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STUDY DESIGN

Study design of Heart failure Events reduction with Remote Monitoring and eHealth Support (HERMeS)

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Abstract

Aims The role of non-invasive telemedicine (TM) combining telemonitoring and teleintervention by videoconference (VC) in patients recently admitted due to heart failure (HF) ('vulnerable phase' HF patients) is not well established. The aim of the Heart failure Events reduction with Remote Monitoring and eHealth Support (HERMeS) trial is to assess the impact on clinical outcomes of implementing a TM service based on mobile health (mHealth), which includes remote daily monitoring of biometric data and symptom reporting (telemonitoring) combined with VC structured, nurse-based follow-up (teleintervention). The results will be compared with those of the comprehensive HF usual care (UC) strategy based on face-to-face on-site visits at the vulnerable post-discharge phase.

Methods and results We designed a 24 week nationwide, multicentre, randomized, controlled, open-label, blinded endpoint adjudication trial to assess the effect on cardiovascular (CV) mortality and non-fatal HF events of a TM-based comprehensive management programme, based on mHealth, for patients with chronic HF. Approximately 508 patients with a recent hospital admission due to HF decompensation will be randomized (1:1) to either structured follow-up based on face-to-face appointments (UC group) or the delivery of health care using TM. The primary outcome will be a composite of death from CV causes or non-fatal HF events (first and recurrent) at the end of a 6 month follow-up period. Key secondary endpoints will include components of the primary event analysis, recurrent event analysis, and patient-reported outcomes.

Conclusions The HERMeS trial will assess the efficacy of a TM-based follow-up strategy for real-world 'vulnerable phase' HF patients combining telemonitoring and teleintervention.

Keywords Chronic heart failure; Telemedicine; mHealth; Outcomes research; Chronic care model; Transitional care

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Introduction

Despite the improvement in pharmacological treatment and other non-pharmacological approaches, heart failure (HF) remains a huge public health problem in developed countries.[1] Population studies have shown a rising prevalence of HF that leads to an increase in medical resource use and expenditure.[2] A significant proportion of such health expenditure is due to hospital admissions, and therefore, efforts to improve the delivery of chronic care and avoiding readmissions in these patients have been promoted in recent years.[3]

Readmission rates due to HF are high and tend to concentrate in the first few months after hospitalization.[4,5] For this reason, new multidisciplinary transitional care interventions have been focused on the so-called 'vulnerable phase' that comprises the period that begins immediately after hospital discharge and extends from 3 to 6 months during post-discharge follow-up.[3,6] Transitions of care in this period, including actions such as discharge planning, drug conciliation, and education, should ideally start during hospitalization before discharge.[5] Telemedicine (TM) has been proposed as one of the key components that may help to improve outcomes in transitional HF care programmes. Potential TM interventions include daily control of biometric data and symptoms (telemonitoring) and telemedical interventions such as structured follow-up based on telephone calls or videoconference (VC) to provide delivery of evidence-based care.[7,8]

Trials assessing separately the efficacy of structured follow-up (telephone) or telemonitoring have shown mixed results probably owing to differences in (i) the TM models evaluated, (ii) the HF patient populations included, and (iii) the health care contexts.[7–12] All these factors may explain why current clinical practice guidelines do not make specific recommendations regarding the use of non-invasive TM in the management of patients with HF.[1] Thus, the exact role and the potential benefits of delivering HF care by means of TM need further evaluation particularly in the setting of new transitional care models. In these new models, delivery of care based on the combined use of telemonitoring (to provide early detection of worsening and enabling early preventive therapeutic interventions) and teleintervention (to provide evidence-based structured follow-up by means of VC) is an appealing approach.

