele-cardiology

OSICAT

Version 14.0 July 27, 2018 revised September 06, 2018

English translation dated September 8, 2021

RCB ID no.: 2012-A01672-41

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This protocol has been designed and drafted based on version 1.0 of 3 Sept. 2008 of the DIRC Sud-Ouest et Outre-Mer [Interregional Clinical Research Delegation - South-West and Overseas.

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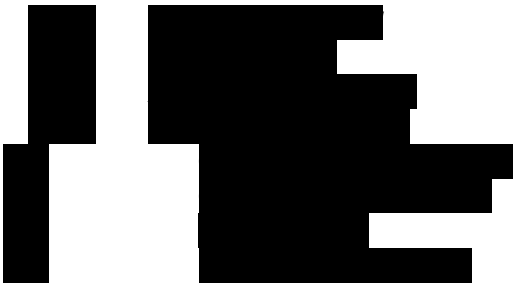

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LIST OF ABBREVIATIONS

LTD: Long-Term Disease

ANSM: French National Agency for Medicines and Health Products Safety

BNP: Basic natriuretic peptide

COPD: Chronic Obstructive Pulmonary Disease

CCMP: Common Classification of Medical Procedures

CRC: Clinical Research Center

CNIL: French National Commission for Data Processing and Freedom

CPP: Committee for the Protection of Persons

CRAM: Regional Health Insurance Fund

TPE: Therapeutic Patient Education

ECG: ElectroCardioGraphy

eCRF: electronic Case Report Form

SAE: Serious Adverse Event

UPG: Uniform Patient Groups

UHG: Uniform Hospitalization Groups

GSM: Global System for Mobile

SRN: State Registered Nurse

MSA: Agricultural Mutual Benefit Society

NABM: Nomenclature of Medical Biology Procedures

NIR: List Enrolment Number

NYHA: New York Heart Association

PMSI: IT System Medicalization Program

RGTS: General Scheme for Employed Workers

RSI: Social Security Scheme for Self-employed Workers

ASS: Aftersales Service

RAAS: Renin-Angiotensin-Aldosterone System

CST: Clinical Study Technician

T2A: Price per Activity

LMV: Light Medical Vehicles

GRDP: General Regulation on Data Protection

1. PROTOCOL/SUMMARY OF THE RESEARCH

STUDY SPONSOR: CDM e-Health
TITLE: Optimization of the Ambulatory Monitoring for Patients With Heart Failure by Tele-cardiology - **OSICAT**
MAIN INVESTIGATOR: Prof. Michel Galinier, Head of Department of the Cardiology Department Rangueil Teaching Hospital Center, TOULOUSE
OBJECTIVES OF THE STUDY: **Primary objective:** To assess the impact of a tele-cardiology program on morbidity-mortality in heart failure patients *versus* standard monitoring. **Primary assessment criterion:** The primary assessment criterion is a composite criterion combining the number of unplanned hospitalizations for any cause and death from any cause during the 18-month comparative period in both groups. **Secondary objectives:** To: 1) assess the effect of management by tele-cardiology versus standard management on hospitalizations and deaths of cardiovascular origin. 2) compare the kinetics of evolution in quality of life between day 0 and month 18 in the 2 groups. 3) assess the differential cost-efficacy and cost-utility ratios of both patient management strategies. 4) assess societal acceptability of management by tele-cardiology among healthcare professionals and patients. 5) collect data concerning the hospitalizations and deaths during the extension period of the tele-cardiology program among the patients who wished to participate in the latter. **Secondary assessment criteria:** 1) Comparison of the number of events (deaths and hospitalizations of cardiovascular origin) between the 2 groups after 18 months. 2) Comparison of the means of the Short Form-36 (SF-36) quality of life scale scores in the 2 groups, at inclusion and at 18 months. 3) Measurement of the annual cost of treatment in both groups from the point of view of the hospital and the health insurance scheme. 4) Measurement of the social acceptability of the tele-cardiology program for patients and healthcare professionals 5) Annualized numbers of hospitalizations for any cause, and numbers of deaths from any cause occurring during the extension period for the patients who wished to participate in the latter. 6) Annualized numbers of hospitalizations and numbers of deaths of cardiovascular origin occurring during the extension period for the patients who wished to participate in the latter.

NUMBER OF PATIENTS: *990 patients (495 patients per group)*

RESEARCH DESIGN

National, multicentric study.

The patients will be randomized to one of the following 2 groups:

- Standard management
- Tele-cardiology: personalized telephone support and supervision of their signs and symptoms at home via telemonitoring.

STUDY EXTENSION PERIOD

All the patients who were included in the comparative period will be contacted by the investigating center to propose them an appointment with the investigating physician. During this appointment, the investigating physician will present this extension phase with continuation of the monitoring with the tele-cardiology program.

The patients who accept to participate in the extension period will sign an informed consent form for this period.

INCLUSION CRITERIA:

- Men or women of 18 years of age or older.
- Heart failure patients having been hospitalized for cardiac decompensation during the past 12 months.
- Patients having a landline telephone or with access to the GPRS network at their homes.
- Patients having given their free informed written consent to participate in the study.
- Patients subscribing to a social insurance scheme.

INCLUSION CRITERIA DURING THE EXTENSION PERIOD

Participation in the open extension period will only be offered to patients who participated in the comparative period of the study, did not withdraw prematurely from the latter and having given their free informed written consent to participate.

EXCLUSION CRITERIA:

- Patients for whom no echocardiographic data are available.
- Patients whose BNP is less than 100pg/ml or whose NT-proBNP is less than 300pg/ml
- Patients suffering from a disease resulting in a life expectancy of less than 12 months (apart from heart failure).
- Patients undergoing dialysis for kidney failure.
- Patients with a heart transplant or a ventricular assistance device.
- Inotrope-dependent patients.
- Patients without the necessary autonomy to use the tele-cardiology equipment.
- Patients participating in another therapeutic clinical trial.
- Pregnant or breast-feeding women, or women of childbearing age not using an effective contraception method.
- Patients under guardianship, wardship or placed under conservatorship

STATISTICAL ANALYSIS OF THE DATA:

- The primary analysis will be performed using the intention-to-treat (ITT) principle.
- Comparison of demographic and clinical data at inclusion in both arms.
- Analysis of the primary efficacy criterion using Poisson regression model with adjustment to an offset variable equal to the duration of follow-up of each patient
- Additional subgroup analyses according to [redacted], NYHA classification, [redacted]
- The number of readmissions for heart failure, the cumulative number of hospitalization days, the quality of life scores and the costs of management will also be analyzed as secondary objectives.

- **STUDY EXTENSION PERIOD**

The patients entering the extension period will be divided into two groups:

- "Standard management / Tele-cardiology" group: patients from the "standard management" group of the comparative period entering the study extension period.
- "Tele-cardiology / Tele-cardiology" group: patients from the "tele-cardiology" group of the comparative period entering the study extension period.

All the analyses related to the patients participating in the study extension period will be presented by group (Standard management / Tele-cardiology vs. Tele-cardiology / Tele-cardiology) and overall.

SCHEDULED NUMBER OF CENTERS: 46 centers

DURATION OF THE INCLUSION PERIOD: 42 months

DURATION OF PARTICIPATION OF EACH PATIENT: 18 months
An extension period using the monitoring by the tele-cardiology program will be offered to all patients who wish for this, until the tele-cardiology program is marketed.

2. OVERALL DESCRIPTION AND RATIONALE OF THE STUDY IN THE LIGHT OF CURRENT KNOWLEDGE

2.1. CURRENT STATE OF KNOWLEDGE

2.1.1. HEART FAILURE

Heart failure is defined as a disease of the cardiac pump causing a reduction in peripheral perfusion rates and oxygen supply to the perfused organs; it is the progressive form of the majority of cardiovascular disorders. A distinction is drawn between two major types of cardiopathy: so-called ischemic (following coronary heart disease) and non-ischemic. Heart failure is characterized by repeated episodes of cardiac decompensation which lay the basis for multiple hospitalizations. It is characterized by progression towards either myocardial degeneration or serious ventricular arrhythmias leading to episodes of sudden death (1). The pathophysiology is essentially based on two major mechanisms, one related to hemodynamic changes (reduction in cardiac and peripheral perfusion) and the other corresponding to compensatory neurohumoral activation, the purpose of which is to ensure among other aspects peripheral perfusion rates. These changes partially explain the pattern of symptoms of heart failure patients which is classified either as signs of left, right or global heart failure or as major and minor criteria (2).

Prevalence of heart failure has been constantly on the increase over the past twenty years, affecting 1 to 2% of the population in developed countries, essentially owing to the constant ageing of their populations (3, 4, 5). In France, it affects approximately 1 million individuals, representing 2% of health expenses, more than 75% of which are related to hospitalizations. Heart failure was considered a public health problem by the preparatory group for definition of the national aims of the public health law of 2004.

