Clinical Research Plan

HumanITcare

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Abbreviations

Abbreviation	Full name
AA	Adverse event
AAG	Serious adverse event
CITY	Unexpected adverse event
API	Application programming interface
BPC	Good Clinical Practice
CDD	Direct data capture
CEIm	Drug Research Ethics Committee
CRD	Data Collection Notebook
CV	Cardiovascular/es
DD	Device deficiency
EAD	Adverse effect of the device
EAGD	Serious device adverse events
EAID	Unexpected adverse effect of the device
eCRD	Electronic Data Collection Notebook
EHFScB	European Heart Failure Self-care Behavior Scale
EIC	European Innovaton Council
EU	European Union
fevi	Left ventricular ejection fraction
HFmrEF	Heart failure with mid-range ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
IA	Artificial intelligence
IC	Heart failure
IT	Information technologies
LVAD	left ventricular assist device
MDPQ	Mobile Device Competency Questionnaire
NT-pro BNP	Propéptido natriurético cerebral N-terminal
NYHA	New York Heart Association class
PIC	Clinical Research Plan
PSSUQ	Post-Study System Usability Questionnaire
RRP	Patient-reported outcomes
SDK	Software development kit
THEIR	System Usability Scale

TM	Telemonitoring (Remote Monitoring)
UC	Usual care (Traditional follow-up)

1 Generalities

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Centers in which the study is planned to be carried out

Clinical Hospital of Barcelona
Denia Hospital
Hospital of Alcoy
Lozano Blesa Clinical Hospital of Zaragoza
Torrejón Hospital
General University Hospital of Elche
Vinalopó Hospital
Hospital of Terrassa
Sant Joan de Reus University Hospital

2 Synopsis of clinical research

HumanITcare has implemented a cloud platform for telemonitoring of chronic patients through wearable medical devices and an alarm-based system that issues health alerts when a patient's biomedical

measurement is outside a predefined clinical range. The platform frees doctors and caregivers from reviewing each patient's data for anomalies, speeding up the decision-making process and reducing hospital visits. With the present study we aim to validate the effectiveness of the app for patients and digital platform for medical professionals by evaluating the increase in the quality of life of patients and measuring the reduction in the incidence of the main critical events of HF. Additionally, the study will validate the new API interoperability standards and platform architecture and evaluate the usability of the platform by delivering satisfaction questionnaires to patients and professionals at the end of the study.

This study is being carried out within the framework of a European project promoted by the European Innovation Council (EIC).

Evidence to date

In 2020, a single-center study was carried out at the Torrevieja Hospital in which an early version of the digital platform was validated. (Sanchez et al., 2020). A total of 32 patients participated, 16 as the control group and 16 as the study group. The study group was monitored remotely using the HumanITcare digital platform and wearable devices (smart scale, blood pressure monitor, pulse oximeter and smart watch) for 3 months, while the control group continued normal clinical practice.

The results showed that patients monitored by the HumanITcare platform are less likely to return to the emergency department. Additionally, the study group showed a reduction in hospital readmissions and 92% of patients would recommend using the platform. Finally, 100% of clinical professionals agreed that the platform improves health care and services, saves time on visits and satisfies remote medical care, which is an easy-to-use and easy-to-use system. learn to use. In addition, professionals affirm that the way of interacting with the system is pleasant and that the platform fulfills all the expected tasks.

3 Product under investigation

HumanITcare is telemedicine software for monitoring patients who require continuous and remote monitoring of their health status. It is a platform that processes information that comes from questionnaires and/or different sensors interconnected to the patient's App and that is transmitted to a medical portal so that the health professional can make decisions for therapeutic or diagnostic purposes or set alarms when the parameters are above or below thresholds defined by the clinician himself.

HumanITcare has different functionalities related to this data:

- Tracking and monitoring of health data obtained through interconnected sensors:
- blood pressure monitor
- pulse oximeter (pulse and oxygen saturation)
- smartwatch (heart rate, physical activity and sleep)

- smart scale (weight)
- thermometer (temperature)
- glucometer (blood glucose)
- monitoring of self-reported responses through questionnaires (validated symptoms, quality of life, self-care questionnaires, etc.)
- annotation of data from the patient's medical history (necessary for correct monitoring, since alerts must be personalized to each condition)
- configuration of medical alerts (healthcare professionals can define several alerts per patient when certain parameters are above or below thresholds defined by the same clinician).

The platform intelligently monitors users in a fully automated manner, with real-time communication of their data, with special emphasis on passive data, thus demanding less attention from them.

The HumanITcare software offers the doctor the possibility of viewing all this monitored information in each user's profile to be able to interpret it more easily along with their history. This allows you to see:

- The evolution of chronic diseases
- Patient adherence to treatment
- The evolution of a patient after an intervention
- The need to make possible changes in medication or treatment due to a detected complication

All information about the product is found in the Researcher's Manual.

4 Rationale for clinical research design

Evaluation of preclinical trial results

The preclinical tests in order to verify the effectiveness and safety of the HumanITcare software have been brought together in the validation and verification documents of the MDSW Test Plan and MDSW Test Report software, following the indications of the MDR Regulation 745/2017 and the EN 62304:2006 standard. /A1:2015. This standard establishes a series of activities to be carried out during the software development and maintenance process, necessary to generate quality, highly reliable and secure medical software. HumanITcare complies with all activities required by the standard to determine the risks resulting from the operation of the software. These activities are detailed in the Software Development Plan document.

Clinical data evaluation

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 with HF die within the first year and the rest die within 5 years (Tripoliti et al., 2017). Furthermore, these patients have a high risk of rehospitalization, their associated healthcare costs are enormous, and the longer the life expectancy, the higher the prevalence of the disease. (McDonagh et al., 2021). Symptoms of IC commonly include shortness of

breath, excessive tiredness, and swelling of the legs that may worsen with decompensation. (Schiff et al., 2003), so traveling to medical centers represents a disadvantage for these people. Remote monitoring technologies provide a feasible solution that allows for earlier identification of decompensation and better adherence to lifestyle changes and medication (Brahmbhatt & Cowie, 2019). Although telemonitoring using smartphones shows potential to reduce both the frequency and duration of hospitalizations for HF (Koulaouzidis et al., 2016) cannot be associated with reduced mortality from any cause (Koehler et al., 2011). Therefore, there is a need to search for more effective and precise methodologies. In recent years, the use of portable devices (wearables) that allow daily monitoring of the patient's physiological data combined with Artificial Intelligence (AI) has shown enormous potential to predict diseases related to the cardiovascular system, their adverse events and the patient's health status (Lee et al., 2022), including patients with HF (Guidi et al., 2015).

HumanITcare is a platform that allows this remote monitoring through the integration of different medical devices and self-reported data. The platform allows you to customize a monitoring plan so that healthcare professionals can adapt this tool to the needs of a specific patient group or at the individual patient level.

The HumanITcare platform has been used in different therapeutic areas to improve personalized patient monitoring. Some of the areas in which an improvement in patient monitoring and health status has been demonstrated would be cardiology (IC - (Sanchez et al., 2020); cardiac rehabilitation - (Calvo-López et al., 2023), palliative care (Castillo Padrós et al., 2022), respiratory diseases, or oncology, among others.

