# Study Protocol

NCT05708846

13th November 2023

# Clinical Study Protocol

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| **Protocol Title:** | "Observational study for the improvement of a digital health platform for remote monitoring of patients with heart failure." |
| **Study type:** | Observational study with software as a medical device. |
| **Protocol Version Date:** | 5th version, 13th November 2023 |
| **Principal Investigator:** | Julio César Blázquez, MD<br>Hospital de Torrevieja, Chief of Internal Medicine Unit<br>blazquez_jul@gva.es |
| **Sponsor:** | FollowHealth, S.L.<br>C/Aristides Maillol, 17<br>08028, Barcelona |
| **Investigation product:** | ● HumanITcare digital platform software<br>● In-platform alarm-based system |
| **Class of device:** | CE marked - Class I (MDD) at the beginning of the study |
| **Indication:** | Heart Failure |
| **Confidentiality:** | This is a confidential document. It contains proprietary information of FollowHealth, S.L.. Any viewing or disclosure of such information that is not authorized in writing by the Sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study. |

**SIGNATURE PAGE(S)**

**Protocol number:** FOLLOWHEALTH-2023-01

**Protocol title:** “Observational study for the improvement of a digital health platform for remote monitoring of patients with heart failure.”

Principal Investigator of the study:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm and the local legally applicable requirements.

Julio César Blázquez Encinar

# SYNOPSIS

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| **Sponsor:** | FollowHealth, S.L.<br>C/Aristides Maillol, 17<br>08028 Barcelona |
| **Study Title:** | "Observational study for the improvement of a digital health platform for remote monitoring of patients with heart failure." |
| **Protocol Version:** | 5th version, 13th November 2023 |
| **Study Design:** | Multicenter, Observational study |
| **Indication:** | Heart Failure |
| **Background and Rationale:** | This study is being conducted in the framework of a European project promoted by the European Innovation Council. An earlier version of the platform was validated in a study conducted in 2020 at Hospital de Torrevieja focused on Heart Failure. The rationale for this study is in line with HumanITcare's goal of incorporating artificial intelligence tools to optimize the digital platform. |
| **Study Objectives:** | *Primary endpoint*<br>A. Create a labeled and diverse dataset with the following data:<br>- Physiological parameters: heart rate, calories consumed, steps count, physical activity, oxygen saturation, heart rate variability measurements, stress levels, sleep tracking data, systolic and diastolic blood pressure, weight, BMI<br>- Socio-demographic data: sex, age, ethnic group, employment, level of education, number of people living with the patient, caretaker<br>- Risk factors: comorbidities, diabetes, hypertension, smoking, alcohol consumption, heart disease history<br>- Medication tracking: lipid-lowering medication, PCSK9 inhibitors, beta-blockers, anticoagulation agents, ACE inhibitors, anti-arrhythmic drugs, anti-inflammatory drugs, aldosterone antagonists, angiotensin receptor/neprilysin inhibitor, diuretics, antidiabetic agents, Vericiguat, SGLT2 inhibitors, Ivabradina<br>- Symptomatology questionnaire for patients<br>- NYHA-class<br>- Left Ventricular Ejection Fraction (LVEF)<br>- Clinical interventions: hospital readmission, mortality, emergency department visits, non-fatal HF events<br>- Health questionnaire answers: self-care, quality of life<br>- Classified alarms with their respective timestamp and annotation by the MD<br>- Measurement ranges for each personalized alarm and their changes<br>B. Implementation of machine learning models to improve the current alarm-based system to provide a relevance level for each new alarm by reducing the number of irrelevant alarms and thus fostering personalized follow-up. |

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| | *Secondary endpoints*<br>Development and implementation of ML event prediction algorithms that will add new self-generated alarms to the system. These alarms should forecast:<br>● Untracked hospital interventions, such as emergency department visits or hospital readmissions.<br>● Changes of medication with their particular estimated dose.<br>● Clinical events, such as mortality.<br>Assessment of patient and medical professional's satisfaction with and usability of the digital platform at the end of the study by means of the "System Usability Scale" (SUS) and the "Post-Study Usability Questionnaire" (PSSUQ). |
| **Study Population:** | Approximately, 500 patients |
| **Eligibility criteria:** | *Inclusion criteria*<br>● Heart failure (HF) patients with NYHA Functional Class >= II (according to 2021 EU guidelines).<br>● Patients who have suffered an acute decompensation of HF (first and recurrent) in the 30 days prior to enrollment in the study.<br>An acute decompensation of HF is defined as a new episode of symptoms and signs that requires intravenous decongestive treatment or an increase in oral diuretics, either on an outpatient basis (e.g., hospitalization for HF during the day or at home) or in the emergency service or that requires an unplanned hospital admission.<br>● NT-pro BNP ≥300 pg/mL or BNP ≥100 pg/mL at the time of inclusion in the study for patients without ongoing atrial fibrillation/flutter. If there is ongoing atrial fibrillation/flutter, NT-pro BNP should be ≥600 pg/mL<br>● Patients must have had an echocardiogram during their HF hospitalization or the previous 12 months.<br>● Prior to the initiation of any procedures, the hospital will ensure that an informed consent document completed by the patient is obtained.<br>● All patients will be eligible regardless of the level of LVEF: HFrEF, HFmrEF, and HFpEF.<br><br>*Exclusion criteria*<br>● Oncology patients with metastasis or with chemotherapy treatment ongoing<br>● Patients participating in other studies or trials.<br>● Patients not willing to participate.<br>● Patients over 150 kg |