It is the primary cause of hospitalization after 60 years of age, in most cases unscheduled, contributing to congestion of the emergency services. Hence, in the U.S.A. (6, 7), it results in one million hospitalizations per year and the hospital admission rate for heart failure increased by 19% between 1990 and 1999 among the female population (8).

2.1.2. MANAGEMENT OF HEART FAILURE

2.1.2.1. CURRENT MANAGEMENT

Current management aims to improve quality of life by:

- relieving the symptoms (shortness of breath, fatigue, edema, etc.);
- allowing the activities of daily life;
- preventing decompensation episodes and reducing the number and duration of hospitalizations;
- delaying progression of the disease and reducing its mortality.

Treatment of heart failure always involves:

- non-drug treatment, with prescription of new dietary habits and regular physical activity;
- well-codified and effective drug treatment for heart failure with demonstration performed based on the aforementioned criteria.

Treatment with intracardiac devices (biventricular pacing) is playing an increasing role in heart failure that remains symptomatic despite optimum treatment. In case of an inadequate result, an indication for a left ventricular assist device or heart transplant is discussed in some patients. At a very advanced stage (NYHA refractory stage IV) palliative care should be offered (2).
Therapeutic patient education (TPE) supplements the treatments (9).

The combination of the constant increase in prevalence of heart failure owing to ageing of the population and the decrease in hospitalization capacity of our healthcare system (10) calls for development of outpatient management of these patients (11). It is responsible for 100,000 hospitalizations per year in France, i.e. more than 5% of total hospital admissions and represents the primary cause of hospitalization of subjects of more than 65 years of age. The hospitalization period for heart failure is usually long, with the mean inpatient duration being around ten days in France with 2 to 3 hospitalizations per year, suggesting that the economic impact of this disease is therefore mainly related to repeated hospitalizations.
A survey performed in Canada showed that owing to saturation of the downstream services, 35% of these patients leave the emergency service directly without any hospitalization in cardiology or geriatrics, which predisposes to early rehospitalizations (12). The rehospitalization rate is particularly high after an initial hospital admission for cardiac decompensation; 40% after 1 year on average (13, 14, 15). In Europe, in the EuroHeart Failure Study register where the patients were

included after hospitalization in a cardiology department, the rehospitalization rate is 24.2% after 3 months (16). In the Canadian Alberta register (12) where a third of the patients leave the emergency service directly, the rehospitalization rate reaches 20% after one month and 60% after one year.

The treatment can be further optimized, particularly in elderly subjects in whom beta blocking agents are underused (17, 18) in spite of the recommendations of the Cardiology and Geriatric Societies (19). Indeed, if beta blocking treatment has not been instituted within 90 days following hospitalization, there is little chance that it will be subsequently undertaken; as for the dosages, they are rarely increased during monitoring (20). Finally, the latest 2012 recommendations emphasize the value of broad prescription of mineralocorticosteroid antagonist receptors from stage II onwards (21), whereas their prescription currently only involves one third of patients (22, 23).

The cost of this disorder based on the available sources of data derived from the routine databases, such as the PMSI and health insurance reimbursement data, estimate on the basis of 147,631 patients registered in LTD for a heart failure diagnosis that the amounts reimbursed by health insurance (outpatient and hospital expenditure) are around 1605 million Euros. Public hospital expenditure accounts for the first expense item (49.6%), with private hospital expenditure accounting for 10.6% of expenses. The economic burden of heart failure shows an upwards trend, since a 3.6% annual increase in LTD owing to heart failure is observed, highlighting the importance of implementing "avoidability" strategies.

2.1.2.2. NEW MANAGEMENT STRATEGIES

Global, multidisciplinary, coordinated management, including therapeutic education of heart failure patients has extensively shown its efficacy during recent years in reducing rehospitalization frequency (24, 25, 26, 27) and is currently recommended by the academic societies (28). Hence, in the meta analysis of 33 randomized, controlled studies by Roccaforte, the frequency of hospitalizations for all causes is reduced by 23% and that related to heart failure by 42% (29). Although the management methods vary from one study to another, the meta analysis by McAlister (30) shows that management based on home monitoring is more effective, particularly in elderly subjects with restricted mobility. Even though the benefit in terms of mortality is still less well established, with the latter showing a non-significant 15% decrease in the intervention arm of the COACH study which is the most extensive to date (31), this global management is recommended by all the academic societies (21, 28, 32).

Daily communication of weight and symptoms allows early detection of the first signs of clinical deterioration, resulting in intervention by the patient's general practitioner (33, 34, 35, 36). It has in fact been demonstrated that the initial symptoms of worsening of heart failure occur 8 to 12 days before hospitalization (37) and measurement of thoracic impedance in patients wearing pacemakers reveals detects a reduction in this parameter, which is inversely correlated with pulmonary capillary pressures, 18 days on average before hospitalization (38). However, studies focusing on simple **telephone management** by a specialized nurse, which is readily accepted by patients, the majority of whom comply with this approach (39, 40), yielded contradictory results: this type of monitoring allowed a reduction in hospitalizations for heart failure and deaths in the DIAL study (41) and the trial conducted by Reigel (34) following a hospitalization for heart failure, but it did not have any effect in the study performed by DeBusk (42) focusing on less severe patients and did not reduce the hospitalization rates during a further two trials performed in the United States (WHARF study, 43) or in the Netherlands (44).

Alongside this type of telephone supervision, **telemonitoring** methods have been more recently developed allowing passive recording of physiological data such as weight, blood pressure, heart rate and O_2 saturation. In the TEN-HMS study, monitoring of these parameters by self-measurement in the mornings and evenings resulted in a significant reduction in mortality versus standard management (35). Finally, telemonitoring methods "on board the patient" exist, with some defibrillator-resynchronizer manufacturers having equipped their bioimpedance measuring device box, measuring the water content of the chest (44, 45) or pulmonary pressures, but they currently remain restricted to patients who are candidates for electrical treatment of their heart failure. Using standard telephone lines, these new types of monitoring make it possible to overcome geographical barriers and therefore be accessible to the majority of patients (46). A pilot study (47) confirmed feasibility and safety of rapid return home. Following hospitalization for heart failure, patients receive home monitoring by a specialized nurse (48) who, assisted by a coordinating cardiologist, by means of "telemonitoring" incorporated in a structured telephone support system, thus presides over the outpatient care of heart failure patients (49).

The most recent bibliographical data on this subject indicate however contradictory results. The last Cochrane meta analysis focusing on 25 studies, 11 assessing telemonitoring (2710 patients), 16 assessing structured telephone supervision (5613 patients) and 2 assessing both these types of intervention, notes a significant 34% reduction in mortality owing to telemonitoring, whereas the 12% reduction observed with telephone monitoring does not achieve the degree of

significance, combined with a significant decrease in hospitalizations for heart failure of 31% and 33% respectively under the effect of these two types of intervention (50). In the majority of the studies, both these methods are well accepted by patients and reduce healthcare costs (50). Since then however, the most extensive study (Tele-HF) focusing on telemonitoring has been published, finding neutral results (51). In this research, which included 1653 patients recently hospitalized for heart failure, daily telemonitoring of symptoms and weight did not modify, in comparison to usual treatment, the primary criterion combining death and rehospitalization, regardless of the cause after 6 months, which occurred respectively in 52.3 and 51.5% of the patients or rehospitalizations (49.3% vs. 47.4%) (52). In this study however, 14% of the patients allocated to telemonitoring never used this system and at the end of follow-up, only 55% of the patients used it 3 times a week. These neutral results are reminiscent of those of two studies published in 2009. In the HHH study, which included 461 patients, weekly telemonitoring of vital signs (weight, heart rate, blood pressure, symptoms), whether or not combined with monthly monitoring of the ECG by a Holter system, did not show, after a 12 months' follow-up, any significant effect on hospitalizations for heart failure or deaths versus usual treatments (53). In the Home-HF study, which included 182 patients hospitalized for heart failure, daily telemonitoring of weight, blood pressure, SaO_2 and symptoms did not have any significant effect, after 6 months' follow-up, on the number or duration of hospitalizations versus usual treatments (54).

An analysis of these negative experiences makes it possible to **put forward several explanations** for these contradictory results (55, 56, 57, 58), which might originate, apart from underuse of the system by the patients: from the patients included and the recruiting centers who might not be representative of heart failure patients in the actual world (predominance of subjects originating from an urban environment, affluent socioprofessional category, least severely affected patients...), with optimum usual treatment of the patients in the control group testified by a particularly low annual mortality rate in these trials in relation to the cohort data; from the absence of inclusion of educational response in the telemonitoring systems; from monitoring of the alarms by personnel unskilled in managing heart failure patients; from an excessively short telemonitoring period, usually limited to 6 months in the previous studies (52).

A new telemonitoring trial is therefore required that provides an answer to these various criticisms.

Ultimately, development of this new form of managing a chronic disease could reduce the disparity in access to care throughout France and improve the prognosis of heart failure patients. This

approach calls for validation of the tools by a thorough methodological approach in the form of a clinical trial and structuring of a new care provision scheme.