5 Risks and benefits of the product in investigation, clinical procedure and clinical research

Benefits

During the usual clinical practice of monitoring newly decompensated HF patients, the patient must monitor their vital signs daily and, if alarming values occur, communicate this by telephone or through a visit to the emergency room to the medical team in charge of their case. That's why hea digital platform for medical professionals and the application for patients provides the following benefits:

1. Greater patient participation. The patient app can provide patients with the tools and resources needed to self-manage their condition and improve their understanding of treatment plans and lifestyle changes, leading to greater patient engagement and adherence.

2. Increased quality of life. With the app, patients can monitor their symptoms, vital signs and medications from their homes, which it is very beneficial in patients who have mobility problems such as patients with insufficiencycardiac surgery.

3. Better outcomes for patients. Telemonitoring can help medical professionals identify early signs of deterioration in patients with HF and trigger timely interventions to prevent exacerbations, ultimately leading to improved clinical outcomes.

4. Digital health tools. Integrating telemonitoring with other remote monitoring technologies and digital health tools can provide a more complete view of a patient's health status and improve overall management of their condition in real time.

Adverse reactions

The safety profile will be evaluated by recording, reporting and analyzing initial medical conditions, adverse events, physical examination findings, including vital signs and laboratory tests.

The notification of adverse events will be carried out as established by the latest guideline on Safety Notification in clinical investigations with medical devices for compliance with Regulation (EU) 2017/745 (MDCG 2020-10/1-*Safety reporting in clinical investigations of medical devices under the Regulation* (EU) 2017/745).

Associated risks

The benefit/risk ratio for patients using HumanITcare is very high or high, since there are potentially no risks from the use of the product or the tests performed.

The manufacturer FollowHealth SL, Through risk management documents, establishes and commits to maintaining a continuous process during the life cycle of the product and its accessories to identify the hazards associated with a product, estimating and evaluating the associated risks, controlling these risks and monitoring the effectiveness of the controls.

This process follows the instructions of the EN ISO 14971:2019 standard and is carried out as follows:

- The risks are analyzed.
- The risks are evaluated.
- Actions are implemented to control risks.
- Residual risks are evaluated.
- The benefit versus risk is analyzed if there is an unacceptable residual risk after the implementation of the corrective actions.
- All product production and post-production information is collected to carry out a review of the risk management carried out.

The procedure for carrying out product risk management is explained in detail in the associated documentation that can be found in the risk management plan and associated procedures: Risk Management Plan.

The results of the analysis, including the identification of the main risks, their evaluation and the corrective measures to be applied, are collected in the Risk Management Matrix.

It should be noted that no residual risks associated with the use of HumanITcare have been described.

6 Objectives and hypotheses of clinical research

6.1 Main objectives

- To evaluate the effectiveness of telemonitoring to improve the quality of life of patients with HF.
- To study the impact of telemonitoring on patients' psychological well-being, including anxiety, depression, and sense of control over their condition.
- To evaluate the feasibility and acceptability of integrating telemonitoring technologies and digital health tools, and investigate their potential impact on patient outcomes as well as treatment adherence.
- Identify any adverse events or unintended consequences associated with telemonitoring of patients with heart failure, such as privacy issues or technical problems.

6.2 Secondary objectives

- To evaluate the role of telemonitoring in identifying early signs of deterioration in patients with heart failure and triggering timely interventions to prevent exacerbations.
- Improve clinical outcomes for patients with heart failure, as well as reduce hospital readmissions.

6.3 Hypothesis

The hypothesis of the study is that the implementation of a telemonitoring system in patients with heart failure will improve the quality of life and psychological well-being in patients, which will result in a decrease in symptoms of anxiety and depression, as well as a increased feeling of control over your state. Additionally, the incorporation of digital health and telemonitoring tools is expected to increase treatment adherence and improve patient clinical outcomes. On the other hand, telemonitoring is expected to be feasible and acceptable to patients, without generating significant adverse events or unwanted consequences. Ultimately, it is hypothesized that telemonitoring will allow early identification of signs of worsening in patients with heart failure, enabling timely implementation of therapeutic interventions to prevent exacerbations and optimize the clinical management of these patients.

7 Clinical research design

7.1 Generalities

7.1.1 Study type

This is a multicenter, randomized (1:1) controlled trial.

7.1.2 Duration of the investigation

Patients will be monitored for 3 months. The duration of the study has been defined based on the period of time in which recently decompensated HF patients are more likely to relapse and suffer harmful clinical events, and therefore to present a deterioration in their perception of quality of life.

7.1.3 Variables

Endpoint principal

- Composite of quality of life, self-care and adherence to treatment by the patient (Change in the scale value of each questionnaire at 3 months)

The variables are quantified using validated scales. These measures are:

- Patient-Reported Self-Care Behavior Scale Measures (EHFScB Scale)
- Quality of life assessed through the "Minnesota Questionnaire for People with Heart Failure (MLHF questionnaire)"
- Patient adherence to treatment and medication intake (SMAQ Simplified Medication Adherence Questionnaire)

Secondary endpoints

- Quality of life evaluated through the "Minnesota Questionnaire for People with Heart Failure" (Change in the value of the questionnaire scale at 3 months)
- Patient-Reported Self-Care Behavior Scale Measures (EHFScB Scale) (Change in Questionnaire Scale Value at 3 Months)
- Patient adherence to treatment and medication intake (SMAQ Simplified Medication Adherence Questionnaire) (Change in the value of the questionnaire scale at 3 months)
- Death from cardiovascular (CV) causes (Total number of patients who died in 3 months)

- Mortality from any cause (Total number of patients who died in 3 months)
- Acute HF decompensation (first and recurrent) during the follow-up period (Number of total decompensations in 3 months).

An acute decompensation of HF is defined as a new episode of symptoms and signs that requires intravenous decongestive treatment or increased oral diuretics either on an outpatient basis (e.g., day or home hospitalization for HF) or at home. emergency department or requiring an unplanned hospital admission.

- Hospital readmission due to HF decompensation (Total number of hospitalizations in 3 months)
- Hospital readmission for CV causes (Total number of hospitalizations in 3 months)
- Visits to the emergency room due to HF decompensation (Total number of visits to the emergency room in 3 months)
- Visits to the emergency room for CV causes (Total number of visits to the emergency room in 3 months)
- Medical care costs (Sum of costs for medication consumption, hospitalization, emergency care and medical transportation in 3 months)

7.1.4 Sample calculation

The sample calculation has been made based on the fact that a change of 5 points on the scale of the Minnesota Questionnaire for People with Heart Failure (MLHF questionnaire) between the control group and the experimental group (telemonitored) is clinically significant. (Rector, n.d.). Assuming an alpha risk = 0.05 and a beta error of 20%, we need to recruit a total of 253 participants divided into a control group and an experimental group.

7.2 Subject selection

The target population includes patients recently decompensated by Heart Failure (HF).

All recruited subjects will meet the inclusion criteria and none of the exclusion criteria and will provide written informed consent.

7.2.1 Inclusion criteria

- Patients with heart failure (HF) with NYHA functional class >= II (according to 2021 EU guidelines).
- Patients over 18 years of age.

- Patients who have suffered acute HF decompensation (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 increased oral diuretics either on an outpatient basis (e.g., day or home hospitalization for HF) or at home. emergency department or requiring an unplanned hospital admission.*

- NT-pro BNP ≥300 pg/ml at study inclusion for patients without ongoing atrial fibrillation/flutter. If ongoing atrial fibrillation/flutter, NT-pro BNP should be ≥600 pg/mL
- Patients must have had an echocardiogram during their HF hospitalization or in the previous 12 months.
- Before starting any procedure, the hospital will ensure that the patient obtains an informed consent document.
- All patients will be eligible regardless of LVEF level: HFrEF, HFmrEF and HFpEF.
- Patients with minimal skills in handling mobile applications.