We piloted this strategy in a single-centre proof-of-concept clinical trial (The *insuficiència Cardíaca Optimització Remota* [iCOR] Heart Failure Remote Optimization).[7] In this small study, we demonstrated that adding a combination of telemonitoring and teleintervention to an existing comprehensive HF programme reduced the risk of non-fatal HF events and the risk of HF and cardiovascular (CV)-related readmissions as compared with structured follow-up based on face-to-face appointments. These benefits were seen across pre-specified subgroups of patients and were accompanied by a reduction in hospital costs and improvement in patient-centred outcomes.[7,13]

In order to confirm the results of the iCOR study and to assess the scalability of this mobile health (mHealth) based model of care in other health care areas and settings, we designed the 'Heart failure Events reduction with Remote Monitoring and eHealth Support' (HERMeS) trial. The HERMeS trial is a nationwide, multicentre, randomized study aimed to assess the effect of a TM-based comprehensive management programme on CV mortality and non-fatal HF events compared with usual care (UC) in patients with chronic HF. In this study, TM is delivered using mHealth technology that allows the combined use of telemonitoring of signs and symptoms and teleintervention by means of VC.

The present article provides a full description of the HERMeS trial design and the mHealth-based TM platform specifically designed for this study.

Study design

The HERMeS trial is a multicentre, randomized (1:1), controlled, open-label, blinded endpoint adjudication (PROBE) investigator-initiated study (ClinicalTrials.gov Identifier: NCT03663907).

Patients will be recruited for 24 months in 10 centres across Spain (*Appendices S1*, *S2*, and *S3*) and followed up for a fixed period of 6 months. The study protocol was approved by the institutional review boards of the coordinating centre (Bellvitge Biomedical Research Institute, *Institut d'Investigació Biomèdica de Bellvitge* [IDIBELL], Barcelona, Spain) and the recruiting centres. The study will be executed in accordance with the principles of the Declaration of Helsinki (1996); the International Conference on Harmonization Good Clinical Practice; and local, national, and international regulations, including the legal regulations about personal data confidentiality (Organic Law 3/2018 of 5 December on the protection of personal data and the guarantee of digital rights and, by extension, General Data Protection Regulation [EU] 2016/679). All enrolled patients will provide written informed consent for participation in the study.

The trial was designed and will be implemented by the HERMeS Steering Committee (*Appendix S4*). Safety will be reported by local investigators in accordance with the current legislation that regulates pharmacovigilance in Spain. Endpoint adjudication for the components of the primary outcome of the study will be performed by an independent endpoint committee (clinical endpoint committee [CEC]) blinded to the group allocation and to the recruiting centre on an ongoing basis according to the reporting of major events (death, readmissions, and non-fatal HF events) made by the local investigators (*Appendix S5*).

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Population and recruitment

The main inclusion criteria are (i) age ≥ 18 years, HF diagnosis according to European Society of Cardiology criteria, (ii) a recent hospital discharge after HF hospitalization (≤30 days), and (iii) written informed consent to participate. Detailed inclusion and exclusion criteria are shown in *Table 1*.

Randomization and stratification

Eligible patients before discharge or attending outpatient clinics, in a period of 30 days from discharge, will be screened and invited to participate in the study provided they fulfil inclusion and exclusion criteria. Participants will be randomized in a 1:1 ratio to control (UC arm) or intervention group (TM arm). Randomization will be stratified at each centre and according to the presence or absence of frailty to ensure balanced assignment of frail patients to each group. For the purpose of this study, frailty will be defined according to the criteria specified in *Table 2* in line with the definition used in the iCOR study.[7] The randomization process will be carried out centrally by a dedicated algorithm of the Research Electronic Data Capture (REDCap®) platform.

Study assessments and follow-up

All the patients included in the study will be followed up for 6 months (*Figure 1*). Briefly, patients included in the TM arm will be telemonitored and followed up according to a specific clinical pathway that includes pre-planned structured follow-up contacts with the health care team using VC. Patients in the UC arm will be followed up according to the UC of each recruiting centre. Because all the recruiting centres have active and mature ongoing HF programmes, no maximum number of pre-planned contacts has been defined, particularly in the UC arm. Details of the TM platform and the follow-up strategies of the two groups will be described later.