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| | ● Patients who do not use Catalan, Spanish, English, Portuguese, Italian, Dutch, German, Swedish, Hungarian, Romanian, or French.<br>● Patients without a mobile phone<br>● Patients without internet connection<br>● Patients with moderate or severe cognitive impairment without a competent caregiver.<br>● Patients with severe psychiatric illness.<br>● Patients with planned cardiac surgery.<br>● Patients with planned heart transplant or LVAD implant. |
| **Recruitment strategy:** | When a patient is eligible according to the criteria, he/she must complete the informed consent provided on day 0. Each hospital will decide when to include their patients according to their particular clinical practice (either in the process of discharge planning or during the first follow-up visit, i.e.. 1 or 2 weeks after discharge). Patients will be monitored for 6 months, with a recruiting period of 6 months. The last subject included will then finish the study after one year from the first day of the study. |
| **Data Analysis:** | There is no power calculation associated with the study since it is an observational study. Once the algorithms are developed, model performance in terms of accuracy will be evaluated by means of C statistic, area under the receiver operating characteristic curve, and creation of a calibration plot. Furthermore, the models will be evaluated in terms of fairness and potential bias using metrics including statistical parity, group fairness, equalized odds, and predictive equality. |
| **Study Schedule:** | February - March 2023: CEIm approval<br>April 2023: study kick-off<br>October 2023: recruitment period completed.<br>April 2024: last patient, last visit<br>May 2024: results analysis and final report draft |
| **Clinical Procedures:** | Phase 1: Hospitals selection and coordination. CEIm approvals.<br>Phase 2: Study execution:<br>Day 0. Patient enrollment: study explanation, informed consent completion, patient data completion, provision of medical devices and access credentials, and first questionnaires.<br>Day 0 until the end of the study:<br>- Physiological constants monitored.<br>- Patient answers to questionnaires.<br>- Control calls in case of missing data<br>- Report every hospital readmission, mortality, emergency department visit or non-fatal HF event of each patient.<br>- Report changes of medication and their doses by the medical professional.<br>- Patient in-person follow-up: at day 0, at day 7, at month 3, at month 6.<br>Last day. Follow-up visit. Completion of last questionnaires. Return |

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| | the medical devices. |
| **Questionnaires:** | ● Minnesota Living with Heart Failure Questionnaire (MLHF) (Bilbao et al., 2016)<br>● European Heart Failure Self-care Behaviour Scale (EHFScB scale) (Jaarsma et al., 2009)<br>● Symptom report questionnaire: seven questions to capture the worsening of the symptoms of heart disease, mainly worsening of the HF, and one question to capture general deterioration.<br>● "System Usability Scale" (SUS) (*Brooke, J. (1986) SUS—A Quick and Dirty Usability Scale. Usability Evaluation in Industry, 189-194. - References - Scientific Research Publishing*, n.d.) and the "Post-Study Usability Questionnaire" (PSSUQ) (Lewis, 1992) will be delivered at the end of the study.<br>● Mobile Device Proficiency Questionnaire (Roque & Boot, 2018) |

# Table of contents

## 1 Identifier

“Observational study for the improvement of a digital health platform for remote monitoring of patients with heart failure.”

## 2 Administrative section

### 2.1 Sponsor

FollowHealth, S.L.
C/Aristides Maillol, 17, 08028 Barcelona

### 2.2 Principal Investigator(s)

Julio César Blázquez, MD
Hospital de Torrevieja, Chief of Internal Medicine Unit
Mail: blazquez_jul@gva.es

### 2.3 Ethics Committee

CEIm Hospital General Universitario de Alicante, Spain

### 2.4 Clinical centers

The study will comprise a total of 500 patients, approximately.

## 3 Regulatory status and activities

### 3.1 Regulatory / ethics status

The study will be performed in compliance with the Declaration of Helsinki (version in force; currently Fortaleza, Brazil, October 2013), and is to be conducted in accordance with Good Clinical Practice (CPMP/ICH/135/95).
The study will be conducted in accordance with the protocol and with the relevant legal requirements, following Law 14/2007 of July 3, 2007, on Biomedical Research.
The device class is CE marked - Class I (MDD) at the beginning of the study.