7.2.2 Exclusion criteria

- Oncology patients with metastasis or ongoing chemotherapy treatment.
- Patients participating in other studies or trials.
- Patients who do not wish to participate.
- Patients weighing more than 150 kg.
- Patients who do not speak 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.

7.2.3 Withdrawal criteria

Subjects will be informed that they can withdraw from the research whenever they wish, without this affecting in any way their subsequent medical care.

Complete withdrawal of consent for research means that the subject no longer wishes to use the investigational product and is unwilling or unable to continue participation in the research. Any subject may withdraw full consent to participate in the research at any time during the research. The investigator will discuss with the subject the most appropriate way to withdraw to ensure their health.

Every effort should be made to complete and report observations as widely as possible up to the date of withdrawal. All information must be included in the corresponding data collection notebooks.

The withdrawal criteria established for clinical research are as follows:

- Disease progression
- Withdrawal of consent or desire to terminate treatment or investigational product or failure to cooperate with research requirements
- Toxicity, adverse event, or intercurrent illnesses, in the opinion of the investigator, that justify discontinuation of treatment or investigational product
- Decision of the principal investigator, whether withdrawal is necessary to safeguard the interests of the patient
- Patient death
- New exclusion criteria clinically relevant to participants and affecting their safety
- Failure to comply with or significant deviation from the clinical research plan

If the participant withdraws from the study, their data will be automatically anonymized by the platform at the end of the study. This anonymization is not carried out if the participant gives explicit consent. The withdrawn participant will receive standard follow-up care designated by their respective medical professional.

7.3 Recruitment

After verifying that the selected subjects meet the inclusion and exclusion criteria, they will be offered to participate. A user ID (automatically generated on the HumanITcare platform) will be assigned to each subject who has given written informed consent to participate in the research. User IDs will not be reused for different participants. The investigator must maintain a selection/enrollment record of all selected subjects. This record must be carried out on a separate medium so that only the medical team at each center can relate the user ID to a specific subject.

The participant must personally sign and date the latest approved version of the informed consent form before performing any research-specific procedures.

Written and verbal versions of the patient information sheet and informed consent will be presented to participants, detailing, at a minimum, the following:

- The exact nature of the study

- The implications and limitations of the clinical research plan
- Known side effects and any risks involved with participation

It will be clearly indicated that the participant is free to withdraw from the research at any time and for any reason, without prejudice to future care, and without obligation to indicate the reason for withdrawal.

The participant will be given as much time as they wish to consider the information, and the opportunity to question the researcher to decide whether or not to participate in the study. Written informed consent will then be obtained by the participant's signature and the signature of the person who submitted and obtained informed consent.

7.3.1 Estimated recruitment time

Patients will be included in the study, based on the aforementioned eligibility criteria, for 3 months and will be monitored for 3 months. Each hospital will decide when to include their patients based on their particular clinical practice (either in the discharge planning process or during the first follow-up visit, i.e., approximately 1 week after discharge or after decompensation).

Medical professionals from each hospital will be in charge of recruiting participants. Patients will be recruited for 3 months.

Participants will be randomized in a 1:1 ratio to the control group (UC arm) or the intervention group (TM arm) at the recruitment stage. Randomization will be carried out at each center using the HumanITcare platform, which will indicate the arm to which each patient belongs. Stratification is performed with covariate adaptive randomization methods.

7.4 Investigation procedure

January - February 2023	Selection and coordination of partners. PIC Design Discussion
April 2023	CEIm Presentation
June 2023	CEIms approvals
November 2023	AEMPS approvals
November 2023	Start of the study. Register researchers on the platform. Start patient recruitment.
November 2023	First patient - first visit
January 2023	Last patient - first visit

January 2023	First patient - last visit
April 2023	Last patient - last visit
April 2023	Analysis of results. Draft version of the article

All patients included in the study will be followed for 3 months. The medical professionals responsible for the study will be responsible for including patients in the study following the inclusion criteria. They will explain the characteristics of the study to the patient and ask if they are willing to be included. The patient will sign the informed consent, which includes acceptance of the use of active and passive data. Once accepted, medical professionals will register the user on the platform, which will randomly assign them to the UC or TM arm, complete all required data on their sociodemographics and risk factors, and train them in the proper use of the application and the devices (in the TM case).

The particular clinical practice for the UC and TM arms is specified below:

UC arm tracking

Follow-up of patients in the UC arm will be carried out according to the usual clinical practice of each recruiting center. All recruiting centers have active and mature CI programs in progress and therefore each center will decide how to follow up the patient. However, medical professionals will be required to register each patient on the platform, enter their baseline data (sociodemographic and risk factors) and enter all possible clinical events (death, non-fatal HF event, hospitalization or visit to the emergency room). that the patient could suffer during the entire follow-up period. Doses and medication changes will also be recorded by medical professionals for each patient in the UC arm. Patients will answer health-related questionnaires through the app. The frequency and type of questionnaire will be the same for both study groups and are specified in Table 1. HumanITcare does not giveit will be to himpa axisPatients in the control group (UC) will not have any device for taking measurements, therefore patients in the UC group will not have to enter their vitals through the application.

The monitoring schedule per day is specified below.

- Day 0: First visit and study enrollment before or after hospital discharge for HF, or after acute decompensation. This first visit will include,
    - Explanation of the study to the patient and clarification of doubts
    - Explanation of the terms and conditions, and signing of the informed consent
    - Patients will be registered within the platform and the study group (UC or TM) will be automatically assigned from the software. In this case the UC.
    - Registration of information on sociodemographic variables and patient risk factors on the platform by the medical professional.
    - Patients will answer the European Heart Failure Self-Care Behavior Scale (EHFScB scale), the Minnesota Questionnaire for People with Heart Failure (MLHF), the

Simplified Medication Adherence Questionnaire (SMAQ), and the Mobile Device Proficiency questionnaires. through the app.

- Health questionnaires will be periodically delivered through the app to the patient. Specifically, the self-care, quality of life, and mobile device competency questionnaires will be administered once at the beginning and once at the end of the study, and the medication adherence questionnaire will be answered once each month during the study (see *Table 1*).
- Day 0 until end of study: Medical professionals will track health questionnaire responses through the platform. Doctors will make a follow-up call in case of missing data.
- Day 0 until the end of the study: Medical professionals must report each hospital readmission, mortality or emergency visit for each patient, specifying its cause each time it occurs through the platform. If you cannot register the event now, you can register events later by specifying the corresponding date(s) and duration.
- Day 0 until the end of the study: Medical professionals are required to report each medication change through the platform, whether due to a decision derived from an alarm or derived from a clinical evaluation.
- Day 90 (3 months): Last follow-up visit and end of the study: The patient's follow-up will end 3 months after inclusion in the study (first hospital discharge). Patients must answer the European Heart Failure Self-Care Behavior Scale (EHFScB scale), Minnesota Questionnaire for People with Heart Failure (MLHF), Simplified Medication Adherence Questionnaire (SMAQ), Mobile Device Competency Questionnaire and the “System Usability Scale” (SUS). Medical professionals will change the patient's status to "finished" on the platform.
- Medical professionals will be asked to answer the PSSUQ questionnaire at the end of the entire study period.
- Medical professionals may schedule patients for more in-person visits depending on the specific clinical practice of each center.