The management method studied, referred to in the protocol as the "**tele-cardiology program**" will therefore involve an alternative outpatient strategy in which the patients will receive personalized telephone support and supervision of their signs and symptoms at home by telemonitoring.

Through communication of the data to all the players involved with the patient (referring physicians, general practitioner, cardiologist, privately practicing nurse...), this program will allow optimization of monitoring, particularly via a more rapid and more suitable response.

2.2. HYPOTHESES OF THE RESEARCH AND ANTICIPATED RESULTS

The patients' profile, elderly with comorbidities and therefore with a high risk of dependency, influences the course of the disease and complicates management both in private practice and in hospital. The complexity of the patients' medical and social circumstances and the two aims set by the 2004 law (improvement in patients' quality of life and reduction in mortality and frequency of rehospitalizations) justify implementation of new healthcare organizations.

The large number of players involved makes management complex. Tele-cardiology will encourage continuity of care as well as personalized and coordinated management, which are key factors in reducing the costs and improving the performance of our healthcare system.

The OSICAT project objectives to demonstrate that such an approach is capable of influencing the following dimensions of management:

Safety:

This new healthcare strategy allows traceability of the procedures and prescriptions in addition to management of the alerts triggered. This safety issue is all the more important in the subjects concerned by the study, considered "fragile" and often presenting with atrial and ventricular cardiac arrhythmias, the main cause of sudden death in these patients (60, 61).

Efficacy:

Improvement in coordination of care and reinforcement of monitoring via telephone contact should allow an improvement in prevention and treatment compliance (short-term diuretics and long-term beta blockers) (62) and influence the incidence of undesirable effects and the progression of the complications of heart failure.

Motivation:

The patient is involved in managing his/her chronic disease by regular information on the effects of his/her treatment and controlling his/her symptoms with an alert system that triggers establishment of contact with the Cordiva telephone telemonitoring center.

It should promote development of PTE (31) and rehabilitation (63), which have demonstrated their benefit, particularly in terms of reducing the risk of rehospitalization (64), which is particularly high during this disorder, with 25% of patients being readmitted in Europe within twelve weeks following an initial hospitalization for acute heart failure (65).

Organization of management:

Use of the new information and communication technologies is a response to the discrepancy between care provision and a large population of patients suffering from cardiovascular comorbidities to be monitored in the long term. This entails development, validation and implementation of tools specifically developed in order to ensure optimum supervision at home.

Beyond this remote management aid, the tele-cardiology program ensures that the patient is kept at home with independence and improvement in quality of life. This strategy is not only an effective means of reducing "avoidable" hospitalizations and their implications (costs, induced disorders, loss of independence or quality of life), but also of combating inequalities in access to healthcare.

[redacted]

This new management approach, based on coherent and coordinated relationships between the public and private sector and between healthcare professionals (general practitioners, privately practicing nurses, pharmacists and cardiologists...), focusing on patients and at their service, ought to bring about favorable developments in professional practices.

[redacted]

[redacted]

2.3. BENEFIT / RISK RATIO

Currently, standard management involves conventional monitoring during a consultation, with a visit to the general practitioner or referring cardiologist. Consequently, there is no loss of opportunity for the patients in the control arm, since this type of management by telemonitoring is not a standard management approach. This method of outpatient monitoring does not in principle incur any undesirable effects. The patient weighs him/herself and informs the device box provided and undergoes a telephone interview with the nurse from the call center every three weeks.

We therefore consider the benefit/risk ratio of our project as favorable.

2.4. EXTENSION PERIOD

The extension period will be conducted on an open, non-comparative basis.

The aim of the extension period is to allow patients who wish to do so to follow the telemonitoring program until its marketing, regardless of the randomization group on initial inclusion in the study.

Extension involves continuing the initial program, including personalized telephone support and home telemonitoring supervision in order to optimize patient management, particularly via a more rapid and more appropriate response.

3. OBJECTIVES OF THE STUDY

3.1. PRIMARY OBJECTIVES

To assess the impact of a tele-cardiology program on morbidity-mortality in heart failure patients versus standard monitoring.

3.2. SECONDARY OBJECTIVES

1) To assess the effect of management by tele-cardiology versus standard management on hospitalizations and deaths of cardiovascular origin.

2) To compare the kinetics of evolution in quality of life between day 0 and month 18 in the 2 groups.

3) To assess the differential cost-efficacy and cost-utility ratios of both patient management strategies.

4) To assess societal acceptability of management by tele-cardiology among healthcare professionals and patients.

5) To collect data concerning the hospitalizations and deaths during the extension period of the tele-cardiology program among the patients who wished to participate in the latter.

[redacted]

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3.3. ASSESSMENT CRITERIA

The study assessment criteria will be recorded, regardless of the patient's randomization arm, firstly through the telephone contacts established by a **clinical research technician at 0, 6, 12 and 18 months** and secondly by means of the anonymized hospitalization reports.

The investigators will determine the cardiovascular origin or not of the deaths and the hospitalizations and the programmed or not programmed of the hospitalizations. The investigators will determine the cardiovascular origin or not of the deaths and the hospitalizations and the programmed or not programmed of the hospitalizations.

A panel of experts will meet at the end of the study. The meeting will be prepared beforehand by the sponsor. The aim of this study will be to validate occurrence of the events forming the main criterion and the secondary criteria in order to ensure their proper listing (adjudication committee). This committee will determine, on a blind basis, the relevance and the reasons for the hospitalizations (cardiovascular or other) and deaths and the programmed or unplanned nature of hospitalizations. It will be formed of physicians who are not involved in the study and who are not aware of the arm to which the patients are assigned. The adjudication committee will be chaired by a methodologist of the study, [redacted]

3.3.1. PRIMARY ASSESSMENT CRITERION

The primary assessment criterion is a composite criterion combining the number of unplanned hospitalizations for any cause and death from any cause during the 18-month comparative period in both groups.

3.3.2. SECONDARY ASSESSMENT CRITERIA

1) Comparison of the number of events (deaths and hospitalizations of cardiovascular origin) between the 2 groups after 18 months.
2) Comparison of the means of the Short Form-36 (SF-36) quality of life scale scores in the 2 groups, at inclusion and at 18 months.

3) Measurement of the annual cost of treatment in both groups from the point of view of the hospital and the health insurance scheme.

4) Measurement of the social acceptability of the tele-cardiology program for patients and healthcare professionals

5) Annualized numbers of hospitalizations for any cause, and numbers of deaths from any cause occurring during the extension period for the patients who wished to participate in the latter.

6) Annualized numbers of hospitalizations and numbers of deaths of cardiovascular origin occurring during the extension period for the patients who wished to participate in the latter.

4. Experimental design

The OSICAT project consists of a comparative, randomized, 18-month period followed by a non-comparative extension period for patients from the first period who wished to participate in the latter.

4.1. OVERALL STUDY DESIGN

This study is :

- comparative (management by tele-cardiology versus standard management)
- 2 parallel groups.
- randomized [redacted]
- open-label
- in chronic heart failure patients
- multicentric
- national

It is scheduled to recruit a total of 990 patients over a three-year period in 46 participating centers.

This study comprises an inclusion visit with the investigating cardiologist followed by 4 telephone contacts by Clinical Study Technicians (CST). No hospitalization is scheduled during the study.

4.2. RANDOMIZATION

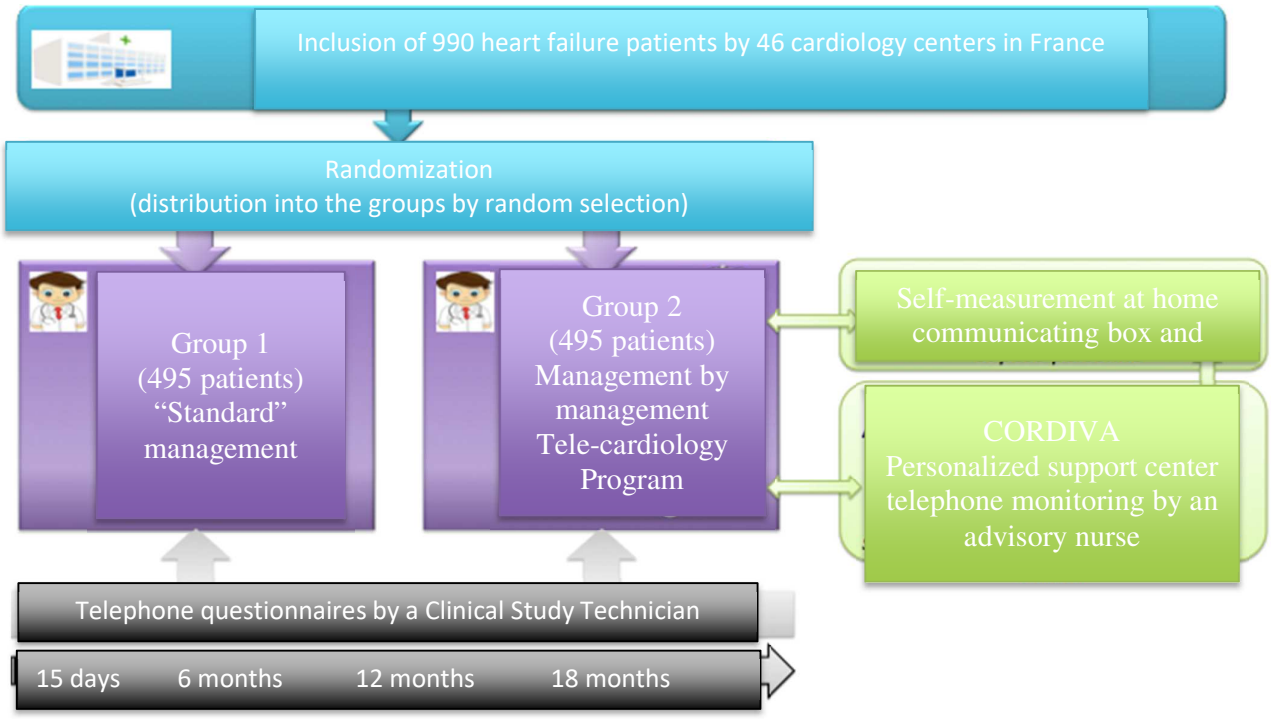
Randomization and allocation of a patient identifier for the duration of the study will be performed by computerized means via the eCRF during the patient inclusion visit.