### 3.2 Informed consent

Participants will be informed of the anonymity and confidentiality of their data. They will be informed of the study, its objectives and methods, orally and by means of an information leaflet. Those patients who wish to participate in the study will receive an informed consent form that they will have to sign in order to continue in the study. The investigators will preserve patient anonymity, using the data collected only for the purposes indicated in this document and also, keeping anonymized data to be able to develop artificial intelligence. Sociodemographic and clinical data and the scales administered will be stored in coded form, and only the investigators will have access to them.
Informed consent will be requested and collected by a research assistant prior to the subject's inclusion in the study.

### 3.3 Data confidentiality

The processing, communication, and transfer of personal data of all participants will comply with the EU Regulation 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and the free movement of data, being mandatory as of May 25, 2018. The legal basis justifying the processing of your data is the consent given at the beginning of the study, in accordance with the provisions of Article 9 of EU Regulation 2016/679.

The data collected for these studies will be collected only by a code identification, so no information will be included to identify the participants. Only the study physician and collaborators with the right of access to the source data (medical record), will be able to relate the data collected in the study to the patient's medical record. The identity of the participants will not be available to any other person except in the case of a medical emergency or legal requirement.

Access to the identified personal information may be granted to the health authorities, the Research Ethics Committee and personnel authorized by the study sponsor, when necessary to verify data and study procedures, but always maintaining confidentiality in accordance with current legislation.

Only coded data will be transferred to third parties and other countries, which in no case will contain information that can directly identify the participant (such as name and surname, initials, address, social security number, etc.). In the event of such a transfer, it would be for the same purpose of the study described above and guaranteeing confidentiality, and after participant’s consent.

If a transfer of coded data were to take place outside the EU, either to entities related to the hospital center where the patient participates, to service providers or to researchers collaborating with us, the data of the participants will be protected by safeguards such as contracts or other mechanisms established by the data protection authorities.

As technology providers of the project, we commit ourselves to perform data processing in accordance with EU Regulation 2016/679 and, therefore, to keep a record of the processing activities we carry out and to perform a risk assessment of the processing we perform, in order to know what measures, we will have to implement and how to do it.

In addition to the rights already provided for in the previous legislation (access, modification, opposition and cancellation of data, deletion in the new Regulation), participants can now also limit the processing of data collected for the project that are incorrect, request a copy or that they be transferred to a third party (portability). To exercise these rights, they should contact the principal investigator of the study or the Data Protection Officer of the Hospital as data controllers. They also have the right to contact the Data Protection Agency if they are not satisfied.

Data cannot be deleted, even if a patient leaves the study, in order to guarantee the validity of the research and to comply with legal duties and drug authorization requirements.

The Investigator and the Sponsor are obliged to retain the data collected for the study for at least 1 year after completion of the study. Thereafter, personal information will only be retained by the facility for health care purposes and by the Sponsor for other scientific research purposes if the patient has given consent to do so, and if permitted by applicable law and ethical requirements.

a) Data Protection Considerations

FOLLOWHEALTH S.L. has cloud servers located in Ireland that comply with the General Data Protection Regulation of 25/05/2018 and the Data Protection Act (LOPD). In addition, the participant's data is encrypted both on the access platform for the research assistant as well as for the technical (IT) administrators of the study and on the server.
Furthermore, FITBIT and/or its suppliers comply with the Privacy shield policy.

b) Data pseudonymity

Participant data encryption: each participant is assigned a randomly generated 8-character participant ID (e.g., "d4w192bg"), and all participant data is connected only to that ID.
Other pseudonymity data: there are 4 types of information that are processed using the industry-standard SHA-256 hash algorithm that ensure pseudonymization:

- Incoming and outgoing call phone numbers.
- Incoming and outgoing text message phone numbers.
- MAC addresses of nearby Wi-Fi routers
- MAC addresses of nearby Bluetooth devices
- The server where the data is to be referenced must be identified.

"Hashing" this data means that each phone number and MAC address is converted into a random string of numbers and letters of 32 characters, but a certain phone number is always transformed into the same random string. It is also impossible (under current mathematical theory) to undo a hash.
Let's take as an example that participant d4maaw called the phone number 617-123-4567 once on Monday and then received two calls from that same number on Tuesday. A researcher analyzing the data obtained from the HumanITcare platform can see when those three calls occur and can tell that they all involve the same phone number but will not be able to tell what that phone number is.
"Hashing" the MAC addresses of Wi-Fi routers has the same effect. A researcher analyzing platform data could say that a participant was near a certain Wi-Fi router at 10 am every morning, Monday through Friday, and therefore could assume that the participant was probably in the same room at 10 am every morning, Monday through Friday, but the data would not reveal the actual MAC address of the router.

c) Data encryption

All data on the phones, on the server and in transit uses industry standard encryption techniques. The phone also uses asymmetric encryption, which means that even the phone cannot read its own data; data recorded on the phone can only be read on the server.
The fact that the server and the platform are encrypted makes it impossible to identify the user. In addition, FOLLOWHEALTH S.L. has a technical team that monitors and protects the cloud, the server and the database.

d) Possible data anonymity breaches

Only one type of data can contain personally identifiable information: GPS data (which record location).