TM Arm Tracking

Patients in the TM arm will be followed with the HumanITcare platform and app according to the guidelines specified below.

- Day 0: First visit and study enrollment before or after hospital discharge for HF, or after acute decompensation. This first visit will include,
    - Explanation of the study to the patient and clarification of doubts
    - Explanation of the terms and conditions, and signing of the informed consent
    - Patients will be registered within the platform and the study group (UC or TM) will be automatically assigned from the software. In this case the TM.
    - Patients will receive a scale, blood pressure monitor, smartwatch and pulse oximeter. The devices will sync with the app (or the carrier's app in some cases). The patient must wear the smartwatch throughout the study period, charging its battery every time it is about to run out and putting it back on just when it is fully charged.
    - Registration of information on sociodemographic variables and patient risk factors on the platform by the medical professional.
    - Patients will answer the European Heart Failure Self-Care Behavior Scale (EHFScB scale), the Minnesota Questionnaire for People with Heart Failure (MLHF), and Mobile Device Proficiency questionnaires via the app.

- Day 0 until the end of the study: Recording of measurements and questionnaires: Patients will be notified through the app each time they need to record a measurement or answer a health questionnaire. Weight, blood pressure (systolic and diastolic), and oxygen saturation (via pulse oximeter) will be recorded daily. The times for each record are specified in the *Table 1*. Smartwatch device measurements are automatically recorded once synchronized with the application. The patients They must wear the smartwatch throughout the study period (except when it is being charged).
- Health questionnaires will be periodically delivered through the app to the patient. Specifically, the symptomatology questionnaire will be delivered twice a week (Monday and Thursday), self-care, quality of life and device competence questionnaires Mobile phones will be delivered once at the beginning and once at the end of the study, and the medication adherence questionnaire will be answered once every month during the study(see Table *1*).
- Day 0 until end of study: Medical professionals will track patients' adherence to the study by verifying their measurements and health questionnaire responses through the platform. Doctors will make follow-up calls in case there is missing data.
- Day 0 to end of study: Medical professionals should note each alarm each time they receive it and verify its relevance. If they cannot evaluate it at the time of appearance, they are allowed to do so later. However, we recommend writing down alarms, if any, daily. Annotations will include adding information about the relevance of an alarm and evaluating the patient's health status.
- Day 0 until the end of the study: Medical professionals must report each hospital readmission, mortality or emergency visit for each patient, specifying its cause each time it occurs through the platform. If you cannot register the event now, you can register events later by specifying the corresponding date(s) and duration.
- Day 0 until the end of the study: Medical professionals are required to report each medication change through the platform, whether due to a decision derived from an alarm or derived from a clinical evaluation.
- Day 7 to 10: First follow-up visit: Medical professionals will schedule patients for an in-person follow-up visit depending on the particular clinical practice of each recruiting center.
- Day 90 (3 months): Last follow-up visit and end of the study: The patient's follow-up will end 3 months after inclusion in the study (first hospital discharge). Patients must answer the European Heart Failure Self-Care Behavior Scale (EHFScB scale), the Minnesota Questionnaire for People with Heart Failure (MLHF), the Mobile Device Competence Questionnaire and the “System Usability Scale” (SUS) . They will then be asked to return the medical devices and medical professionals will change the patient's status to "finished" on the platform.
- Medical professionals will be asked to answer the PSSUQ questionnaire at the end of the entire study period.
- Medical professionals may schedule patients for more in-person visits depending on the specific clinical practice of each center.

7.5 Conducting the research

The sponsor or designated person will carry out the quality assurance and control activities of this research.. The monitor is responsible for supervising that data collection is done correctly, checking that the data collected in the CRD matches the source data and that the protocol is followed appropriately.

The sponsor will arrange for audits to be carried out as part of the implementation of quality assurance to ensure that the research is being carried out in accordance with this clinical research plan, standard operating procedures, good clinical practice (GCP) and all relevant regulatory requirements. The audits will be independent and will be carried out apart from the usual monitoring and quality control activities.

7.6 Monitoring plan

The study will be monitored to ensure that it is conducted and documented in accordance with the good clinical practice (GCP) protocol, and all applicable regulatory requirements.

Monitoring of the clinical study will be done through the following steps:

1. Verification of patient selection: The doctors at each center will be responsible for verifying that patients meet the inclusion and exclusion criteria of the clinical study. As patient randomization is done automatically through the platform, the risk of errors being made is very low.
2. Clinical research evaluation: The company monitor will review clinical research records for each site to ensure that it is conducted in accordance with the PIC, written procedures, and applicable regulatory requirements.
3. Data Quality Assessment: The company monitor will review patient records weekly to ensure that clinical and follow-up data are being collected and recorded correctly. In addition, the quality of the data provided by medical professionals will also be reviewed.
4. Notification of findings: Healthcare facilities will notify the company of any findings that may have implications for patient safety or data integrity.
5. Documentation and archiving: The sponsor and the health centers will maintain a complete record of all monitoring activities and will ensure that all records and documents related to the clinical study are properly archived.

8 Design and statistical analysis

8.1 Methodology and analysis

Specific subgroup analyzes will be performed based on the different baseline data and risk factors available for the project. We will also test interactions between each pair of subgroups and the main effect of treatment.

Independent t tests or Mann-Whitney U tests will be used to compare the questionnaire scores based on the distribution of the data, whether normally distributed or not, respectively.

The incidence of secondary endpoint events in the two study groups will be described using Kaplan-Meier survival curves, which will be compared using the log-rank test. The hazard ratio will also be obtained using Cox proportional hazards regression models comparing the TM and UC groups. The time of each event will be calculated from the day of registration. We will compare the number of readmissions and days of hospitalization between the two groups using the Wilcoxon rank sum test.

9 Data management

All data is collected in the database that acts as eCRD.

Participants will be informed of the pseudonymization and confidentiality of their data. They will be informed of the research, its objectives and methods, orally and in writing.

Participants who wish to participate in the research will receive a consent form for the processing of their data that they must sign in order to continue in it. The researchers will preserve the privacy of the participant's data by using only those data necessary for the purposes of the research and in compliance with the principle of data minimization, keeping them pseudonymized for the main purpose of validating the platform. The data may also be used for scientific purposes in the future.

The sociodemographic and clinical data and the administered scales will be stored in encrypted form, and only the researchers will have access to them.

Informed consent will be requested and collected by a research assistant prior to subject inclusion in the study.

9.1 Data Collection Notebook (CRD) and Source Data Management

Study data must be verifiable against the source data, necessitating access to all original records and subject records. Therefore, the researcher must agree to allow access to subject records and source data must be available for all study data. Subjects or their legal representatives must also allow access to the subjects' medical records and will be informed of this need and will express their agreement when providing informed consent.

The researcher will at all times have full responsibility for the accuracy and authenticity of the clinical and laboratory data that are included in the eCRD. The source documents about the patients will be the doctor's patient records that will be maintained at the center where the study is conducted.

The researcher/center must allow direct access to the source (original) data/documents for activities related to study monitoring, audit, review by ethics committees and inspection by regulatory authorities.