Each patient will be assigned to one of the two study arms via random drawing of lots. Randomization will be centralized and set up for each institution participating in the study. [redacted] The randomization list will be pre-established for each center and for the entire cohort to be recruited.

The patients in the control arm will undergo conventional monitoring, involving return home with monitoring during consultation with their general practitioners or referring cardiologists.

This study will be performed with an open label: the patients and all the persons involved (nurses, referring physicians, CST) will be informed of the randomization arm allocated.

In order to limit data bias, the adjudication committee will assess the relevance of the hospitalizations on a blind basis.



4.3. STUDY SCHEDULE

The patients in the control arm will undergo conventional monitoring, involving return home with monitoring during consultation with their general practitioners or referring cardiologists.

The patients in the tele-cardiology arm will receive the equipment necessary for their monitoring at their homes during the week following their inclusion visit, comprising a communicating electronic balance and a box for answering the questionnaire assessing the progressiveness of their symptoms. During presentation of the study schedule to the patient, before inclusion, the investigating physician will show him/her the equipment to be used.

The equipment provided is "auto-installable", but if the patient deems necessary, the equipment will be installed at the patient's home by privately practicing nurses. They will also need to ensure that the patients know how to use it.

Each patient will answer **8 simple questions** every day:

- Did you experience breathing disorders last night that were more severe than during the previous night?

- Did you need an additional pillow last night in order to breathe more easily?
- Are you coughing more often than usual?
- Are your legs more swollen than usual?
- Do you feel more tired today?
- Have you had, or do you have fever of more than 38.5°C?
- Have you experienced or are you experiencing palpitations?
- Do you find that your physical activity is more restricted today than on previous days?

The patients will be required to answer simply yes/no to all these questions using the device box.

The self-monitoring parameters (weight and answers to the questionnaire) will be remotely transmitted via standard telephone lines (landline, 3G or GPRS) to the secure server.
These data will be analyzed automatically by an expert system that will generate an alert in case of abnormal values, with the aim being to forestall any cardiac decompensation.
The specialized nurses at the Cordiva telephone monitoring center will have access to the alert on working days and must contact the patient in order to check with him/her the relevance of the alert. If the clinical genuineness of the alert is validated, she will advise him/her to contact his/her general practitioner or referring cardiologist. In parallel, the referring physician will have access to a report including weight progression and the patient's symptoms that triggered this alert. Consequently, s/he will be able to implement the measures that s/he considers appropriate.

An information folder will be sent to the patients. (Appendix no. 1). It contains a number of elements of information relating to management of his/her heart failure: physiology of the heart, symptoms of the disease, treatments and dietary and lifestyle rules...
The aim of this folder is to assist exchange concerning specific topics between the Cordiva nurse and the patient.

As soon as the equipment has been received and installed in the patients' homes, the specialized nurses will conduct an initial telephone interview that will last approximately 45 minutes. It will initially allow the nurse to introduce the team and the approach and get to know the patient better (medical history, treatments, psychosocial profile, tobacco and alcohol consumption, physical activity, etc.).
Following this call, the patient and nurse will jointly determine the date of the next phone contact.

During the comparative period, a nurse from the Cordiva telephone monitoring center will contact the patient every 3 weeks to ensure his/her proper understanding of his/her illness and treatment and to assist him/her in managing his/her illness in daily life (compliance, performance of physical exercise, dietary hygiene, experience of the disease...). This call will last 15 minutes on average, but is not limited; the duration is defined depending on the patient's needs.

Following each telephone contact, the nurse will establish educational aims in conjunction with the patient (knowledge of the disease, of the medications, recognition of the signs of cardiac decompensation, adoption of good dietary habits, performance of regular physical activity).

The support center will also be available for incoming calls from the patients, who will thus be able to easily contact a specialized nurse from the Cordiva center 5 days a week on working days. This telephone line does not manage emergencies and will not be a substitute for dialing 15, with the emergency department remaining the principal contact person in case of a vital emergency.

If the patient leaves home temporarily (for a vacation for example), s/he will be able to take the reply box and scales with him/her. Since this equipment is fitted with a GSM chip, it will be possible to continue to record the patient's data. The patient will also be able to provide another telephone number for the interviews with the nurses.

The patient's general practitioner will be involved in this outpatient management from the outset. Indeed, the data collected by means of the scales and box will allow drafting of reports on the progression of his/her patient's symptoms. These reports will be communicated to him/her every 2 months. These reports will also be sent to the referring cardiologist.

Furthermore, in case of a validated alert, the referring physician will have access to a report on the progression of weight and symptoms, thereby allowing him/her to take any measures that s/he deems appropriate.

THE CORDIVA CENTER

Nurses specializing in management of heart failure in addition to therapeutic education, owing to the specific training programs that they have been able to follow, will form the backbone of the team. Indeed, the many experiments conducted in multidisciplinary management of heart failure patients have proven the key role of specialized nurses who establish a link between the patients and the different healthcare players (67, 68, 69, 70).

They will supervise application of the instructions of the referring cardiologist and the general practitioner and will ensure monitoring of the patients' clinical parameters (weight and symptoms). They will have an interview guide at their disposal. Objective elements (state of health, clinical signs and medications) will be collected and entered in a computerized file.

It should be noted that these data will be requested strictly with a view to supporting the patient and will therefore not appear in the trial. Provision is made during patient follow-up for strict separation of the circuits between the data collected by the nurses and those recovered by the CST for the study (the latter will only be used to judge the main assessment criterion).

Concerning assessment of the patients' knowledge and needs, the nurses will use active listening methods (open questions, reformulation, empathy and positive reinforcement).

These methods encourage study of the patient's knowledge of his/her disorder and his/her treatment in order to personalize the information to be conveyed.

The nurses at the Cordiva center have undergone specialized training in conducting the motivational interview.

The nurses from the Cordiva center have also received other training in cardiology and heart failure, "psychic status" of heart failure patients, communication and therapeutic education.

Given the absence of validating training in personalized support in chronic disease, the nurses received in the absence thereof validating training in therapeutic education.

The homogeneity of this informative approach is guaranteed on the one hand by the tools available to the nurses (folder, interview guide) and on the other hand by the intrinsic functioning of the personalized support center (patient monitoring performed by a team of nurses, weekly debriefing of some interviews recorded on the principle of the staffs in the departments and unity of place...).

4.4. STUDY EXTENSION PERIOD

All the patients who were included in the comparative period will be contacted to propose an appointment with the investigating physician. During this appointment, the investigating physician will present continuation of the monitoring of the tele-cardiology program.

The patients who accept to participate in the extension period will sign an informed consent form for this period.

The patients in the tele-cardiology program monitoring group will keep the telemonitoring equipment.

The patients in the standard monitoring group wishing to undergo the monitoring of the tele-cardiology program will be equipped and monitored as described in paragraph 4.3, based on the visit for entry into the extension period.
Feedback of the self-monitoring data (weight and 8 questions) in addition to management of the alerts will be identical to those in the comparative period.

During the extension period, the frequency of the calls by the Cordiva telephone monitoring nurse can be personalized depending on the patient's needs. At least 1 call every 8 weeks must be made.