The GPS data in the app provides sufficient detail to identify individual buildings or street addresses with some degree of confidence, although a fair amount of analysis will be required to transform a set of GPS coordinates into a residential address for a participant. The smartphone app is completely customizable when it comes to data collection, so a particular study could disable GPS data collection from a study, if desired, if it is not part of the research question.

### 3.3 Study registration

The study is intended to be registered before its initiation in the WHO primary register (ClinicalTrials.gov).

### 3.4 Scientific advice / protocol assistance

The study design is based on the previous study focused on Heart Failure with Hospital de Torrevieja and has been adapted to the present context by discussing the design with the multiple participating hospitals.

The technical scope of the study has been designed with the support of Dr. Karim Lekadir, Director of the Artificial Intelligence in Medicine Lab at the Universitat de Barcelona (BCN-AIM), and Dr. Polyxeni Gkontra, tenure-track lecturer at the Universitat de Barcelona and researcher at BCN-AIM lab.

### 3.5 Early termination of the study

The sponsor and other competent authority may terminate the study at any time according to certain circumstances, such as:

- ethical concerns
- when the safety of the participants is questionable or at risk, respectively
- alterations in accepted clinical practice that make it inadvisable to continue a clinical trial
- early evidence of harm from the experimental intervention

### 3.6 Protocol amendments

The content of the protocol may face corrections and updates according to the suggestions received by the sponsor and principal investigator after an evaluation process. Such suggestions should be delivered before the ethics committee approval. Substantial amendments are only applied after the approval of the ethics committee.

# 4 Background and rationale

## 4.1 Background and rationale

Heart Failure (HF) is a prevalent and fatal clinical syndrome that affects the quality of life of millions of people worldwide. Between 17% and 45% of patients suffering from HF die within the first year and the remaining die within 5 years (Tripoliti et al., 2017). Furthermore, those patients have a high risk of rehospitalization, their associated healthcare costs are huge, and the higher the life expectancy, the higher the disease's prevalence (McDonagh et al., 2021). HF symptoms commonly include shortness of breath, excessive tiredness, and leg swelling which may be worsened with decompensation (Schiff et al., 2003), and thus displacement to medical centers represents a handicap for such individuals. Remote monitoring technologies provide a feasible solution that allows earlier decompensation identification and better adherence to lifestyle changes and medication (Brahmbhatt & Cowie, 2019). Although telemonitoring by smartphones showed the potential to reduce both the frequency and the duration of HF hospitalizations (Koulaouzidis et al., 2016; Scherr et al., 2009), there was no association with the reduction of all-cause mortality (Koehler et al., 2011). Thus, it indicates there is a need to look for more effective and precise methodologies. In recent years, the use of wearable devices that allow daily monitoring of patient's physiological data combined with Artificial Intelligence (AI) has shown immense potential in predicting cardiovascular-related diseases, their adverse events and patient's health status (Lee et al., 2022), including that of patients with HF (Guidi et al., 2015).

HumanITcare has implemented a cloud platform and an alarm-based system that delivers health alarms when a patient's biomedical measurement is out of a predefined range. The platform relieves clinicians and caretakers of going through each patient's data to check for anomalies, accelerating the decision-making process and reducing hospital consultations. However, the system is creating many straightforward alarms that are finally being discarded after evaluation by the medical professional. In the present project, we propose to run an observational study in order to create a huge dataset with patients' clinical data that will contain annotations regarding the relevance of each alarm. With the annotated dataset we will be able to implement and train Machine Learning (ML) models that will improve the alarm-based system by making it more robust, trustworthy and reliable.

This study is being conducted in the framework of a European project promoted by the European Innovation Council (EIC). An earlier version of the platform was validated in a study conducted in 2020 at Hospital de Torrevieja focused on Heart Failure. The rationale for this study is in line with HumanITcare's goal of incorporating artificial intelligence tools to optimize the digital platform. While this study is focused on the creation of a diverse and labeled dataset and on the development of artificial intelligence event-prediction algorithms, a forthcoming second study will focus on the validation of the algorithms to assess their clinical effectiveness.

## 4.2 Evidence to Date

A single-center study was performed in 2020 in Hospital de Torrevieja in which an early version of the digital platform was validated. A total of 32 patients participated, 16 as a control group and 16 as a study group. The study group was monitored remotely using the HumanITcare digital platform and wearables (smart scale, blood pressure monitor, pulse

oximeter, and smartwatch) for 3 months, while the control group proceeded with the normal clinical praxis.
The results showed that patients monitored by the HumanITcare platform are 33% less likely to return to the emergency department. Besides, the study group showed a 40% reduction in hospital readmissions, and 92% of patients would recommend using the platform. Finally, 100% of clinical professionals agree that the platform improves health care and services, saves time in visits, and satisfies remote medical care, that it is an easy-to-use system and, moreover, easy to learn how to use it. In addition, the professionals state that the way of interacting with the system is pleasant and that the platform fulfills all the expected tasks.