In both groups, patients and caregivers will receive health education to improve their self-care behaviours. All patients will be trained and encouraged to carry out daily self-monitoring of biometric data (weight, blood pressure [BP], and heart rate [HR]) and symptom self-monitoring in order to detect new episodes of HF that could be managed early with oral diuretic adjustments or intravenous diuretics on an outpatient basis without admission. In both groups, when an acute decompensation is suspected, nurses and physicians will promote diuretic dose adjustments following specific protocols and algorithms (*Appendix S6*) and/or obtain the immediate support of an HF specialist, who will make a decision according to the patient signs and symptoms (e.g. hospitalization, face-to-face visit, and day hospital). In case of unplanned contacts because of development of new symptoms or abnormal biometrics, decision making will depend on the judgement of the attending physician. In both groups, unplanned face-to-face contacts could be made if the clinical situation of the participants warrants it. In both arms, patients and caregivers will be able to contact health care professionals involved in patient care directly by telephone during working hours, depending on the availability of each HF unit.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Age ≥ 18 years • Patients discharged from an HF hospitalization within 30 days of enrolment into the study or in the process of discharge planning • HF diagnosis according to ESC criteria • Written informed consent obtained before any assessment is performed • Patients receiving oral standard medication for CHF • All patients will be eligible regardless of the level of LVEF: HFrEF, HFmrEF, and HFpEF	• Age < 18 years • Participation in another clinical trial • Moderate or severe cognitive impairment without a competent caregiver • Lack of social support • Institutionalized patients • Life expectancy > 1 year (excluding HF) • Institutional-based or end-of-life care • Serious psychiatric illness • Planned cardiac surgery • Planned heart transplantation or LVAD implant • Patients in haemodialysis programme • Death before hospital discharge • The patient is unable or unwilling to give the informed consent to participate • The patient is considered an unsuitable candidate for this study according to the decision of the local investigator • Unstable patients with signs of fluid overload or low cardiac output

CHF, chronic heart failure; ESC, European Society of Cardiology; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction.

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Table 2 Frailty criteria to stratify the patients included in the study before randomization

Frailty criteria[a]
• Age ≥ 90 years
• Age 85–89 years needing caregiver
• Barthel index < 90 points at any age
• Pfeiffer test ≥ 3 mistakes at any age
• Patient is or will be planning a Home Care Program (ATDOM programme)

ATDOM, (*Atenció Domiciliària*) home health care.
[a]Any participant will be considered as fragile if he or she meets at least one of the prior criteria.

Telemedicine group: the PIRENe platform

Follow-up and treatment of patients in the TM arm will be based on the PIRENe platform. The PIRENe platform (Platform for the Provision of Tele-Intervention, Remote Monitoring and Empowerment to people with advanced/complex chroNic [CV] disease based on electronic health [eHealth]) is a comprehensive solution for the care and monitoring of chronic patients, modelled and tested in chronic HF patients (*Figure 2*). This platform allows the provision of multichannel service and monitoring of patients through the following:

1 Patient monitoring of

a Biometric data (weight, HR, and BP);
b Symptom report: seven questions to capture the worsening of the symptoms of heart disease, mainly worsening of the HF, and one question to capture general deterioration (*Table 3*). The questions are posed to answer 'yes' or 'no'.

2 Generation and management of warning alarms notified to the professionals assigned to each patient in case one of the following situations occurs:

a Out-of-range biometric data (according to preset ranges specified in *Appendix S7*).
b Any alarm symptom among the answers to the questionnaire (one 'yes' answer in the questionnaire generates a warning alarm in the platform).
c Absence of biometric measurements on any given day.

FIGURE 1 Flow chart of the study. CV, cardiovascular; HF, heart failure; PROMs, patient-reported outcome measures; TM, telemedicine; UC, usual care.

