# STUDY PROTOCOL

**Study name:** ReDS-guided decongestion strategy in patients hospitalized for heart failure: the ReDS-SAFE HF II trial

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## 1. SUMMARY

Residual congestion in hospitalized heart failure (HF) patients at discharge is one of the main causes of early readmission. The ReDS (Remote Dielectric Sensing) system is a non-invasive, easy-to-use, and rapid technique that accurately measures the proportion of fluid in lung tissue using RADAR technology. A pilot clinical trial (3 centers, 100 patients) led by the Principal Investigator (PI) demonstrated that guiding decongestion using the ReDS system during hospitalization was associated with a significant reduction in the 30-day readmission rate compared to standard clinical practice, without associated safety events.

Our current objective is to confirm the efficacy and safety of a ReDS-guided decongestion strategy in hospitalized congestive HF patients. To achieve this, an independent, randomized, single-blind clinical trial has been designed, enrolling up to 1,014 congestive HF patients in 25 Spanish hospitals. Patients will be randomized to a decongestion strategy, hospital discharge, and early follow-up in HF units based on ReDS system values versus a strategy based on current clinical practice. All patients will be evaluated daily during hospitalization and in two post-discharge visits (at approximately 10 and 30 days) in HF units using the ReDS system. However, information will only be available to clinicians in the intervention group.

The primary efficacy endpoint will be all-cause mortality, HF readmission, or HF-related decompensations at 30 days. The primary safety endpoint will be the rate of symptomatic hypotension, electrolyte imbalances, or worsening renal function at 30 days.

## 2. BACKGROUND AND REFERENCES

Heart failure (HF) is a growing epidemic and a public health priority. Specifically, decompensated HF is the most common cause of hospitalization in individuals over 65 years old and is associated with high morbidity and mortality rates (1,2). Despite advances in pharmacological treatment and the development of HF units for early and close follow-up, readmission rates remain unacceptably high (3).

Congestion is a key feature in the pathophysiology of acute decompensated HF, and residual congestion at hospital discharge significantly contributes to the risk of readmission (3,4). Traditionally, congestion has been assessed non-invasively through symptoms and signs, as well as other tools such as chest X-rays, plasma natriuretic peptide levels, and echocardiography (5). However, these methods are subject to significant interobserver variability and may not be reliable for various reasons.

In recent years, managing congestion using implantable pulmonary artery pressure sensors that provide real-time hemodynamic measurements has been shown to reduce HF readmissions (6). Unfortunately, due to their invasive nature and high cost, their expansion has been very limited.

Therefore, developing non-invasive volume assessment methods to aid in HF management and identify a "euvolemic" state is an attractive concept, particularly during hospitalization and shortly after discharge—a vulnerable period for recurrent congestion and readmission (7,8). Various alternative techniques to traditional congestion parameters have emerged in recent years, including clinical scores, novel analytical biomarkers, ultrasound techniques, and the ReDS system, which uses electromagnetic energy to measure pulmonary fluid content accurately and non-invasively (17).

Observational studies—some conducted by the PI—have shown that ReDS-guided treatment has the potential to reduce HF readmissions when used in a post-discharge follow-up setting (18,19). Our group recently led the first randomized, single-blind clinical trial evaluating the efficacy and safety of a ReDS-guided decongestion strategy in hospitalized HF patients. This independent, multicenter, international pilot study demonstrated that this strategy significantly reduced the 30-day HF readmission rate without compromising patient safety (20). However, the relatively small sample size suggests caution in interpreting its findings as "proof of concept." Therefore, a study designed to confirm these promising results with sufficient statistical power, allowing subgroup analyses and assessing feasibility across a broader range of centers, is urgently needed.

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## 3. HIPOTHESIS

**1. Primary:**

1.1. A ReDS-guided decongestion strategy to assess pulmonary congestion during hospitalization for HF will help optimize patients before discharge and during early outpatient follow-up, improving short-term prognosis (1 month).

**2. Secondary:**

2.1. A ReDS-guided decongestion strategy will be particularly beneficial for patients in whom pulmonary congestion is difficult to estimate (e.g., obesity, renal insufficiency, diuretic resistance).

2.2. ReDS values will positively correlate with plasma natriuretic peptide and CA125 levels, with a greater reduction of both biomarkers in patients assigned to a ReDS-guided decongestion strategy.

2.3. A ReDS-guided decongestion strategy will be as safe as standard management in terms of symptomatic hypotension, electrolyte imbalances, and/or worsening renal function.

2.4. A ReDS-guided decongestion strategy will be cost-effective from the national healthcare system perspective.

## 4. OBJECTIVES

**1. Primary:**

1.1. To evaluate whether a ReDS-guided decongestion strategy during hospitalization for HF and early outpatient follow-up is superior to standard clinical practice in reducing the combined event rate of all-cause mortality, HF readmission, or HF visits requiring diuretic adjustment at one month.

**2. Secondary:**

2.1. To analyze the efficacy of a ReDS-guided decongestion strategy in specific clinically relevant subgroups (obesity, chronic renal insufficiency, diuretic resistance) and epidemiological subgroups (age and sex).

2.2. To correlate ReDS system measurements with plasma natriuretic peptide and CA125 levels at admission, discharge, and outpatient follow-ups.

2.3. To determine the safety of a ReDS-guided decongestion strategy compared to standard clinical practice at one-month post-discharge by evaluating renal function deterioration, symptomatic hypotension, and electrolyte imbalances.