# 5 Study design and endpoints

## 5.1 Study design

This is an observational study involving a European network of hospitals. The study consists of continuous remote patient monitoring using HumanITcare's digital platform and the supplied devices described below. For 6 months, a total of 500 patients suffering from Heart Failure (HF) will have their physiological constants monitored. The recruitment period is stated as 6 months since the beginning of the study.
The main objective is to create a diverse and labeled dataset of patients' parameters to nourish ML prediction algorithms and optimize the in-platform alarm-based system.

## 5.2 Primary and secondary endpoints

*Primary endpoints*

- Creation of a labeled and diverse dataset from a multicenter perspective. The dataset will contain the following data:
    - Physiological parameters: heart rate, calories consumed, steps count, physical activity, oxygen saturation, heart rate variability measurements, stress levels, sleep tracking data, systolic and diastolic blood pressure, weight, BMI
    - Socio-demographic data: sex, age, ethnic group, employment, level of education, number of people living with the patient, caretaker.
    - Risk factors: comorbidities, diabetes, hypertension, smoking, alcohol consumption, heart disease history
    - Medication tracking: lipid-lowering medication, PCSK9 inhibitors, beta-blockers, anticoagulation agents, ACE inhibitors, anti-arrhythmic drugs, anti-inflammatory drugs, aldosterone antagonists, angiotensin receptor/neprilysin inhibitor, other diuretics
    - Symptomatology questionnaire for patients
    - NYHA-class
    - Left Ventricular Ejection Fraction (LVEF)
    - Clinical interventions: hospital readmission, mortality, UCI visits
    - Health questionnaire answers: self-care, quality of life
    - Classified alarms with their respective timestamp and annotation by the medical professionals
    - Measurement ranges for each personalized alarm and their changes

- Implementation of ML models to improve the current alarm-based system using the dataset created. The models should:
    - Provide a relevance level for each new alarm by reducing the number of irrelevant alarms and thus fostering personalized follow-up.
    - Be robust across different new hospitals and reliable and fair across different target populations, considering the diverse sociodemographic data that will be available in the dataset.

*Secondary endpoints*

- Development and implementation of ML event prediction algorithms that will add new self-generated alarms to the system. These alarms should forecast:
    - Untracked hospital interventions, such as UCI visits or hospital readmissions.
    - Changes of medication with their particular estimated dose.
    - Clinical events, such as mortality.
- Assessment of patient and medical professional's satisfaction with and usability of the digital platform at the end of the study by means of the "System Usability Scale" (SUS) (Brooke, 1986) and the "Post-Study Usability Questionnaire" (PSSUQ).

# 6 Subjects/population(s)

## 6.1 Eligibility criteria

Subjects participating in the study must be diagnosed with Heart Failure according to the ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure.
2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure (McDonagh et al 2021)

*Inclusion criteria*

- Heart failure (HF) patients with NYHA Functional Class >= II (according to 2021 EU guidelines).
- Patients who have suffered an acute decompensation of HF (first and recurrent) in the 30 days prior to enrollment in the study.
  An acute decompensation of HF is defined as a new episode of symptoms and signs that requires intravenous decongestive treatment or an increase in oral diuretics, either on an outpatient basis (e.g., hospitalization for HF during the day or at home) or in the emergency service or that requires an unplanned hospital admission.
- NT-pro BNP ≥300 pg/mlL or BNP ≥ 100 pg/mL at the time of inclusion in the study for patients without ongoing atrial fibrillation/flutter. If there is ongoing atrial fibrillation/flutter, NT-pro BNP should be ≥ 600 pg/mL
- Patients must have had an echocardiogram during their HF hospitalization or the previous 12 months.
- Prior to the initiation of any procedures, the hospital will ensure that an informed consent document completed by the patient is obtained.
- All patients will be eligible regardless of the level of LVEF: HFrEF, HFmrEF, and HFpEF.

*Exclusion criteria*

- Oncology patients with metastasis or with chemotherapy treatment ongoing
- Patients participating in other studies or trials.
- Patients not willing to participate.
- Patients over 150 kg
- Patients who do not use Catalan, Spanish, English, Portuguese, Italian, Dutch, German, Swedish, Hungarian, Romanian, or French.
- Patients without a mobile phone
- Patients without internet connection
- Patients with moderate or severe cognitive impairment without a competent caregiver.
- Patients with severe psychiatric illness.
- Patients with planned cardiac surgery.
- Patients with planned heart transplant or LVAD implant.