The source data from the electronic health products used during the research will be considered direct data capture (CDD), and will be stored directly in the database that acts as eCRD.

Likewise, the patient-reported results (PRR) will be recorded directly in the database that acts as eCRD.

The eCRD will not be completed for subjects who are failures to screen.

A complete description of the data that will be collected is presented below in Table 1, specifying which data will be collected for each follow-up arm, and the frequency of recording.

Table 1: *Data collected through the platform for each follow-up arm (TM or UC), specified in bold in the first column.*

Class and tracking arm	Input measure (units)	Units	Registration frequency	Device (Brand)	Collection
Physiological measurements **TM**	heart rate	Barks per minute (bpm)	Continuous. One record every minute.	Smart watches (Garmin, Fitbit)	API or SDK. Patients through the app
	Calories	Kilocalories (kcal)			
	step counting	Steps			
	Physical activity	Minutes (min)			
	Oxygen saturation	Percentage (%)			
	Heart rate variability	Milliseconds (ms)			
	Stress levels	Scale from 0 to 100			
	Accelerometer	Matrix of x,y,z values in milligrams (mG)			
	Dream	Minutes (min)			
	Systolic blood pressure	Millimeters of mercury (mmHg)	Daily. Once 2 hours 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 registration. Patients through the app
	Height	Metro (m)	Initial data		At the time of inclusion. Medical professionals through the platform
	IMC	Kilogram per square meter (kg/m^2)	Daily, depending on weight measurement.		Automatically calculated
	Oxygen saturation	Percentage (%)	Daily. Once 2 hours after taking the medication after breakfast.	Pulse oximeter (Beurer and Lifevit)	API or SDK. Patients through the app
	pulse rate	Barks per minute (bpm)			
Sociodemographics **TM + UC**	Sex	Whole	Initial data		At the time of inclusion. Medical professionals through the platform
	Age	Years			
	ethnic group	White, black, Asian, Pacific Islander, or Latin-South American			
	Employment	Salaried/self-employed, retired, taking			

		care of home and/or family, unemployed, doing unpaid or voluntary work, student, none			
	Education	Primary, secondary, higher level			
	Vigilante	yes or no			
	number of people living with the patient	Whole			
Risk factors **TM + UC**	Comorbidities	Comma separated text	Initial data		At the time of inclusion. Medical professionals through the platform
	Diabetes	Yes or no			
	Hypertension				
	Smoker				
	alcohol consumption				
	History of heart disease				
TM + UC	NYHA Class	Scale from 1 to 4	Initial data and if it is modified		At the time of inclusion. Medical professionals through the platform
TM + UC	Ejection fraction level (LVEF)	Percentage (%)	Initial data and if it is modified		At the time of inclusion. Medical professionals through the platform
Medication **TM + UC**	Lipid-lowering medications	Milligrams per day (mg/day) or grams per day (g/day)	Initial data and if it is modified		Medical professionals through the platform
	PCSK9 inhibitors				
	Beta blockers				
	Anticoagulant agents				
	ACE inhibitors/angiotensin receptor-neprilysin inhibitor				
	Antiarrhythmic drugs				
	Anti-inflammatory medications				
	Aldosterone antagonists				

	Antidiabetic agents				
	vericiguat				
	Diuretics				
	SGLT2 inhibitor (Dapaglifrocin/empagliflocin)				
	Ivabradina				
Symptoms **TM**	chest pain	Yes or no	2 times a week. On Monday and Thursday		Patients via app questionnaire
	Difficulty breathing				
	Edema				
Clinical events **TM + UC**	Hospital readmission	Number and dates	In the occurrence		Medical professionals through the platform
	Urgent visit with intravenous decongestant				
	Emergency Department Visits				
	Death	Yes/No and date			
Questionnaires **TM + UC**	European Heart Failure Self-Care Behavior Scale (EHFScB scale)	From 0 to 100	2 times: when included in the study and at the end of the study at 3 months		Patients via app questionnaire
	Minnesota Questionnaire for People with Heart Failure (MLHF)				
	Mobile Device Proficiency Quiz	From 8 to 40			
	Simplified Medication Adherence Questionnaire (SMAQ)	from 0 to 4	3 times: when included in the study and once a month		

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

- Minnesota Questionnaire for People with Heart Failure (MLHF) (Garin et al., 2008)
- European Heart Failure Self-Care Behavior Scale (EHFScB scale) (Jaarsma et al., 2009)

- Symptom Report Questionnaire: six questions to capture worsening heart disease symptoms, primarily worsening HF, and one question to capture overall deterioration.
- The “System Usability Scale” (SUS) (Brooke, 1995) and the “Post Study Usability Questionnaire” (PSSUQ) (Lewis, 1992) They will be delivered at the end of the study.
- Mobile Device Proficiency Questionnaire (MDPQ) (Roque & Boot, 2018)
- Simplified Medication Adherence Questionnaire (SMAQ) (Ortega Suárez et al., 2011)

9.2 Record keeping

All records related to the conduct of this research must be retained by the researcher for 10 years as specified in Regulation (EU) 2017/745.

Prior to the transfer or destruction of these records, the Promoter must be notified in writing and given the opportunity to continue storing such records. The Investigator will allow representatives of the Sponsor's supervisory members (and applicable regulatory authorities) to inspect all study records, eCRDs and applicable portions of the study patient's and/or hospital's medical records at regular intervals. throughout the study. These inspections are intended to verify compliance with the clinical research plan, the integrity and accuracy of the data filled in the electronic CRD, and compliance with applicable regulations.

The sponsor and the investigator agree to keep the medical records of the research patients confidential. No patient will be identified by name in the clinical investigation report.

9.3 Confidentiality

All material, information (oral or written), unpublished documentation that is provided to researchers, including this Clinical Research Plan, the Data Collection Notebooks and the Investigator's Manual, must be considered the exclusive property of the Promoter, having the category confidential, and being delivered as confidential for review and exclusive use for the purposes of the investigation.

This confidential nature of the information, as well as the obligation to keep it confidential throughout the duration of the investigation, weighs on both the researcher and his collaborators, with the researcher guaranteeing that all his collaborators respect this confidential nature.

Said data and/or material may not be disclosed, in part or in full, by the principal investigator and/or his team to any unauthorized person, without the prior formal written consent of the promoter and must not be used other than the purposes of the study.

It is the obligation of the Researcher and/or his team to consider as confidential and ensure at all times the confidentiality of the documents and results generated during the course of the investigation, except for those that legislation defines as disclosable.

The researcher and/or his team will guarantee that all people involved will respect the confidentiality of any information about the research subjects.

All parties involved in a clinical investigation will maintain the strictest confidentiality so that the personal or family privacy of the subjects participating in it is not violated. Likewise, appropriate measures must be taken to prevent access by unauthorized persons to the research data.

Taking into account the confidential nature, the personal data of the subjects included in the study will comply with the General Data Protection Regulation in force as of May 25, 2018 (Regulation (EU) 2016/679) (if applicable) and with other national law(s) or regulatory requirements applicable in the countries where the research is conducted.

The data from this study will be pseudonymized, since the researcher will receive the data without any identification, although the person who extracts it will keep the information that allows its re-identification. There is technical and functional separation between the researcher and the person extracting the data, as required by the Second Additional Provision of Organic Law 3/2018, of December 5, on the Protection of Personal Data and guarantee of digital rights. Regulation (EU) 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 circulation of such data will apply, and repealing Directive 95/46/EC (General Data Protection Regulation or GDPR).