5. ELIGIBILITY CRITERIA

5.1. INCLUSION CRITERIA

- Men or women of 18 years of age and older.
- Heart failure patients having been hospitalized for cardiac decompensation during the past 12 months
- Patients having a landline telephone or with access to the GPRS network at their homes
- Patients having given their free informed written consent to participate in the study
- Patients subscribing to a social insurance scheme

5.2. EXCLUSION CRITERIA

- Patients for whom no echocardiographic data are available.
- Patients whose BNP is less than 100pg/ml or whose NT-proBNP is less than 300pg/ml
- Patients suffering from a disease resulting in a life expectancy of less than 12 months (apart from heart failure).
- Patients undergoing dialysis for kidney failure.
- Patients with a heart transplant or a ventricular assistance device.
- Inotrope-dependent patients.
- Patients without the necessary autonomy to use the tele-cardiology equipment.
- Patients participating in another therapeutic clinical trial.
- Pregnant or breast-feeding women, or women of childbearing age not using an effective contraception method.
- Patients under guardianship, wardship or placed under conservatorship

5.3. RECRUITMENT METHODS

Recruitment will be performed prospectively based on the cardiology consultations of the centers participating in the study or following hospitalization for cardiac decompensation. During these consultations, the patients will receive the information concerning the study and will be allowed a consideration period.

For each patient, the treating physician will be informed of his/her participation in this study, in addition to the extension period, if the patient has accepted the latter.

5.4. INCLUSION CRITERIA DURING THE EXTENSION PERIOD

Participation in the open extension period will only be offered to patients who participated in the comparative period of the study, did not withdraw prematurely from the latter and having given their free informed written consent to participate.

6. MANAGEMENT OF THE TELEMONITORING EQUIPMENT

6.1. SUPPLY OF THE EQUIPMENT

The equipment consists of:

- communicating scales [redacted] via bluetooth;
- A communicating box [redacted] via landline network or GSM (SIM card inserted into each box).

NB: these items of equipment are not considered medical devices and consequently, they are not distributed by a laboratory or pharmacy. They can be replaced by equivalent devices during the study.

The equipment is supplied by the company CDM e-Health.

Following the first call to the patients, the specialized nurses of the monitoring center issue an order for dispatch of the equipment to the patient in question.

6.2. PACKING OF THE EQUIPMENT

The scales and box are packed in two separate cartons.

Once the equipment dispatch order has been issued, a configuration phase of the SIM card inserted in the box is performed by the CDM e-Health IT department.

These 2 items of equipment are subsequently packed in a single carton by the specialized nurses of the CDM e-Health monitoring center.

[redacted]

6.4. DISPATCH AND MANAGEMENT OF THE EQUIPMENT

As stated above, dispatch of the consignments is ordered by the specialized nurses from the monitoring center. Dispatch is subsequently performed by registered mail with handing over against a signature.

ASS and management of technical incidents are provided by the CDM e-Health IT department (a free phone number is made available to the patients).

6.5. MANAGEMENT OF THE TELEMONITORING EQUIPMENT DURING THE EXTENSION PERIOD

The same procedures and principles will be applied as during the comparative period, referring to sections 6.1, 6.2., 6.3 and 6.4

7. CONCOMITANT TREATMENT(S) AND PROCEDURE(S)

7.1. AUTHORIZED CONCOMITANT TREATMENT(S)/PROCEDURE(S)

All former treatments and treatment modifications are allowed.

7.2. FORBIDDEN CONCOMITANT TREATMENT(S)/PROCEDURE(S)

Whether or not prior therapeutic education has been received does not represent an inclusion or exclusion factor within the context of this study. Following their inclusion, patients never having received therapeutic education may, furthermore, participate in one of these programs without resulting in withdrawal from the study.

During their participation in the OSICAT study, the patients will not be able to take part in another research protocol. If they nevertheless wish to be incorporated in another protocol and if this is in their interest with regard to the disease, they will initially be required to undergo an OSICAT study withdrawal visit.

8. DESCRIPTION OF THE MEDICO-ECONOMIC ASSESSMENT

A cost-efficacy-type analysis will be performed. [redacted]

A supplementary cost-utility analysis will be performed.

[redacted]

[redacted]

[redacted]

[redacted]

9. DESCRIPTION OF ASSESSMENT OF SOCIETAL ACCEPTABILITY

Societal acceptance for patients on the one hand and for professionals on the other hand will be studied by means of semi-structured interviews according to the referenced methods (79, 80). [redacted]

[redacted]

[redacted]

10. RESEARCH SCHEDULE

10.1. RESEARCH CALENDAR

- Start of inclusions: 2nd quarter of 2013
- Duration of the inclusion period: 42 months
- Duration of participation of each patient: 18 months
- Total duration of the research for the comparative period: 5 years
- Duration of the extension period: until marketing of the tele-cardiology program

10.2. SUMMARY TABLE OF PATIENT MONITORING

	Inclusion D0	Telephone visit 1 Month 0 (+/- 15 days)	Telephone visit 2 Month 6 (+/- 15 days)	Telephone visit 3 Month 12 (+/- 15 days)	Telephone visit 4 or end of study visit Month 18 (+/- 15 days)	Extension period until marketing of the tele-cardiology program
Informed consent	✓					✓
Inclusion/exclusion criteria	✓					
Demographic data[1]	✓					
Clinical examination	✓					
Recording of history	✓	✓				
Concomitant treatments	✓	✓	✓	✓	✓	
Randomization	✓					
Main assessment criterion			✓	✓	✓	✓
SF36		✓		✓	✓	
Medico-economic questionnaire			✓	✓	✓	
Adverse events			✓	✓	✓	✓
Vital status					✓	✓
Semi-structured interviews and observations for health organization case studies						
Patient societal acceptability		✓	✓	✓	✓	
Healthcare professional societal acceptability interviews	✓	✓	✓	✓	✓	
Observation of the participating hospital institutions	✓	✓	✓	✓	✓	

[1]Demographic data: [redacted] sex[redacted]

10.3. INCLUSION VISIT

The inclusion visit is performed by the investigating physician. Before any examination related to the research, the investigator obtains the patient's free, informed, written consent.

OBTAINING OF CONSENT

During the inclusion visit, the investigating physician informs the patient and answers all his/her questions concerning the aim, nature of the constraints, foreseeable risks and anticipated benefits of the research. S/he also states the patient's rights within the context of biomedical research and checks the eligibility criteria. The investigating physician subsequently issues the patient a copy of the information note and informed consent.

The investigating physician is responsible for obtaining the patient's written informed consent. The consent form must be signed before performing any clinical or paraclinical examinations required by the research.

If the patient gives his/her consent to participate, the patient and the investigator write their names and first names in plain text before dating and signing the consent form.

The different copies of the information note and consent form are subsequently distributed as follows:

- A copy of the information note and signed consent is issued to the patient.
- The original copy is kept by the investigating physician (even if the patient changes address during the research period) in a safe place inaccessible to third parties.
- At the end of the inclusions or on completion of the research at the latest, a copy of each consent form is forwarded to the sponsor or to the latter's representative according to the practicalities communicated in due course to the investigators.

OBTAINING OF CONSENT FOR THE EXTENSION PERIOD

During the visit for entering the extension period, the investigating physician informs the patient and answers all his/her questions concerning this extension period of the tele-cardiology program.

The investigating physician subsequently issues the patient a copy of the information note and informed consent.

The investigating physician is responsible for obtaining the patient's written informed consent.

If the patient gives his/her consent to participate, the patient and the investigating physician write their names and first names in plain text before dating and signing the consent form.

The different copies of the information note and consent form are subsequently distributed as follows:

- A copy of the information note and signed consent is issued to the patient.
- The original copy is kept by the investigating physician in a safe place inaccessible to third parties.
- At the end of the extension period, a copy of each consent form is forwarded to the sponsor or to the latter's representative according to the practicalities communicated in due course to the investigating physicians.

INCLUSION ASSESSMENT:

During the inclusion visit, the investigating physician of each center must ensure that the inclusion criteria are fulfilled and that no exclusion criteria are present.

During this initial visit, the demographic data ([redacted] sex), the patients' history and concomitant treatments and the presence of risk factors (heredity, tobacco, dyslipidemia) will be collected and a clinical examination will be performed.
The clinical examination will include:

- Measurement of weight and height,
- NYHA class assessment,
- assessment of the presence of chronic kidney disease, COPD, a coronary disorder, arterial hypertension or diabetes mellitus,
- measurement of arterial blood pressure and heart rate,

The investigator must specify whether the patient presents with left, right or global heart failure and whether ischemic or non-ischemic cardiopathy is involved.

During this initial visit, the patient must submit a laboratory assessment dating back less than 3 months comprising measurement of potassium, blood urea and creatininemia. A measurement of telediastolic diameter and left ventricular ejection by echocardiography according to the Simpson Biplan method must also have been performed within the past 12 months.

If the patient has already followed a therapeutic education program corresponding to the definition below, the date of this education must be stated.