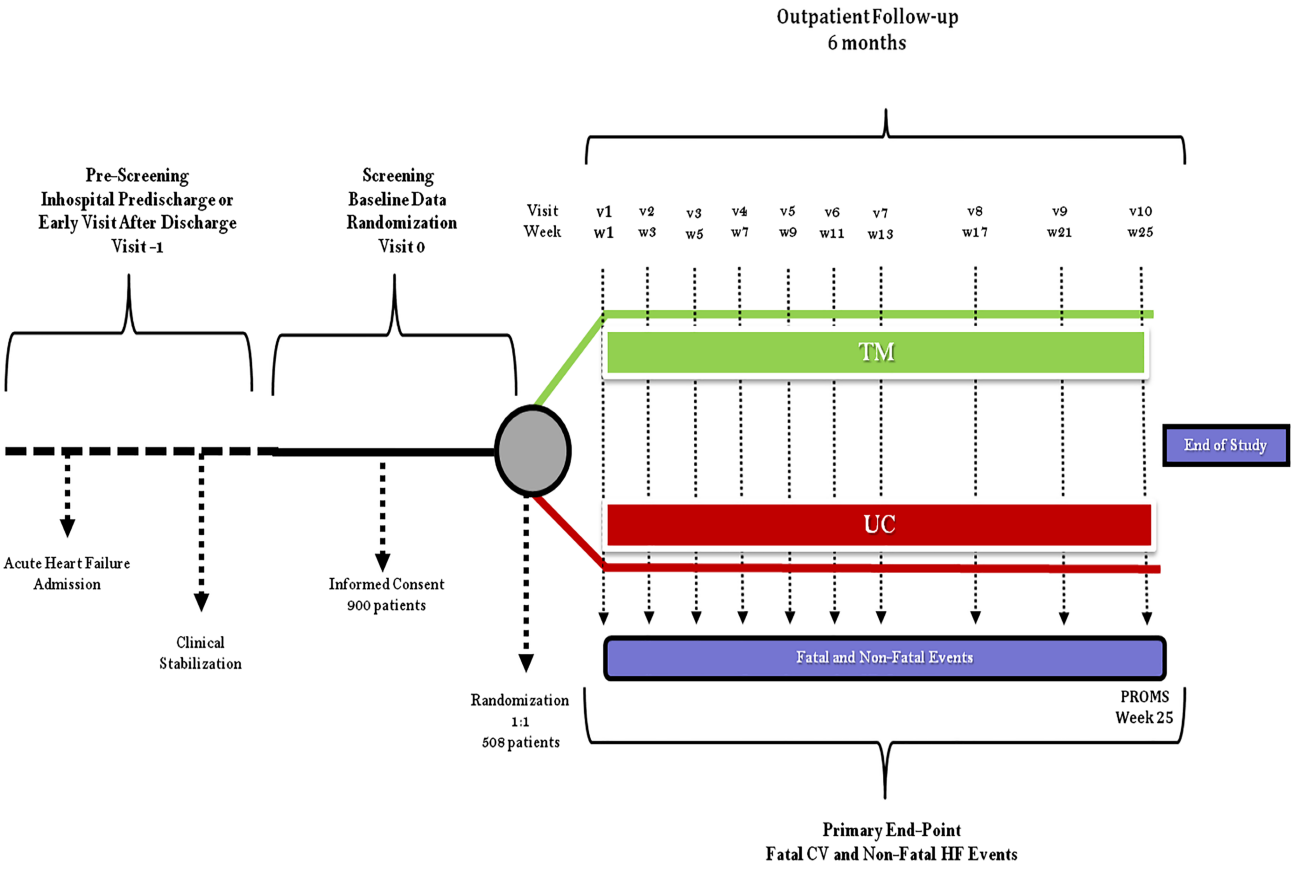

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FIGURE 2 The PIRENe platform (Platform for the Provision of Tele-Intervention, Remote Monitoring and Empowerment to people with advanced/complex ChroNic [CV] Disease based on e-Health).