"Good Clinical Practices" will be applied, which were adopted in the EU in July 1996 and are imposed by Directives 2001/20/EC, Directive 2001/83/EC, 2005/28/EC and the art. 47 of Regulation 536/2014, applying the set of internationally recognized ethical and scientific quality requirements, which must be met in the planning, implementation, registration and communication of clinical research involving human beings.

Furthermore, the Researcher and the Promoter undertake to respect the principles of confidentiality of personal data in relation to the subjects, the Researcher and their collaborators involved in the study.

Specs:

a) Data protection considerations

FOLLOWHEALTH S.L has cloud servers located in Ireland that comply with the General Data Protection Regulation of 05/25/2018 and the LOPD. In addition, participant data is encrypted both on the access platform of the research assistant and the study's technical (IT) administrators and on the server. There is no international data transfer.

In addition, FITBIT and/or its suppliers comply with the European Data Protection Regulation and the participant must accept their privacy policy in order to use the device.

a) Pseudonymization

Participant Data Encryption: Each participant is assigned a randomly generated 8-character ID (e.g. "d4w192bg"), and all participant data is connected only to that ID.

b) Data encryption

All data on phones, on the server and in transit uses industry standard encryption techniques. The phone also uses asymmetric encryption, meaning that even the phone can't read its own data; Data recorded on the phone can only be read on the server.

The fact that the server and platform are encrypted makes it impossible to identify the user. Furthermore, FOLLOWHEALTH S.L. It has a technical team that monitors and protects the cloud, the server and the database.

c) Possible confidentiality violations

Only one type of data can contain personally identifiable information: GPS data (which records location). The GPS data in the app provides enough 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.

10 Modifications to the PIC

Any modification in the conditions authorized for clinical research that is considered relevant cannot be carried out without the prior favorable opinion of the corresponding Clinical Research Ethics Committee and the authorization of the Spanish Agency for Medicines and Health Products.

Without prejudice to the above, if the modification refers exclusively to specific documents that must be evaluated only by the Clinical Research Ethics Committee, only the favorable opinion of said Committee will be required for its application. On the contrary, if the modification refers to the documentation that must be evaluated only by the Spanish Agency for Medicines and Health Products, only its authorization will be required.

If circumstances arise that could endanger the safety of the subjects, the sponsor and the researcher will adopt the appropriate urgent measures to protect the subjects from any immediate risk. The promoter will inform both the Spanish Agency for Medicines and Health Products and the Clinical Research Ethics Committees involved in the investigation of said circumstances and the measures adopted as soon as possible.

Relevant modifications are considered those that are detailed in the Instructions for carrying out clinical research with health products that will be published by the Ministry of Health and Consumer Affairs.

The request must be submitted in writing, dated and signed by the promoter and researcher, to the Spanish Agency for Medicines and Health Products and to the corresponding Clinical Research Ethics Committees. The request will comply with the provisions of the Instructions for carrying out clinical research with health products that will be published by the Ministry of Health and Consumer Affairs.

If the sponsor proposes to introduce modifications to a clinical investigation that may have a substantial impact on the safety, health or rights of the subjects, or on the robustness or reliability of the clinical data generated by the investigation, it shall inform the Member States in which the clinical research is to be carried out, within a period of one week and through the electronic system mentioned in article 73 of the MDR, the reasons and nature of these modifications. The promoter will include an updated version of the corresponding documentation referred to in Chapter II of Annex XV of the MDR as part of the notification. Modifications to the corresponding documentation must be clearly identifiable.

The Member State shall evaluate any substantial modification of the clinical investigation in accordance with the procedure established in Article 71 of the MDR.

The promoter may apply the modifications referred to in section 1 at least 38 days after the notification provided for in said section, unless:

a) the Member State in which the clinical investigation is to be carried out has notified the sponsor of its refusal for the reasons indicated in Article 71(4), or taking into account considerations of public health or health and safety of users, public order , either
b) an ethics committee of that Member State has issued a negative opinion in relation to the substantial modification of the clinical research, which, in accordance with national law, is valid throughout the territory of that Member State.

The Member State or States concerned may extend the period indicated in paragraph 3 for a further seven days for the purpose of consulting with experts.

The request for authorization of the modification will be accompanied by the clinical research plan in which the proposed modification has been included.

11 Deviations from the clinical research plan

Any change, divergence or deviation from the study design or procedures defined therein is considered a deviation from the PIC. Here are some deviations:

- Final number of patients enrolled in the program in the recruitment phase.
- Modifications in the training or recruitment process.
- Estimated time for the pilot phase.
- Modifications in the generation of alerts from where the information is sent.

The impact of possible deviations on the veracity of the data generated and on the conclusions that can be drawn from the research on the performance and safety of the HumanITcare product, will be evaluated by the promoter.

In emergency circumstances, deviations from the PIC to protect the rights, safety and well-being of subjects may proceed without prior approval from the sponsor and the CEIC. Such deviations must be documented and notified to the sponsor and the CEIC as soon as possible.

12 Civil liability insurance

FollowHealth S.L. has contracted civil liability insurance, if necessary a copy of the policy can be provided.

13 Ethical aspects

13.1 Ethical conduct of research

This research will be carried out in accordance with the ethical principles originating from the Declaration of Helsinki and its most recent amendments, in accordance with the approved clinical research plan, the ICH-GCP guidelines, the Clinical Trials Regulations. of the EU and other national laws or regulatory requirements applicable in the countries where the study is carried out.

13.2 Ethics committee

Prior to the initiation of the investigation, the sponsor is responsible for ensuring that the clinical investigation plan and consent form have been reviewed and approved by a relevant CEIC. The CEIC must be properly constituted and perform its functions in accordance with the ICH-BPC guidelines and local requirements, as applicable.

The CEIC will approve all modifications to the clinical investigation plan (except logistical or administrative changes), updates to written informed consent documents, patient recruitment procedures (e.g. advertisements), written information to be provided to patients, the investigator's manual, available safety information, payment information, the investigator's curriculum vitae and/or other qualification evidence and any other documents requested by the CEIM and the Regulatory Authority (Competent Authority), as appropriate.

13.3 Regulatory authorities - Authorization/approval/notification

The clinical research plan and all applicable documentation will be presented or notified to the health authorities in accordance with the regulations of the countries involved in the research.

13.4 Subject information and consent

The researcher will obtain free written consent from each subject after adequate explanation of the objectives, methods, anticipated benefits, potential dangers and many other aspects of the research, which are relevant to the subject's decision to participate. The research subject must have sufficient time to consider participating in the research before obtaining consent. The informed consent form must be signed and dated by the subject and the researcher who has provided information about the research before the subject is exposed to any research-related procedures.

The Patient Information Sheet and the Informed Consent Form will be delivered to the subject, in the recruitment phase, by the researcher. Any doubt, question or explanation requested by the subject will be resolved by the researcher before the IC is signed and returned.

The researcher will explain that the subject is completely free to refuse to participate in the research or withdraw from it at any time, without consequences for their subsequent care and without the need to justify their decision.

The subject will receive a copy of the informed consent documents.

Research subjects will be informed of new information and new consent will be obtained.

14 Adverse events and product deficiencies

The safety profile will be evaluated by recording, reporting and analyzing initial medical conditions, adverse events, physical examination findings, including vital signs and laboratory tests.