### 6.2 Recruitment and screening

For the creation of the dataset, many hospitals have been contacted. Patients will be included in the study based on the eligibility criteria mentioned and must complete the informed consent provided on day 0. Patients will be monitored for 6 months after being included in the study on day 0. Each hospital will decide when to include their patients according to their particular clinical practice (either in the process of discharge planning or during the first follow-up visit, i.e.. 1 or 2 weeks after discharge).
The recruitment period is defined as 6 months. That means patients will be incorporated into the study from its start until the sixth month. The last subject included in the study will then finish the study after one year from the first day of the study (study KICKOFF: first patient - first day).
Medical professionals from each hospital will be in charge of recruiting the participants. The recruitment rate is specific for each hospital, and it may vary depending on the month.
If the recruitment target is not reached for a specific center at the end of the recruitment period (6 months), the latter may be extended until the accorded number of participants recruited is satisfied under the hospital decision.

### 6.3 Criteria for withdrawal/discontinuation of participants

There are several situations in which the participant may be withdrawn from the study, including the development of an exclusion criterion during the execution of the study, withdrawal of informed consent, and when the participant is unwilling to continue the study.
The withdrawn participants do not have to be replaced.
If the participant withdrawals from the study, his/her data must be anonymized at the end of the study. This anonymization is not performed if the participant gives explicit consent. For the protection of the withdrawn participant, he/she must be provided with the standard follow-up care designated by his/her respective medical professional.

## 7 Statistical analysis plan and power calculation

Machine learning models are data-hungry models. This means that the performance of the model will potentially increase with the increase of the dataset and classified events in each classification class. We could simplify the classification task by categorizing alarms as relevant or irrelevant, thus reducing it to a binary classification problem. We will probably have to deal with an unbalanced problem as we might receive a lot of irrelevant classified alarms and few relevant ones. In an unbalanced classification problem as in our case, the best measurements to assess model performance are precision and sensitivity. Precision is defined as the fraction of well-classified instances from class A among all instances that were classified as class A. Sensitivity instead is defined as the fraction of instances from class A that were classified as pertaining to class A. A recent study by Juba and Le (Juba and Le, 2019) proved that even using data augmentation techniques to deal with an unbalanced dataset, adding more training data is the best solution for measuring precision and recall.
Furthermore, we pretend to train the algorithm not just to solve the binary classification problem but also to be able to give specific recommendations in terms of changes in medication, hospital readmissions, and others. Thus, the sample size might have to be big enough to cover a huge range of possible outcomes.

For instance, a similar study (Koulaouzidis et al., 2016) with 308 HF patients telemonitored for around 9 months predicted whether patients would undergo hospital readmission during the following day based on the day-to-day physiological measurements of each patient. Performance accuracy was high. However, more specific measures such as the sensitivity were very low, putting patients at a high risk of misclassification.

During model development and training, k-fold cross-validation will be implemented to fine-tune the model parameters and ensure robustness. Additionally, part of the data won't be used during training and validation in order to test model performance on new data never seen by the algorithm. After the implementation of the AI system into the platform, a randomized controlled trial will be carried out in hospitals that didn't participate in the present observational study to externally validate the ML models. In this future study, a quantitative sample size evaluation will be possible by comparing clinical outcomes between the control and study group.

Therefore, the sample size for the present study has been determined qualitatively taking into consideration the reasons mentioned above, that during the 3 first months after HF decompensation is when patients present more harmful events, and the budget available for the project. The plan is to include the maximum number of participants while accomplishing a relevant socio-demographic diversity in the final cohort. We consider that a total of 500 patients will give sufficient data diversity and classified events (alarms + unexpected interventions) to ensure a robust model performance.

Once the algorithms are developed, model performance in terms of accuracy will be evaluated by means of C statistic, the area under the receiver operating characteristic curve, and by creating a calibration plot. Furthermore, we will evaluate the models in terms of fairness and potential bias using metrics such as statistical parity, group fairness, equalized odds, and predictive equality.

# 8 Conduct

## 8.1 Summary of the study schedule

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| September 2022 | Kick-off. First meeting with Hospital de Torrevieja, the study leaders. |
| September - December 2022 | Partners selection and coordination.<br>Discussion of protocol design and alarm system configuration. |
| January - March 2023 | CEIms approvals |
| April 2023 | Study kick-off. Register investigators on the platform.<br>Initiate patient recruitment. |
| April 2023 | First patient - first visit |
| October 2023 | First patient - last visit |
| October 2023 | Last patient - first visit |
| April 2024 | Last patient - last visit |
| May 2024 | Results analysis and final report draft |
| June 2024 | Improvement of the ML models |

Please note that these are preliminary dates that may be subject to change during the execution of the clinical study.

## 8.2 Study management, study monitoring, data and sample management

### 8.2.1 Study management and clinical procedures.

- Recruitment phase: once the CEIm protocol has been approved for each hospital, the assigned medical professionals responsible for the study will be in charge of including patients in the study, following the inclusion criteria. They will explain the study characteristics to the patient and ask if they are willing to be included in the study. The patient will sign the informed consent that includes the acceptance to use active and passive data. Once accepted, the medical professionals will register the user into the platform, fill in all the data required about their socio-demographics and risk factors, and will train the patient on the proper use of the app and devices.
  The specific calendar for each hospital will depend on its particular involvement and protocol approval date.