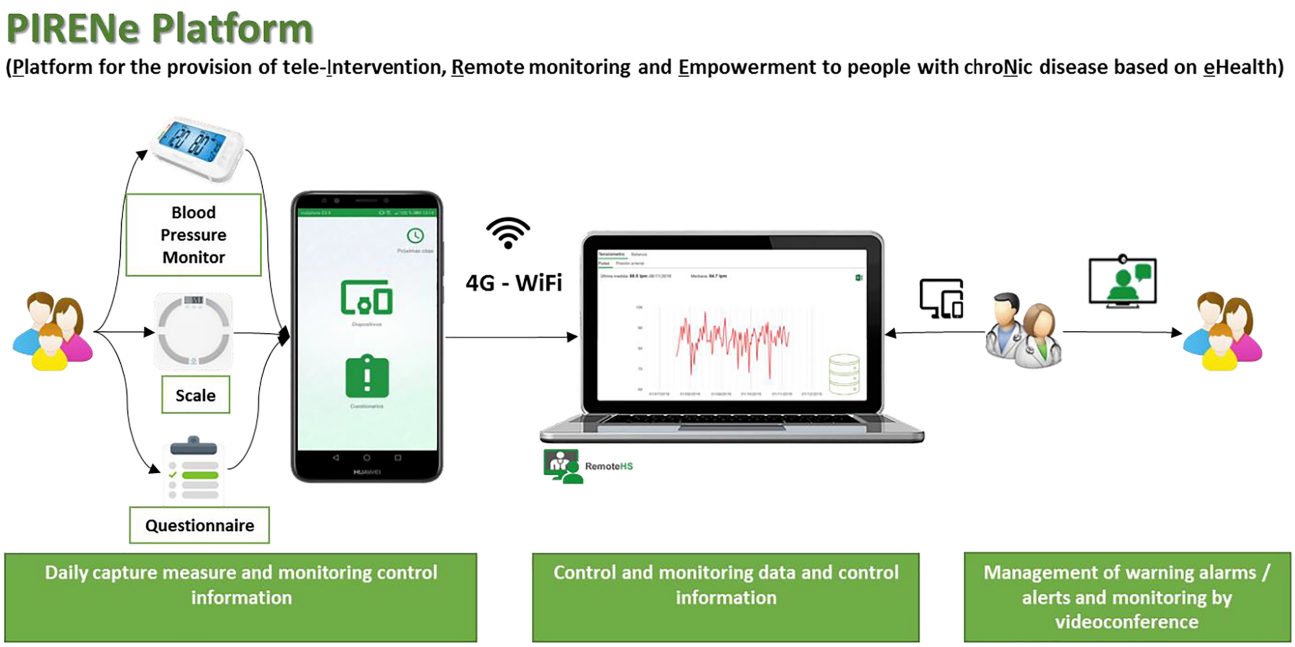

Table 3 Daily symptom telemonitoring

Symptom report	Answers
1. My feet are more swollen than usual.	Yes/No
2. I feel more fatigued, tired or with a sensation of choking.	Yes/No
3. I had bad nights because of shortness of breath or sensation of choking.	Yes/No
4. I needed more pillows to breathe better at night lying on my bed.	Yes/No
5. I had to sleep seated because of shortness of breath or sensation of choking when lying on the bed.	Yes/No
6. I felt weaker or more dizzy than usual.	Yes/No
7. I had more breast pain than usual.	Yes/No
8. In general, I feel worse than usual.	Yes/No

This will allow medical professionals to contact the patient proactively and thus be able to act earlier.

3 Follow-up via teleconsultation (videoconferencing, audio conferencing, mailing, and management of incoming and outgoing calls) between professionals and patients/caregivers

The platform is composed of three key technical elements: (i) a health care web application interface for health care professionals (PIRENe Platform website). This application is a clinical workstation designed to store basic patient information. It allows videoconferencing, management of agendas (patient and health care professionals), and the specific gateway assigned to each patient, as well as to retrieve biometric values and responses to the symptoms questionnaire to be assessed by the nursing and medical staff; and (ii) a household patient interface (app version for smartphone with Android operating system of the PIRENe platform). This is the gateway to the TM platform for receiving and sending information (4G or WiFi). By means of the designed app, patients and caregivers will manage the daily monitoring of biometric data retrieved from peripheral devices (scale and BP/HR monitor) by Bluetooth, and symptoms will be retrieved from questionnaires available in the app. Planned VCs will also be launched through the app (4G or WiFi); and (iii) monitoring devices: digital scale and BP/HR monitor with Bluetooth connection provided to the patients. Linking of data between medical devices, gateway, and the clinical workstation will be performed according to national regulations for the of handling personal data. At the beginning of follow-up, each patient randomized to the TM arm will be provided with the equipment detailed in *Appendix S8*.