*According to the WHO, "**therapeutic education** for patients is intended to help patients acquire or maintain the skills they need to optimally manage living with a chronic disease. It is an integral and continuing part of patient care. It comprises organized activities, including psychosocial support, designed to make patients aware of and inform about their disease and about health care, hospital organization and procedures, and behavior related to health and disease, so that they (and their families) understand their disease and their treatment, collaborate with each other and take responsibility for their own care as a means of maintaining or improving their quality of life. Oral or written information and advice on prevention may be given by a healthcare professional on a number of occasions, but are not equivalent to therapeutic education of the patient" (83).*

Following this visit, the patients will be randomized to two arms (centralized and computerized randomization):

- one supervised on an outpatient basis by telemonitoring (so-called "telemonitoring arm") comprising daily measurement of weight, daily collection of a self-declaration of symptoms and personalized educational enhancement by the specialized nurses of the CDM e-Health monitoring center;
- the other monitored conventionally (so-called "control arm").

In order to perform randomization, the investigator will need to connect to the secure site hosting the online eCRF using a personal identifier and a password known to him/her alone. S/he will be required to enter the patient data needed for inclusion, which s/he will subsequently need to validate and sign electronically (with his/her password) in order to initiate randomization. Following validation of the contents and confirmation of all the eligibility criteria on the eCRF, randomization is performed (by clicking a "start randomization" button) according to the characteristics determined by the statistician. The site subsequently immediately informs the investigator of the group to which the patient belongs in addition to the latter's identifying number. The investigator's name will be recorded automatically and associated with the included patient no.

The patients in both arms will receive instructions in order to ensure that the patients are treated correctly in accordance with the institutional recommendations for optimum management of their heart failure.

The CST will be coordinated by the Clinical Research Center (CRC) of Toulouse Teaching Hospital Center.

A fax notifying of the patient name, contact details and identifier will be sent to the CST in order to inform them of the patients' inclusion (regardless of the group). On the other hand, in order to inform the nurses at the monitoring center of a patient's inclusion in the telemonitoring arm, they will be sent a fax notifying of the name and contact details, but not the patient identifier no.

The equipment required for the telemonitoring group will be delivered to the patients' homes during the week following the inclusion visit.

The initial telephone contact by the CST (telephone visit at month 0) must take place during the days following the inclusion visit.

10.4. TELEPHONE VISITS

These visits will be conducted in the form of telephone contacts by the CST and will take place at 0, 6, 12 and 18 months with a margin of more or less 15 days. The CST will be coordinated by the Clinical Research Center of Toulouse Teaching Hospital Center.

The CST responsible for monitoring will be required to call the patient by telephone or in case of difficulty in contacting him/her, call a person assisting the patient and question him/her on various matters:

- Medico-economic questionnaire (month 6, 12 and 18)
- Societal acceptability questionnaire for the patients (month 0)
- SF-36 questionnaire (at months 0, 12 and 18) (administered only to the patient)
- Occurrence and reason for hospitalization.
- If the patient has died, the CST must obtain information from the investigator who included the patient concerning the cause and date of death. S/he will thus complete the end of study visit page of the eCRF.
- Occurrence of other adverse events
- Modification of concomitant treatments

The CST must enter the data collected in the eCRF.

The last visit in the comparative period will be telephone contact by the CST at 18 months.

For the patients in the standard management group only, during the last telephone contact, the CST must ask the patient whether s/he has scales at home and if so, whether s/he uses them at least once a week.

10.5. PREMATURE END OF STUDY VISIT

If the patient dies or a patient in the "intensive management" group withdraws from the study prematurely, the CST must be kept informed in order to schedule an end of study telephone visit as soon as possible. Since the nurses at the monitoring center are informed earlier of this type of event (systematic telephone call made in case of absence of data transmission), they will be entrusted with informing the CST using the end of study notification sheet.

During the last telephone contact, the CST must collect the assessment criteria from the patient or from the physician in case of death.

10.6. RULES FOR TERMINATING THE RESEARCH

The patients will be monitored until their death or until the end of the study (18 months).

The data of the hospitalization and death events will be collected within 18 months post inclusion.

Data collection will be continued over the extension period for the patients accepting to participate in the latter.

In case of withdrawal of consent, only the events beginning between inclusion and withdrawal of consent will be collected.

Premature withdrawal from the protocol will be performed:

- either as a result of a deliberate decision by the patient
- or by necessity, following a decision by the investigator in the following cases:
  - non-compliance with the study conditions
  - onset of a serious adverse event or undesirable effect
  - pregnancy

10.7. CONSTRAINTS RELATED TO THE RESEARCH AND POSSIBLE COMPENSATION OF THE PATIENTS

During the study, the patients randomized to the telemonitoring arm will be contacted every 3 weeks and data concerning the evolution of their disease will be collected daily.

As part of routine monitoring, the patient consults his/her general practitioner or referring cardiologist whenever s/he needs to do so.

The telecommunications process studied here does not involve any known undesirable effects.

We are not offering any financial compensation to patients receiving telemonitoring in one group or not modifying their daily life in the other.

Patients included in OSICAT cannot simultaneously participate in another research program. There is no inclusion period and the patients will not be enrolled in the national file of persons engaged in biomedical research.

11. MANAGEMENT OF ADVERSE EVENTS AND NEW FACTS

11.1. DEFINITIONS

Adverse event (Article R.1123-39 of the French Public Health Code)

Any harmful manifestation occurring in an individual participating in biomedical research, regardless of whether this manifestation is related or unrelated to the research.

Serious adverse event (Article R.1123-39 of the French Public Health Code and ICH E2B guideline)

Any adverse event which:

- ✓ results in death,
- ✓ endangers the life of the individual participating in the research,
- ✓ requires hospitalization or extension of hospitalization,
- ✓ causes an invalidity or a significant or lasting handicap,
- ✓ results in a congenital abnormality or malformation,
- ✓ or any event considered medically serious

and with regard to the medication, regardless of the dose administered.

Unexpected undesirable effect (Article R.1123-39 of the French Public Health Code)

Any undesirable effect of the product, the nature, severity or evolution of which is inconsistent with the information appearing in the dossiers for requesting the opinion of the CPP and for submitting a marketing authorization application to the competent authority.

New fact (order of 24 May 2006)

Any new item of safety data liable to result in reassessment of the benefit/risk ratio of the research, or which might be sufficient in order to consider modifications in the documents concerning the research, conduct of the research and if applicable, in use of the product.

11.2. DESCRIPTION OF THE EXPECTED SERIOUS ADVERSE EVENTS

The serious adverse events related to evolution of the disease are death or hospitalization of the patients for a cardiovascular cause.

No serious adverse events associated with the research are expected.

11.3. APPROACH TO BE ADOPTED IN CASE OF AN ADVERSE EVENT OR A NEW FACT

The investigator must notify the sponsor, immediately as and from the day on which s/he becomes aware thereof, of any serious adverse events or new facts, if occurring:

- as and from the date of signing consent,
- throughout the duration of patient monitoring scheduled by the research,
- up to 30 days after the end of monitoring of the participant scheduled by the research, when liable to be due to the research,
- until pregnancy reaches its term, when a pregnancy declaration is involved,
- without any limitation of duration when the SAE is liable to be related to the experimental management (serious event that may occur at an interval from exposure).

This declaration will be made using the declaration form located in the Investigator Study File

Since occurrence of death or hospitalizations is the main assessment criterion, both these SAEs will not be declared.

The study sponsor should be informed by telephone or fax <u>within 24 working hours</u> of occurrence of the serious adverse event.

The serious adverse event **declaration form,** duly completed for the attention of the sponsor, **should be filled in and forwarded <u>within 48 working hours</u>.**

[redacted]

All these events must be monitored until **completely resolved**. Additional information (supplementary declaration sheet) concerning evolution of the event, if not mentioned in the initial report, is to be forwarded to the sponsor by the investigator.

Becoming pregnant during the course of or immediately following a research program does not constitute an SAE. A pregnancy must however be reported according to the same methods as an SAE, since it will undergo specific monitoring until its outcome. Any abnormality observed in the fetus or infant will then be reported. Any voluntary termination of pregnancy (VTP), medical termination of pregnancy (MTP) or miscarriage must be the subject of a pregnancy notification and if requiring hospitalization, must be reported according to the same methods as for an SAE.

11.4. DECLARATION AND RECORDING OF UNEXPECTED SAES AND NEW FACTS

The sponsor/vigilance unit immediately declares any unexpected SAEs and new facts occurring during the research:

- to the National Agency for Medicines and Health Products Safety (ANSM);
- to the competent Committee for the Protection of Persons (CPP). The Committee ensures, if necessary, that the subjects participating in the research have been informed of the undesirable effects and that they confirm their consent.

12. STATISTICAL ASPECTS

12.1. SAMPLE SIZE CALCULATION

Calculation has been performed based on a type I error alpha risk of 0.05 and a power of 90%. We hypothesize that the intervention will help reducing the number of rehospitalizations and deaths (combined criterion) in the telemonitoring group versus the control group. We choose a bilateral hypothesis test. We have taken several hypotheses as a basis for this calculation:

- The first starts from a frequency of the combined criterion without intervention of 42% and a reduction in the relative risk of 46% (according to the bases of the Cochrane meta analysis; taking account of a bilateral hypothesis, for a power of 90% and an alpha risk of 5%), the number of subjects required per arm is 118, i.e. a total of 236 subjects.