- Execution of the study: during the study, patients and medical professionals will evolve as mentioned below.

- **Day 0**: First visit and study enrollment either before or after HF hospital discharge or HF decompensation. This first visit will include,
  - Explanation of the study to the patient and doubt clarification
  - Explanation of the terms and conditions, and signature of the informed consent
  - Medical professionals will register the patient to the HumanITcare platform together with their personal credentials. They will train patients on the proper use of the app and medical devices.
  - Patients will be given a blood pressure monitor, a smartwatch and, a pulse oximeter. Devices will be synchronized with the app (or with the provider's app in some cases). The patient should wear the smartwatch during the entire study period, charging its battery whenever it is about to run out and putting it back on just after it is fully charged.
  - Registration of the following patient variables into the platform by the medical professional:
    - Socio-demographic data: Age, sex, ethnic group, employment, education level, caretaker, number of people living with the patient
    - Risk factors: Comorbidities, diabetes, hypertension, smoking, alcohol consumption, heart disease history
    - Height
    - New York Heart Association (NYHA) Functional Classification
    - Left Ventricular Ejection Fraction (LVEF)
    - Medication use and doses
  - Patients will answer first the European Heart Failure Self-Care Behaviour Scale (EHFScB scale), the Quality-of-life SF-12 and the Mobile Device Proficiency questionnaires through the app.
- **Day 0 until the end of the study:** Registration of measurements and questionnaires: Patients will be notified through the app whenever they need to register a measurement or answer a health questionnaire.
  Weight, blood pressure (systolic and diastolic) and oxygen saturation (through the pulse oximeter) will be registered daily.
  Times for each registration are specified below. Smartwatch device measurements are automatically registered once synchronized with the app.
  Health questionnaires will be delivered periodically through the app to the patient. Specifically, the symptomatology questionnaire will be delivered twice a week (on Mondays and Thursdays) and the self-care and quality-of-life questionnaires will be answered periodically (specified below).
- **Day 0 until the end of the study:** Medical professionals will follow up on patient's adherence to the study by checking their measurements and health questionnaire answers through the platform. Clinicians will make a control call in case of missing data.
- **Day 0 until the end of the study:** Medical professionals are required to annotate each alarm whenever they receive it and check its relevance. If they are unable to evaluate it at the time of appearance, they are allowed to do it later. However, we strongly recommend annotating the alarms, if there are

any, on a daily basis. Annotations will include adding information about the relevance of an alarm by assessing the health status of the patient.

- **Day 0 until the end of the study:** Medical professionals must report every hospital readmission, mortality, emergency department visit or non-fatal HF decompensation of each patient whenever it happens through the platform. If they are unable to register the event at the moment, events can be registered later on through the platform with their corresponding date/s and duration.
- **Day 0 until the end of the study:** Medical professionals are required to report every medication change through the platform, both due to an alarm-derived decision or derived from a clinical evaluation.
- **Day 7 to 10:** First follow-up visit: Medical professionals will cite the patients for in-person follow-up visits.
- **Day 90 (3 months):** Second follow-up visit: Medical professionals will cite the patients for in-person follow-up visits.
- **Day 180 (6 months):** Last follow-up visit and end of the study: The patient monitoring will finish after 6 months from inclusion to the study (first hospital discharge). Patients should answer the European Heart Failure Self-Care Behaviour Scale (EHFScB scale), the Minnesota Living with Heart Failure questionnaire, the Mobile Device Proficiency Questionnaire, the “System Usability Scale” (SUS) and the “Post-Study Usability Questionnaire” (PSSUQ). Then, they will be required to return the medical devices and medical professionals will change the status of the patient to “finished” on the platform.

  Medical professionals will be asked to answer the SUS and PSSUQ questionnaires at the end of the whole study period.
- Medical professionals may cite patients for more in-person visits depending on the specific clinical practice of each center.

#### 8.2.2 Adverse event reporting

HumanITcare will provide technical support to patients and medical professionals during the whole period of the study. Bugs and technical inquiries will be delivered through the same platform or by telephone call or email to the project manager of the company.
In all cases, the information regarding adverse events needs to be reported to the company and recorded.

#### 8.2.3 Data collection

A full description of the data that will be collected and the frequency of registry is presented below in Table 1.