As mentioned earlier, the follow-up of patients is based on a standardized clinical pathway. The assessments performed at each visit (evaluation schedule) are shown in *Table 4*.

Usual care group

Patients randomized to the UC arm will be followed up for 6 months, with no maximum number on planned face-to-face contacts, and will receive the standard of care considered UC at each centre. As mentioned before, all participating centres

Table 4 Evaluation schedule

Variables	V1 Baseline[a]	V2 Week 3	V3 Week 5	V4 Week 7	V5 Week 9	V6 Week 11	V7 Month 3	V8 Month 4	V9 Month 5	V10 Month 6
Demographic	x									
Aetiology of HF	x									
CV risk factors	x						x			x
Co-morbidity	x						x			x
Treatment	x									x
BP, HR, weight	x	x	x	x	x	x	x	x	x	x
Height, BMI	x									
NYHA	x	x	x	x	x	x	x	x	x	x
Signs and symptoms	x	x	x	x	x	x	x	x	x	x
EKG	x						x			x
Echocardiography[b]	x									x
Laboratory values[b]	x						x			x
EQ-5D, VAS	x									x
Barthel, Pfeiffer, FRAIL	x									
Socio-economic variables	x									
EHFSCBS	x						x			x
Satisfaction	x									x
Events	x	x	x	x	x	x	x	x	x	x
Technological use	x									x

[a]The initial visit will be the only face-to-face visit of the study. The rest of the visits will be by videoconference in the TM arm.
[b]In the first visit, the last data available before the visit will be recorded; and in the final visit, the last data available before the visit will be recorded, when available (non-mandatory data).
BMI, body mass index; BP, blood pressure; CV, cardiovascular; EKG, electrocardiogram; EHFSCBS, European Heart Failure Self-care Behaviour scale; EQ-5D, European Quality of Life 5 Dimensions; FRAIL, fatigue, resistance, ambulation, illnesses, loss of weight; HF, heart failure; HR, heart rate; NYHA, New York Heart Association; TM, telemedicine; VAS, visual analogue scale.

have active integrated HF programmes in place delivering (i) nurse-based coordination of care, (ii) education to patients and caregivers, (iii) pro-active up-titration of HF disease-modifying drugs, (iv) cardiac rehabilitation and other usual interventions provided in HF programmes, and (v) open access clinics to treat HF worsening without hospital admission. The participating centres represent a wide range of HF models deployed in different settings (tertiary, secondary, and community hospitals and home-based primary care programmes), coordinated by different specialties (cardiology, internal medicine, and primary care) in the various Spanish regions with differences in the organization of health care. In both arms, unplanned contacts will be permitted in the event of clinical deterioration.

Data collection

The medical history, relevant clinical and demographic information, a physical examination, laboratory tests, functional, cognitive, and socio-family evaluation, and the technology skills of patients included in the study (*Appendix S9*) will be obtained at baseline and at the final study visit. Clinical events will be prospectively captured by investigators and reported through a dedicated formulary of the electronic case report form. These events will be allocated and validated by CEC members during the study. All data will be registered in the REDCap® platform.

Outcomes and event adjudication

The primary outcome will be a composite of death from CV causes or non-fatal HF events (first and recurrent) at the end of the 6 month follow-up period as previously used in other studies.[14,15] A non-fatal HF event is defined as a new episode of worsening of symptoms and signs consistent with acute decompensated HF requiring intravenous decongestive therapy (e.g. diuretics) either on an outpatient basis (e.g. day-case HF hospital or at home) or in the emergency department ($<$24 h), or requiring unplanned hospital admission ($>$24 h) or complicating the course of a non-CV admission.

Key secondary endpoints will include components of the primary event analysis (all-cause, CV and HF death, and/or hospitalization), days spent in the hospital (length of stay for readmission), emergency visits, patient-reported outcome measures such as self-care behaviour and health-related quality of life (European Quality of Life 5 Dimensions), and patient-reported experience measures.

As stated previously, the CEC will adjudicate all the events reported during the HERMeS trial to be used for the analyses of the primary and secondary endpoints (*Appendix S10*), according to pre-specified criteria (*Appendix S11*).