- If we formulate a lower hypothesis for the frequency of the combined criterion, i.e. 32% and estimate the reduction in the relative risk of occurrence of the

combined criterion at 30% (according to the data observed in Germany, with the same device, but for cohort management, with an open label, without randomization, still taking account of a bilateral hypothesis, for a power of 90% and an alpha risk of 5%), the number of subjects required per arm is 446, i.e. a total of 890 subjects.

- **The data of the French and European registers point in favor of a frequency of occurrence of the combined criterion of 35%, still maintaining the same analysis conditions, i.e. a power of 90% and an alpha risk of 5%, if the reduction in the relative risk is 30%, the number of subjects required per arm is 393, i.e. a total of 786 subjects to which we add 10% of loss to follow-up, i.e. a scheduled overall cohort of 864 rounded up to a total of 870 subjects.** We thus guarantee that we are not eventually faced with a problem of lack of power. Finally, we compared our hypothesis with the most recent bibliographical data in the area (Lancet 2013 Jan 5; 381(9860):29-39; Cochrane Database Syst Rev. 2012 Sept. 12;9.). It emerges from this analysis that our figures are similar to those of these research programs, backing us in the hypothesis of a total of 870 patients.

12.2. STATISTICAL METHODS USED

All the study participants will be analyzed in the group to which they have been assigned (intent to treat analysis) in order to avoid an attrition bias. The two arms will be compared using a Student's test for continuous variables having a normal distribution, using a CHI2 test for discreet variables and using a Wilcoxon rank sum test for the categorial variables and continuous variables that are not normally distributed. Adherence to the intervention will be evaluated based on the number of days with teletransmitted weighing. The baseline demographic and clinical variable will be compared between the control group and telemonitoring group using descriptive statistics. It will be verified, despite random allocation of the patients to the two groups, whether significant differences concerning these variables might occur, in which case account will be taken thereof in the subsequent analyses relating in particular to the main objective of the study and the multivariate analyses. The rate of events (number of rehospitalizations or deaths) in the intervention group will be compared with that of the control group using Poisson regression with adjustment to an offset variable equal

to the duration of follow-up of each patient. Adjustments might be performed if confusion variables showed a significantly different distribution in the two groups. In case of overdispersion of the Poisson regression models, we will employ negative binomial regression (Poisson gamma regression). The periods of a composite variable (first hospitalization or death) will be represented for each of the groups using Kaplan Meier curves. These curves will be compared with each other using a log-rank test. We will also estimate the corresponding hazard ratios and their 95% confidence intervals using Cox proportional hazard models.

Additional subgroup analyses (stratified analyses) will be performed as [redacted] NYHA classification [redacted]. The interactions between these strata and the variable of interest will be systematically investigated. The number of readmissions for heart failure, the cumulative number of hospitalization days, the quality of life scores and the costs of treatment will also be analyzed as secondary objectives.

It is not possible at present to perform a blind study concerning the telephone telemonitoring section. As matters stand, we have decided on an open-label study, as with all the studies performed with this type of device. We have envisaged two solutions in order to offset the bias, particularly in terms of information:

- on the one hand, a per protocol analysis. This option might favor the telemonitoring arm, since one may believe that patients who comply with the telemonitoring will also comply with the lifestyle rules and the medications. Conversely, patients who comply with telemonitoring are maybe those who lead the least monitoring. At any rate, we will perform the analysis in intent to treat as initially scheduled; the per protocol analysis will be a supplementary approach.
- on the other hand, the risk in this study is that patients may be “under-medicalized” or “over-medicalized” in their management with regard to the recommendations of the moment apart from the intervention itself. Data concerning the various different aspects of management will be collected and analyzed subsequently in order to check for deviations from the study protocol.

The assessment criteria are criteria of limited subjectivity: death and hospitalization. Furthermore, these criteria will be assessed and certified based on a dossier by an independent study committee. The reason or grounds for each hospitalization will be identified and validated by this committee.

Study Extension period

The patients entering the extension period will be allocated to one of the following two groups:

- “Standard management / Tele-cardiology” group: patients from the “standard management” group of the comparative period entering the study extension period.

- "Tele-cardiology / Tele-cardiology" group: patients from the "tele-cardiology" group of the comparative period entering the study extension period.

All the analyses relating to the patients participating in the study extension period will be presented by group (Standard management / Tele-cardiology vs. Tele-cardiology / Tele-cardiology) and all in all.

The demographic variables will be presented for the patients included in the extension period.

For each patient, the annualized number of hospitalizations of all causes and the annualized number of hospitalizations of cardiovascular origin will be calculated for the comparative period and for the extension period.
The number of hospitalizations during the period of interest will be multiplied by the ratio [365 days / total number of monitoring days during the period of interest].
These numbers will be presented descriptively.

The number of deaths of all causes and the number of deaths of cardiovascular origin occurring during the extension period will be described. Overall survival will be represented using Kaplan Meier curves.

13. MONITORING OF THE RESEARCH

This study does not require setting up of a monitoring committee.

14. RIGHTS OF ACCESS TO THE SOURCE DATA AND DOCUMENTS

14.1. ACCESS TO THE DATA

The sponsor is responsible for obtaining the consent of all the parties involved in the research in order to guarantee direct access to all the places where the research is conducted as well as to the source data, source documents and reports for the purpose of quality control and auditing by the sponsor.
The investigators will make the documents and individual data that are strictly necessary for monitoring, quality control and audit of the biomedical research available to the persons who have access to these documents in accordance with the currently applicable laws and regulations (articles

L.1121-3 and R.5121-13 of the French Public Health Code) and in particular Regulation 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of individuals with regard to the processing of personal data and the free movement of such data (General Regulation on the Protection of Data - GRPD).

The contact details of the Data Protection Officer designated by the promoter are as follows:

[redacted]
Air Liquide
Data Protection Officer
75, Quai d'Orsay
75007 Paris - France
https://www.airliquide.com/fr/groupe/contactez-nous-rgpd

14.2. SOURCE DATA

Any document or original object allowing proof of the existence or accuracy of an element of data or a fact recorded during the research is defined as a source document.

The originals of the laboratory assessments, the hospital reports, the death certificates, the data in the patient's medical records and the scoring scales completed by the patient, the telephone call sheets and the eCRF will form the source data of this protocol.

14.3. DATA CONFIDENTIALITY

In accordance with the currently applicable laws (articles L.1121-3 and R.5121-13 of the French Public Health Code), the individuals having direct access to the source data will take all the necessary precautions with a view to guaranteeing the confidentiality of the data concerning the research, the persons engaged therein and more particularly with regard to their identity in addition to the results obtained. These persons, in the same manner as the investigators themselves, are bound to professional secrecy.

The practicalities for management of the patients randomized to the telemonitoring group or accepting to participate in the extension period do not allow maintenance of their anonymization from the sponsor's standpoint.

Consequently, the sponsor has submitted the research to the National Commission for Data Processing and Freedom (CNIL).

In the database, the patients will be identified by means of a patient code. This coding will consist of the center number (four digits), followed by the chronological number of inclusion (four digits) in this center.

The sponsor will ensure that each person engaged in the research has given his/her written consent to access to the individual data concerning him/her and strictly necessary for quality control of the research.

15. QUALITY CONTROL AND ASSURANCE

15.1. INSTRUCTIONS FOR DATA COLLECTION

All the data specified by the protocol must be recorded on the eCRF and an explanation must be provided for each element of missing data. The data must be recorded as their collection progresses.

15.2. MONITORING OF THE RESEARCH

The setting up and monitoring of the study delegated to the service provider companies acting on the sponsor's behalf. The research will be monitored by a clinical research associated (hereinafter known as the monitoring CRA) acting on the sponsor's behalf. S/he will be entrusted, before the coordinating physician, with:

- logistics and monitoring of the research,
- compiling the reports concerning the latter's state of progress,
- checking updating of the case report form (request for additional information, corrections...),
- communicating the SAEs to the sponsor.

S/he will work according to the standard operating procedures, in collaboration with the clinical research technicians (CRT) of the Clinical Research Center (CRC) of Toulouse Teaching Hospital Center.

The CRC will be responsible for coordinating the trial among the different centers and coordinating the work of the CRT entrusted telephone data collection.

15.3. QUALITY CONTROL

The monitoring CRA commissioned by the sponsor regularly visits each investigating center, during implementation of the research (in addition to 4 to 6 weeks thereafter in order to ensure that implementation of the study is progressing correctly in each center), several times during the

research according to the rate of the inclusions and at the end of the research as well as during the extension period. During these visits, the following elements will be reviewed:

- informed consent,
- compliance with the research protocol and with the procedures defined therein,
- quality of the data collected in the case report form: accuracy, missing data, consistency between the data and the source documents (medical records, appointment books, originals of the laboratory results, etc...).