*Table 1: Data collected*

| Class | Input measurement (units) | Units | Frequency of registry | Device (Brand) | Collection |
|---|---|---|---|---|---|
| Physiological measurements | Heart rate | Beats per minute (bpm) | Continuous. One registry every minute. | Smartwatch (Garmin, Fitbit) | API or SDK. Patients through the app |
| | Calories | Kilocalories (kcal) | | | |
| | Steps count | Steps | | | |
| | Physical activity | Minutes (min) | | | |
| | Oxygen saturation | Percent (%) | | | |
| | Heart rate variability | Miliseconds (ms) | | | |
| | Stress levels | Scale from 0 to 100 | | | |
| | Accelerometer | Array of x,y,z values in millig-units (mG) | | | |
| | Sleep | Minutes (min) | | | |
| | Systolic blood pressure | Millimetre of mercury (mmHg) | Daily. Once 2h after taking the medication after breakfast. | Blood pressure monitor (Beurer, Lifevit) | API or SDK. Patients through the app |
| | Diastolic blood pressure | | | | |
| | Weight | Kilogram (kg) | Daily. Once always at the same time and with the same clothes. | Scale (Lifevit) | API or SDK or manual regitsry. Patients through the app |
| | Height | Meter (m) | Initial data | | At the time of inclusion. Medical professionals through the platform |
| | BMI | Kilogram per squared meter (kg/m²) | Daily, depending on weight measurement. | | Computed automatically |
| | Oxygen saturation | Percent (%) | Daily. Once 2h after taking the medication after breakfast. | Pulse oximeter (Beurer, Lifevit) | API or SDK. Patients through the app |
| | Pulse rate | Beats per minute (bpm) | | | |
| Socio-demographics | Sex | Integer | Initial data | | At the time of inclusion. Medical professionals through the platform |
| | Age | Years | | | |
| | Ethnic group | White, Black, Asian, Pacific Islander or Latino-South American | | | |

| | | | | | |
|---|---|---|---|---|---|
| | Employment | Employed/Self-employed, retired, unemployed, doing unpaid or voluntary work, student, none | | | |
| | Education | Primary, secondary, higher-level | | | |
| | Caretaker | Yes or not | | | |
| | nº of people living with patient | Integer | | | |
| Risk factors | Comorbidities | Text separated by commas | Initial data | | At the time of inclusion. Medical professionals through the platform |
| | Diabetes | Yes or not | | | |
| | Hypertension | | | | |
| | Smoking | | | | |
| | Alcohol use | | | | |
| | Heart disease history | | | | |
| | NYHA-class | Scale from 1 to 4 | Initial data and if modified | | At the time of inclusion. Medical professionals through the platform |
| | Level of Ejection Fraction (LVEF) | Percent (%) | Initial data and if modified | | At the time of inclusion. Medical professionals through the platform |
| Medication | Lipid lowering medication | Milligrams per day (mg/day) or grams per day (g/day) | Initial data and if modified | | Medical professionals through the platform |
| | PCSK9 inhibitors | | | | |
| | Beta blockers | | | | |
| | Anticoagulation agents | | | | |
| | ACE inhibitors / Angiotensin receptor-neprilysin inhibitor | | | | |
| | Anti-arrhythmic drugs | | | | |
| | Anti-inflammatory drugs | | | | |
| | Aldosterone antagonists | | | | |
| | Antidiabetic | | | | |

| | | | | | |
|---|---|---|---|---|---|
| | agents | | | | |
| | Vericiguat | | | | |
| | Diuretics | | | | |
| | SGLT2 inhibitor (Dapaglifrocina/empagliflocina) | | | | |
| | Ivabradina | | | | |
| Symptoms | Chest pain | Yes or not | 2 times per week. On Mondays and Thursdays | | Patients through app questionnaire |
| | Shortness of breath | | | | |
| | Oedema | | | | |
| Clinical events | Hospital readmission | Number and dates | At occurrence | | Medical professionals through the platform |
| | Non-fatal HF event | | | | |
| | Emergency department visits | | | | |
| | Death | Yes/No and date | | | |
| Questionnaire | European Heart Failure Self-Care Behaviour Scale (EHFScB scale) | From 0 to 100 | 4-5 times: when included in the study, 7 days after discharge, 1 month, 3 months, 6 months | | Patients through app questionnaire |
| | Minnesota living with heart failure questionnaire (MLHF) | | | | |
| | Mobile Device Proficiency Questionnaire | From 8 to 40 | 2 times: when included in the study and at the end of the study | | |
| | Morinsky-Green medication adherence 4-item questionnaire | From 0 to 4 | 4 times: when included in the study and once every month | | |

The questionnaires delivered to the patients are specified below and added in the Annex 1:

- Minnesota Living with Heart Failure Questionnaire (MLHF) (Bilbao et al., 2016)
- European Heart Failure Self-care Behaviour Scale (EHFScB scale) (Jaarsma et al., 2009)
- Symptom report questionnaire: six questions to capture the worsening of the symptoms of heart disease, mainly worsening of the HF, and one question to capture general deterioration.
- "System Usability Scale" (SUS) (*Brooke, J. (1986) SUS—A Quick and Dirty Usability Scale. Usability Evaluation in Industry, 189-194. - References - Scientific Research Publishing*, n.d.)(Brooke, 1986) and the "Post-Study Usability Questionnaire" (PSSUQ) (Lewis, 1992) will be delivered at the end of the study.
- Mobile Device Proficiency Questionnaire (MDPQ) (Roque & Boot, 2018)(Roque and Boot 2018)

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**ANNEX 1:**

**Symptom report questionnaire**

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