Statistical methods

Sample size

According to our previous data,[7] the expected event rate for the primary endpoint (CV death or non-fatal HF event) in the control group would be 49% after 6 months of follow-up. To obtain a reduction of 25% in the rate of the primary endpoint in the group managed with TM, and assuming an alpha risk = 0.05 and a beta error of 20%, we need to recruit 508 analysable patients (254 patients in each arm). We estimate that a 25% reduction in the primary endpoint would drop the expected event rate of this endpoint from 49% in the control group (UC) to a 36% in the TM group. Thus, in our opinion, this reduction is clinically relevant.

Analysis of primary and secondary outcomes

Details on the final statistical analyses will be defined in a dedicated complete statistical analysis plan after the last patient's last visit and before the database lock.

a Time to first event analysis:The incidence of events in the two study groups (TM and UC) will be described using Kaplan–Meier survival functions, which will be compared using the log rank test. Additionally, we will use Cox proportional risk regression models to obtain the hazard ratio of each of the events under study by comparing TM (as exposure to study) with UC as a reference group.

b Recurrent event analysis:A bivariate negative binomial regression analysis will be performed to determine the effect of the intervention on CV hospitalizations and non-fatal HF events (first and recurrent). Coefficients from this method will be estimated by accounting for the positive correlation among the recurrent outcome and death as a terminal event, by linking the two simultaneous equations (readmission count and death) with shared frailty.[16] In addition, each patient's follow-up time will be used as an offset in the models to account for differences in the follow-up. By using this methodology, the potential for bias due to death as informative censoring is minimized, an issue commonly seen in acute HF studies. Risk estimates from this method are presented as incidence rate ratios and 95% CIs.

The subgroup analyses for the primary event will be previously specified in the final statistical analysis plan, based on relevant clinical characteristics such as the left ventricular ejection fraction (LVEF), age, or gender, among others. Once defined, the interactions between the subgroups and the type of management (TM vs. UC) in the primary event will be evaluated.

Discussion

The HERMeS trial is an unique clinical trial since it (i) integrates mHealth as a management tool in patients with HF combining two key elements of TM (telemonitoring and structured teleintervention); (ii) evaluates the impact of the simultaneous use of these two modalities of TM in the most 'vulnerable phase' of patients with HF; (iii) integrates mHealth in pre-existing HF programmes with a high standard of care and covering a broad range of care models and settings; and (iv) includes real-world patients in terms of co-morbidities, frailty, or range of LVEF.

Beyond telemonitoring and teleintervention, the PIRENe platform allows promoting self-care and self-efficacy of patients by providing them with up-to-date information about the individual progression of their own biometrics and self-perceived health status. From our previous pilot experience, we believe that the care delivered with the modality of TM used in the present study will translate into an improvement of outcomes. Particularly, combining, from one side, teleintervention by VC to deliver structured pre-planned interventions and, from the other side, telemonitoring of signs and symptoms, may be an effective strategy especially for those patients with HF in the so-called 'vulnerable phase' , the period that encompasses discharge from an acute HF admission and the following early post-discharge period. Besides, from the subgroup analyses of the iCOR study,[7] we believe that the benefit will extend to all HF patients in the 'vulnerable phase' regardless of LVEF,[13] presence of frailty, depressive symptoms, or co-morbidities. The purpose of the HERMeS trial will also include validation of the main results of the iCOR study in a nationwide 'vulnerable phase' HF patient's cohort and confirm the robustness of the results among different clinical subgroups of patients and diverse health care settings. According to all these aspects, the HERMeS trial will address the current gap of knowledge regarding the right strategy in the managed care in early post-discharge period or 'vulnerable phase' in patients with HF and will allow the generalization of the results found in the iCOR study. Additionally, it will help to define the profile of patients that could benefit most from a mHealth-based management strategy combining telemonitoring and teleintervention in integrated care settings.