The provisions of the latest Safety Notification guide in clinical research with medical devices have been taken into account for compliance with Regulation (EU) 2017/745 (MDCG 2020-10/1-*Safety reporting in clinical investigations of medical devices under the Regulation* (EU) 2017/745).

14.1 Security parameters and definitions

14.1.1 Adverse event (AA)

Any adverse medical event in a patient or other clinical research participant participating in a trial of a medical device, which does not have to have a causal relationship with the product investigated.

Therefore, an AE can be any unfavorable and unintentional sign, symptom or illness temporarily associated with the use of the product, whether or not considered related to the product.

14.1.2 Device deficiency (DD)

Any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational product, including errors in use or insufficiency of information provided by the manufacturer or inadequacy of information provided by the manufacturer.

14.1.3 Adverse Device Effect (ADE)

All adverse and involuntary responses to the medical device.

All cases that the qualified medical professional or sponsor consider to have a reasonably presumed causal relationship with the product are considered effects of the product.

This also includes any event resulting from inadequacies or inadequacies in the instructions for use or deployment of the product and includes any event resulting from user error.

14.1.4 Serious adverse event (SAE)

A Serious Adverse Event (SAE) is defined as an AE that meets one of the following conditions:

- Death during the study period (this means that the AE contributes directly or indirectly to the patient's death).
- Threat to life (defined as a subject at immediate risk of death at the time of the event).
- Requires or prolongs hospitalization.
- Causes a permanent or significant disability or disability (for example, the event disrupts the participant's normal daily activities).
- Any other significant medical event that, based on appropriate medical judgment, may endanger the subject and may require medical or surgical intervention to prevent one of the above outcomes.

All adverse events that do not meet any severity criteria should be considered as **non-serious adverse events**.

The investigator must report in the data collection notebook (CRD) all adverse events that are immediately suspected or those that are spontaneously reported by study participants, regardless of their attribution.

The AAG must be communicated to the promoter immediately by a personal telephone call.

The collection of information about AEs begins with the signing of the consent form. The subject will be questioned about any new adverse events or the evolution of previous adverse events.

Information about adverse events should be communicated as follows:

- Description
- Duration and resolution: start date and resolution date
- Maximum intensity of symptoms
- Causal relationship with study treatment
- Maximum seriousness
- Measures adopted and resolution of the event

14.1.5 Serious adverse device effects (SAEs)

A serious adverse device effect (SAED) is any adverse medical event observed in a patient that can be attributed in whole or in part to the product and that gave rise to any of the characteristics or led to a characteristic of a serious adverse effect.

An EAGD is also any event that could have led to these consequences if appropriate measures had not been taken or intervened or if the circumstances had been less opportune.

All cases judged by the reporting qualified medical professional or the promoter.

14.1.6 Unexpected adverse event (AAI)

An unexpected adverse event is any experience whose nature and severity of the event does not correspond to the information about the study condition or intervention in the clinical investigation plan, consent form, product manual, or investigator manual. Reports that add significant information about the specificity or severity of a known and already documented serious adverse event constitute unexpected events. For example, a more specific or more serious problem than that described in the Investigator's Manual would be considered "unexpected."

14.1.7 Unexpected Adverse Device Effect (EAID)

Any serious adverse health or safety effect of the product, or any life-threatening problem or death caused by or associated with a product, if such effect, problem or death was not previously identified as to its nature , severity or degree of impact on the research plan or request (including a supplemental plan or request), or any other serious unforeseen problem associated with a product that is related to the rights, safety or well-being of the subject.

14.2 Reportable events

For the purposes of the guidance cited above and based on the definitions described above, the following events are considered reportable events in accordance with Article 80(2) of the MDR:

a) Any serious adverse event that has a causal relationship with the investigational product, the comparator or the investigational procedure or when such a causal relationship is reasonably possible.

b) Any product deficiency that could have resulted in a serious adverse event if appropriate action had not been taken, intervention would not have been required, or circumstances would have been less fortunate.

c) Any new findings in relation to any of the events mentioned in letters a) and b).

14.3 Assessment of causality of adverse events

Investigators will request information about AEs/SAEs/DDs each time they come into contact with a patient. All AEs/SAEs/DDs reported by the patient or study personnel will be recorded in the patient's medical record and CRD.

The researcher will evaluate the causality of each AA/AAG/DD that is recorded in the corresponding CRD.

To ensure consistency in causality assessments, researchers should apply the following general rules:

Is there a reasonable possibility of a causal relationship between the study device and an adverse event based on the facts, evidence, scientific data, and appropriate medical judgment?	
AND	A temporal relationship between the AA/AAG/DD and the device under study that indicates a possible causal relationship, when the existence of other devices, therapeutic interventions or underlying disorders do not sufficiently explain the observed event.
NO	A temporal relationship between the AA/AAG/DD and the device under study that indicates an unlikely causal relationship, or the AA/AAG can be satisfactorily explained by the existence of other devices, therapeutic interventions, or underlying disorders.

Board 2. *Causality of AEs*

The sponsor and investigators will use the following definitions to evaluate the relationship of the serious adverse event to the investigational device, comparator, or investigational procedure.

Causality categories include:

1. Unrelated: The relationship with the product, comparator or procedure can be excluded when:
   - the event is not temporally related to the use of the investigational device, or the procedures related to the application of the investigational product;
   - the serious adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
   - The interruption of the application of the medical device or the reduction of the activation/exposure level - when clinically feasible - and the reintroduction of its use (or the increase in the activation/exposure level) do not impact the serious adverse event;

- the event affects a place in the body or an organ that cannot be affected by the product or procedure
- the serious adverse event may be attributed to another cause (for example, an underlying or concurrent disease/clinical condition, an effect of another device, medication, treatment or other risk factors)
- the event does not depend on a false result given by the investigational device used for the diagnosis, if any;

To establish non-relationship, all of the criteria listed above may not be met at the same time, depending on the type of device/procedure and the serious adverse event:

2. Possible: The relationship with the use of the investigational device or comparator, or the relationship with the procedures, is weak but cannot be completely ruled out. Alternative causes (for example, an underlying or concurrent disease/clinical condition or/and an effect of another device, medication or treatment) are also possible. Cases where the relationship cannot be assessed, or no information has been obtained, should also be classified as possible.

3. Probable: The relationship with the use of the investigational product or comparator, or the relationship with the procedures, appears relevant and/or the event cannot be reasonably explained by another cause.

4. Causal relationship: the serious adverse event is associated with the investigational product, the comparator or with the procedures beyond a reasonable doubt when:

    - the event is a known side effect of the product category to which the product belongs or similar devices and procedures;
    - the event has a temporal relationship to the use/application or procedures of the investigational device;
    - The event affects a place in the body or an organ that:
        - the product or procedures under investigation are applied;
        - on which the investigational product or procedures have an effect
    - the serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known);
    - Discontinuing the application of the medical device (or reducing the trigger/exposure level) and reintroducing its use (or increasing the trigger/exposure level) impact the serious adverse event (when clinically feasible);

- other possible causes have been adequately ruled out (for example, an underlying or concurrent disease/clinical condition or/and an effect of another device, medication or treatment);
- the damage to the subject is due to an error in use;
- the event depends on a false result given by the investigational device used for diagnosis where applicable;

To establish the relationship, not all of the criteria listed above may be met, depending on the type of device/procedure and the serious adverse event.