Each visit will be the subject of a monitoring report by a written account.

15.4. DATA MANAGEMENT

An electronic case report form (eCRF) will be used to enter and manage the data. The software solution [redacted] will be supplied by the company [redacted]. [redacted] will also be in charge of data storage and technical maintenance of the electronic case report form (the company called upon by [redacted] to perform data storage will be the company [redacted]).

This electronic case report form will be accessible on line (SSL secure access) via any Internet navigator (Google Chrome ≥ V10, Mozilla Firefox ≥ V10, Internet Explorer ≥ V7 for PC; Safari ≥ V4 for Mac); it will not require installation of any additional software. Access will be performed via an Internet address specifically dedicated to the study (the corresponding domain name will be purchased after obtaining prior administrative authorizations; the sponsor will inform the CPP thereof as soon as the definitive address is obtained).

The user accounts will be created by [redacted], on request by the monitoring CRA. For security reasons, each new user will initially receive identifiers valid solely for the 1st connection; s/he will be asked on initial connection to change his/her password so that only s/he knows the latter.

The data will be collected by simply keying in:

- By the investigating physician during the inclusion visit and during the visit for inclusion in the extension period;
- By the investigating physician for hospitalizations and deaths occurring during the comparative period and extension period;
- By the CST of the Clinical Research Center of Toulouse Teaching Hospital Center during the monitoring telephone calls.

In order to ensure traceability of the data, for each page, data recording will systematically require the user's password in order to sign electronically and timestamp his/her entry.

Likewise, any modifications in the eCRF will systematically require the user's password in order to sign electronically and timestamp his/her entry.

The monitoring CRA will subsequently be entrusted with monitoring the data. The CRA will be able to send a request to the physician in case of missing or aberrant data. This request will also be timestamped and signed electronically and likewise the physician's reply.

The data are validated in accordance with the data management plan defined jointly between the coordinating investigator and the Methodology and Data Management Center.

Once all the data in the case report form are considered valid by the monitoring CRA, the latter will lock (freeze) the page(s) in question (or the entire case report form once the latter has been fully completed).

The process for freezing/thawing the data is conducted according to the procedure implemented in the Methodology and Data Management Center (export from the database of all the frozen data in CSV format, capable of subsequently being imported into SAS).

All the data are backed up daily at 11 p.m. (storage organization called upon: [redacted]), with storage for 1 month on a dedicated server and the whole will subsequently be archived monthly on tape.

15.5. AUDIT AND INSPECTION

An audit may be performed at any time by persons commissioned by the sponsor and independent from the persons responsible for the research. Its aim is to ensure the quality of the research, validity of its results and compliance with the currently applicable legislation and regulations.

The investigators undertake to comply with the requirements of the sponsor and the competent authority with regard to an audit or inspection of the research.

The audit may apply to all stages of the research, ranging from development of the protocol to publication of the results and archiving of the data used or produced within the context of the research.

16. ETHICAL AND REGULATORY CONSIDERATIONS

The sponsor and the investigator(s) undertake to ensure that this research is conducted in compliance with law no. 2004-806 of 9 August 2004, as well as in accordance with Good Clinical Practices

(I.C.H. version 4 of 1 May 1996 and decision of 24 November 2006) in addition to the Declaration of Helsinki (Ethical principles applicable to medical research in human subjects, Tokyo 2004).

The research is conducted according to the present protocol. Except in emergency situations requiring implementation of specific therapeutic procedures, the investigator(s) undertake to comply with the protocol in all respects, particularly with regard to obtaining of consent in addition to notification and monitoring of serious adverse events.

This research received a favorable opinion of the Committee for the Protection of persons (CPP) of Limoges on 30 May 2013 and authorization by the ANSM on 11 February 2013.

The sponsor of this research has taken out a civil liability insurance policy with the insurer [redacted].

The data recorded on the occasion of this research undergo computerized processing by service provider companies acting on behalf of the sponsor, in compliance with law no. 78-17 of 6 January 1978 concerning data processing, files and freedom, amended by law 2004-801 of 6 August 2004. Consequently, the sponsor has submitted the research to the National Commission for Data Processing and Freedom (CNIL).

PROTOCOL AMENDMENT

Any substantial modification, i.e. any change liable to a have a significant impact on protection of persons, on the conditions of validity and results of the research, on the quality and safety of the products being tested, on interpretation of the scientific documents that support progress of the research or concerning the practicalities for conducting the latter, is subject to a written amendment submitted to the sponsor; the latter must obtain, prior to its implementation, a favorable opinion of the CPP and an authorization from the ANSM.

Non-substantial modifications, i.e. those not having any significant impact on any aspect of the research whatsoever, are communicated to the CPP by way of information.

All amendments to the protocol must be brought to the attention of all the investigators participating in the research. The investigators undertake to observe the contents thereof.

Any amendment that modifies patient management or the benefits, risks and constraints of the research forms the subject of a further information note or a new consent form, obtaining of which follows the same procedure as that mentioned above.

17. STORAGE OF THE DOCUMENTS AND DATA RELATING TO THE RESEARCH

The following documents relating to this research are archived according to Good Clinical Practices:

– By the investigating physicians:

- for a period of 25 years following the end of the research

- The protocol and any amendments to the protocol
- The case reports forms
- The source dossiers of the participants having signed consent
- All the other documents and correspondence relating to the research
- The original of the signed informed consents of the participants

All these documents are under the investigator's responsibility throughout the regulatory archiving period.

– By the sponsor:

- for a period of 25 years following the end of the research

- The protocol and any amendments to the protocol
- The original of the case report forms
- All the other documents and correspondence relating to the research
- A copy of the signed informed consents of the participants
- The documents relating to the serious adverse events

All these documents are under the sponsor's responsibility throughout the regulatory archiving period.

They may not be moved or destroyed without the sponsor's consent. At the end of the regulatory archiving period, the sponsor will be consulted for destruction. All the data, documents and reports may undergo an audit or inspection.

18. RULES CONCERNING PUBLICATION

18.1. SCIENTIFIC COMMUNICATIONS

The data provided by the investigating centers are analyzed respectively by Dr. [redacted] (Epidemiology and community health laboratory of Toulouse Teaching Hospital Centre) and Prof. [redacted] (Epidemiology service of Toulouse Teaching Hospital Centre) for the medical part, by Prof. [redacted] (Medical Information Department of Toulouse Teaching Hospital Centre) for the medico-economic part and by Prof. [redacted] (University of Toulouse - UMR 5044 CNRS) for the societal part. This analysis yields a written report, which is submitted to the sponsor, who will communicate it to the Committee for the Protection of Persons and the competent authority.

Any written or oral communication of the results of the research must receive the prior consent of the coordinating investigator and the sponsor of the research and if applicable, any committee formed for the research.

A scientific committee will be formed. Its aim will be to validate the procedure and the publication plan of the articles produced based on the data of the comparative period and/or the extension period. It will be made up of the following members: [redacted].

Publication of the main results mentions the name of the sponsor, of all the investigators who included or monitored patients in the research, of the methodologists, biostatisticians and data managers who participated in the research. Account will be taken of the international rules for writing and publication (Vancouver Agreement, February 2006).

18.2. COMMUNICATION OF THE RESULTS TO THE PATIENTS

In accordance with law no. 2002-303 of 4 March 2002, the patients are informed, on their request, of the overall results of the research.

18.3. ASSIGNMENT OF DATA

The conditions for assigning all or part of the research database are decided by the research sponsor and are the subject of a written contract.

19. INVESTIGATOR'S AGREEMENT (SIGNATURE PAGE)

I have acquainted myself with the protocol entitled:

"Optimization of the Ambulatory Monitoring for Patients With Heart Failure by Tele-cardiology - **OSICAT**"

RCB ID no.: 2012-A01672-41

I hereby accept the contents and the methods of conducting this study.

I will do my best to perform the recruitments scheduled for the study during the inclusion period.

I will provide copies of the protocol and all the data that the Sponsor has supplied me to all the personnel involved. I will discuss these documents with the members of this personnel in order to ensure that they are perfectly informed about the tele-cardiology program which is the subject of the study and concerning the study schedule.

I hereby accept to archive the study documents *(the protocol and any amendments to the protocol, backup of the e-CRF on a medium appropriate to data archiving, the elements of correspondence, original document in hard-copy form, the source dossiers of the participants having signed consent, the original informed consent form signed by the participants, etc.)* for a period of 25 years.

I hereby accept to refrain from publishing all or part of the data concerning the present study, as stipulated by the clinical study contract signed between CDM e-Health and the investigator.

Investigator's name *(block capitals)*:

Date: Signature:

CDM e-Health
Name *(block capitals)*:
Capacity:

Date: Signature:

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APPENDICES

APPENDIX 1: CORDIVA FOLDER

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APPENDIX 2: IDENTIFICATION OF THE ALERT LEVELS

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