In the care process focused on transitions of care, there are potential advantages of using a modality of TM that combines telemonitoring and teleintervention. Firstly, it allows remote monitoring of biometric data and/or symptoms to enable the early detection and monitoring of decompensation and other clinical events that would otherwise lead to readmission; secondly, it establishes a channel of communication with patients from their home to conduct structured follow-up after discharge, either by the means of telephone calls or VC. These virtual pre-planned encounters may allow nurses educating the patient and the caregiver in order to promote patient empowerment and adequate self-care behaviours. Moreover, remote monitoring is a source of individual biometric and symptoms data that can be leveraged to create opportunities for drug optimization, because they may facilitate the decision-making process of up-titration of HF disease-modifying drugs in these patients.[7,8] The target population that can benefit most from this management strategy is the one that has a higher risk of presenting new HF (fatal or non-fatal) events. Early detection means early treatment, thus slowing disease progression and reducing clinical events and health care costs.[7,17,18] As previously mentioned, the iCOR study[7] demonstrated the positive impact of combined remote monitoring and teleintervention on HF patients during the transition between discharge and early post-discharge ambulatory care. Therefore, in o ur study, we built a mHealth platform capable of providing the combination of these two modalities of TM during the so-called 'vulnerable phase' of HF where most adverse events concentrate in these patients.[5]

In the current health care context of aging and multiple co-morbidities, these models of remote care have many advantages. In contrast with usual HF programme models, where only highly selected patients are candidates to be managed in hospital-based units and delivery of care is based on face-to-face encounters, these new remote management transitional care models delivered using mHealth platforms allow extending a high standard of care to real-world patients who are often expelled from specialized hospital care. Interestingly, in our previous study, we showed that the efficacy of TM combining telemonitoring and teleintervention was similar in all patients regardless of age, frailty, co-morbidities, and ejection fraction.[7,13] This approach will reduce patient inequalities in access to good quality of care. The organization of care around the natural place for patients (home) by means of TM will engage productive interactions with primary care professionals. This fact will promote a truly integrated care in these patients and will raise de bar of quality of care among primary care professionals.

The development that we propose can transform the current management process in symptomatic patients with HF, particularly in those in the 'vulnerable phase' of the disease. This may eventually translate in new recommendations in clinical practice guidelines regarding the use of TM in the managed care of patients with HF and subsequently in the design of prevention policies or procurement of public health systems. The methods and approaches we evaluate in the setting of HF management may find a broader application elsewhere in cardiology and other areas of medicine involving the management of chronic conditions. Our study may help, through big data analysis of biometric data, to refine prediction models, redesign clinical protocols, and prompt earlier preventive interventions.[19]

This project represents an important step in linking technology with clinical science and incorporates mHealth as another tool for the follow-up of patients with HF. Previous studies have evaluated mobile technology by using it in the form of either telephone calls or electronic messages.[7,9,11,17] However, the evaluation of the efficacy of mHealth combining both remote monitoring and teleintervention by VC on outcomes and disease progression in the ambulatory management of HF[20] particularly in patients with HF in the 'vulnerable phase' has not previously been addressed. The HERMeS trial will provide the adequate framework to address this gap of knowledge.

In summary, this project has the potential for significant advances in clinical management, resulting in direct improvements to the lives of many thousands of HF patients.

Conclusions

The HERMeS trial will assess the efficacy of TM combining telemonitoring and teleintervention in real-world HF patients with recent hospitalization. We believe that this mHealth-based strategy of delivering managed care will translate into a significant reduction in mortality or hospital readmissions in these high-risk patients in the 'vulnerable phase' of the disease.

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Conflict of interest

The authors declare that they have no conflicts of interest relevant to the content of this manuscript.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. The HERMeS trial participating centres.
Appendix S2. The HERMeS trial participating centres (collaborating investigators).
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Appendix S4. The HERMeS steering committee.
Appendix S5. The HERMeS clinical endpoint committee (CEC).
Appendix S6. Algorithm in case of suspected HF decompensation.
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Appendix S9. Functional, cognitive and frailty assessment, patient-reported outcome measures (PROMS) and patient-reported experience measures (PREMS) performed in the trial.
Appendix S10. The HERMeS clinical endpoint committee (CEC) adjudication workflow.
Appendix S11. The HERMeS clinical endpoint committee (CEC) adjudication criteria for events.

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