The sponsor and investigators will distinguish between serious adverse events related to the investigational product and those related to procedures (any procedure specific to the clinical investigation). An adverse event may be related to both the procedures and the device under investigation. Complications caused by concomitant non-clinical investigational treatments are considered unrelated to the clinical investigation plan. Likewise, those routine diagnostic or patient management procedures, performed independently of the clinical research plan, if they are not described by the clinical research plan, the complications caused by them are also considered unrelated.

In some particular cases, the event may not be adequately evaluated because the information is insufficient or contradictory and/or the data cannot be verified or complemented. The promoter and investigators will make every effort to define and categorize the event and avoid these situations.

Where no investigator assessment is available and/or the sponsor is unsure of the serious adverse event classification of serious adverse events, the sponsor should not exclude the relationship; the event of the relationship; the event should be classified as "possible" and notification should not be delayed.

Particular attention will be paid to the assessment of causality of unforeseen serious adverse events. Their occurrence could suggest that clinical research places participating subjects at a greater risk of harm than could be expected beforehand.

14.4 Security plan

14.4.1 Registration and collection of adverse events

During scheduled evaluation visits and for the purpose of evaluating participants (study visits, phone calls, etc.), a uniform methodology will be established for asking the patient about any AEs without suggesting an answer to the questions. Below are some examples of open questions:

How have you been feeling since your last visit?
Have you experienced any new problems with your health since our last contact?

All adverse events occurring during the clinical investigation observed by the investigator or reported by the participant, whether or not attributed to the device under investigation, will be recorded in the CRD as specified in the Clinical Research Plan.

The following information will be recorded: description, start date and end date, severity, assessment of relationship to the investigational device, other suspected drug or device, and action taken. Tracking information should be provided as necessary.

14.4.2 Reporting period for adverse events

The relationship of the AEs to the device will be evaluated by a qualified investigator or by the sponsor/manufacturer and will be followed until resolution or until the event is considered stable.

All EADs that result in a participant's withdrawal from the research or are present at the end of the study should be followed up until a satisfactory resolution occurs.

14.4.3 Notification of AAGs/ EAGDs/ EAIDs

The investigator must report any AAG/EAGD/EAIDs or laboratory problems to the sponsor immediately but no later than 3 calendar days after learning of the event; regardless of the relationship to the device.

Communication will be made by email to the address: help@humanitcare.com. The following information must be specified in the email in order to manage the incident as quickly as possible:

- Name of participating center
- Platform Tracking Plan ID
- User ID (in case the incident is related to a specific user)
- Detailed description of the incident
- Support where the incident occurred (web platform + browser / mobile app + operating system)
- Date on which the described incident occurred

The sponsor must inform the health authorities, the Clinical Research Ethics Committee and the investigators, in accordance with Article 80(2) of the MDR, the ICH-GPC guidelines, the EU Clinical Trials Regulation and other national laws or regulatory requirements applicable in the countries in which the research takes place, of the following:

- All SAEs that have a causal relationship with the investigational product, the comparator or the procedure, or whose causal relationship is reasonably possible.
- Product deficiencies that could have led to an AAG if appropriate measures had not been taken, intervention had not occurred, or circumstances had been less fortunate.
- Any new discovery related to both situations (AAG and deficiencies).

The minimum information to be communicated includes the identification of the subject, identification of the AE, start date, reason why it is considered serious, and name of the person who initially reported the event.

Any additional information regarding previously reported unexpected AEs should also be entered into the relevant form as soon as possible.

Additionally, the information must be entered into the CRD.

14.4.4 Report

The sponsor will report all adverse events that are serious and have reasonable potential causality with the investigated product or procedure, in the opinion of the investigator or the sponsor, to the relevant parties within the stipulated time frames and in accordance with local regulations.

Se utilizará el formato de la MDCG 2020-10/1 Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745 del Appendices 12 Clinical Investigation Summary Safety Reporting Form.

14.4.5 Notification periods

The sponsor shall ensure that all relevant information on suspected serious and unexpected adverse events of the product, which are fatal or life-threatening, is recorded and communicated as soon as possible to the competent authorities of all affected Member States and to the Ethics Committee.

In the case of Spain, notifications will be made to the AEMPS through the mailbox psinvclinic@aemps.es.

In any case, the promoter will send the information immediately and no later than 2 calendar days from the moment the promoter becomes aware of the case. This information must be completed, if possible, within the following eight days.

14.4.6 Expedited notification of other relevant safety information

The sponsor must expeditiously notify all information that could modify the risk/benefit ratio of the medical device under investigation, or determine changes in its administration regimen or in the conduct of the research, for example:

- A qualitative change or increase in an expected SAE/EAGD/EAID, which is considered clinically relevant.
- Unexpected SAEs that occur after the completion of a clinical investigation and are notified by the investigator to the sponsor.
- New developments related to the conduct of the research or the development of the investigational device and that are likely to affect the safety of the subjects.
- Any recommendations from the data monitoring committee, which are relevant to the safety of the subjects.

This relevant information must be notified as soon as possible and no later than 7 calendar days after the promoter has become aware of it. Furthermore, if additional information is obtained that is relevant, it must be notified as quickly as possible.

14.4.7 Monitoring of adverse events

Monitoring of AEs, especially those that could not be classified as “unrelated” due to the relationship with the product under investigation, is necessary until the reference level is reached or the subject remains stable. If a clear explanation is found, it should be entered in the CRD. If the type of AA requires the assistance of another person, the subject will be referred to the local hospital, and information about the subject's progress should also be recorded in the corresponding CRD, even if the subject has withdrawn from the clinical investigation for safety reasons. . Follow-up of AEs will continue until resolution, with confirmation if the subject remains stable, or until follow-up is no longer possible. Follow-up will be necessary for both subjects who attend the participants' clinic and those who are referred to their local hospitals for further treatment.

The safety parameter will be defined as the adverse events that occur, including those leading to withdrawal from the study.

14.4.8 Adverse Events Associated with the Investigational Device

In this study the safety information will be given in the user manual. No relevant adverse effects are anticipated.

15 Suspension or early termination of CI

15.1 Termination and Discontinuation Criteria

The research will be completed when all research subjects have completed all the visits established in the clinical research plan.

However, research can be stopped prematurely:

- For security reasons.
- If the planned recruitment data is not met
- If the research is not being carried out in accordance with the standards of Good Clinical Practice (GCP).

15.2 Completion of the investigation

The end of the research is defined as the moment in which the last subject has completed the last visit, in accordance with REGULATION (EU) No. 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of April 16, 2014 on clinical trials and medical devices. for human use, and repealing Directive 2001/20/EC.

15.2.1 Monitoring and care plan for subjects after the completion of the clinical research

Once the study is completed, the subject will continue with their treatment following the usual protocol, or, if they wish, using our platform by obtaining a license from it.

16 Publishing policy

The results of the research will be made public according to the channels accepted by the scientific community, maintaining in all cases the confidentiality and rights of the participants.

16.1 Preparation of the final clinical research report

Once the recruitment of the last subject is completed, the statistical analysis of the results will be carried out and the final report of the clinical investigation will be prepared.

16.2 Clinical evaluation plan

The analysis of the results and the final report will be part of the development of the Clinical Evaluation Plan (CEP) described in section A of annex XIV of regulation 2017/745, which is being developed as part of the technical documentation for obtaining the marking. CE of the product as a medical device.

17 Literature

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