2.4. To calculate the cost-effectiveness of a ReDS-guided decongestion strategy considering hospital stay duration and reduction of the combined efficacy endpoint.

## 5. METHODOLOGY

### 5.1. Study design (annex 1)

A randomized, single-blind, controlled, multicenter clinical trial (list of investigators and participating centers in annex 2) promoted by the researcher, which evaluates the efficacy and safety of a decongestion strategy guided by the ReDS system compared to standard clinical practice in patients admitted for decompensated heart failure.

### 5.2. Study population

Those adult patients meeting all the following criteria will be included:
1. Hospitalized due to HF as the main reason, including the presence of symptoms and signs of congestion, regardless of the left ventricular ejection fraction (LVEF).
2. NT-proBNP greater than 1000 pg/L or BNP greater than 300 pg/L upon admission.

Patients meeting any of the following conditions will be excluded:
1. Height less than 150 cm or greater than 190 cm or body mass index (BMI) less than 22 or greater than 39, conditions where the use of ReDS is not approved.
2. Patients requiring inotropes or vasopressors upon admission, with mechanical support, or heart transplant recipients.
3. Any malformation or variant affecting the right lung anatomy (e.g., a pacemaker).
4. Patients with any heart disease requiring a planned surgical intervention during the clinical trial (coronary disease, valve disease, or other).
5. Chronic kidney disease on hemodialysis.
6. Life expectancy less than 12 months due to non-cardiological origin.
7. Participation in another clinical trial with intervention.

### 5.3. Variables

1. Primary efficacy variable: combined 30-day outcome of all-cause mortality, heart failure (HF) readmission, or HF-related visits requiring diuretic treatment adjustment.
2. Secondary efficacy variable: individual components of the main variable, proportional change in natriuretic peptides and CA125 between admission and the first post-discharge outpatient visit, New York Heart Association functional class at the first post-discharge outpatient visit, average length of stay, cost of hospitalization for HF, and unplanned visit.
3. Primary safety variable: combined outcome of symptomatic systolic hypotension (<90 mmHg), electrolyte imbalances (potassium below 3 or above 5.5 meq/L), and/or worsening of renal function compared to the baseline visit at the first post-discharge outpatient visit (at least 50% reduction in glomerular filtration rate).
4. Secondary safety variables: individual components of the primary safety variable.
5. Cost-effectiveness variables: average length of stay and cost of the ReDS device.

### 5.4. Protocol

Patients will be identified and selected upon admission. If they meet the selection criteria and confirm their willingness to participate in the study, they will be randomized in a 1:1 sequence through a mobile application specifically designed for the study by P INVESTIGA, to one of the following interventions within 48 hours of hospital arrival:

1) "ReDS-guided strategy." Each day, the clinician responsible for the patient will have access to the ReDS value and will adjust the treatment according to the study's diuretic protocol (annex 3). The responsible physician can discharge the patient if the clinical stability criteria are met, and the ReDS value is below 35% and/or a reduction of 15% or more from the admission ReDS value has been achieved. If the ReDS criteria are not met, the patient must remain hospitalized for another day until these conditions are met. Clinical stability is defined as the presence of at least 2 of the following 3 conditions: i) discharge weight lower than admission weight, ii) at least a 20% reduction in natriuretic peptide from admission, and iii) a score <2 in the Orthoedema score.

2) "Usual clinical practice strategy." The responsible physician will not have access to the ReDS values and will adjust the treatment according to their clinical judgment and local practices. Discharge can be given if the clinical stability criteria are met.
The ReDS technology has been described in detail previously (7, 8, 20). Briefly, the ReDS system consists of 2 sensors that are placed (sitting or supine) on the front (infraclavicular) and back (below the scapula) of the patient's right hemithorax and in 45 seconds accurately quantifies the proportion of fluid in the lung. The sensors are connected via 1 cable to a touchscreen monitor that easily guides the measurement process and stores this information. The accuracy of this technology has been validated with high-resolution chest computed tomography (8) and invasive hemodynamic measurements with a Swan-Ganz catheter (9). Normal ReDS values range between 20% and 35% (i.e., 20-35% of the lung would be fluid). Above 35% is considered congestive, whereas below 20% the lung would be "dry" or dehydrated.

A ReDS device will be distributed per center with a unique serial number, ensuring traceability. Prior training will be provided to the research and clinical staff (both medical and nursing) of each participating center before the study begins by the company distributing the device in Spain (SOREVAN). The prior training for using this technology is very simple, with a learning curve of less than 1 hour, although each participating center already has previous experience with this technology. The device itself guides the operator through a touchscreen before a measurement, graphically informing each step to take to perform a measurement on a patient. The ReDS devices used in the clinical investigation will be utilized following their instructions for use.

### 5.5. Data collection and management

All information at admission, during hospitalization, at discharge, and during the 2 post-discharge outpatient visits will be collected by the researchers in an electronic data collection notebook (CRD) through a mobile application that allows semi-automatic and

anonymized extraction of relevant clinical information by photographing medical reports. The mobile phone application will be developed by P INVESTIGA, a company with extensive experience in this type of app. Specifically, the following will be collected:

**5.5.1 Baseline visit (within first 48 hours of hospital admission)**
- Informed consent with date and signature of the patient and local investigator.
- Demographic data: race, gender, and age, and anthropometric data: weight and height.
- Complete medical history, including main comorbidities and usual medical treatment.
- Usual NYHA functional class before decompensation.
- Vital signs (blood pressure, heart rate, arterial saturation) and daily physical examination findings (weight, signs of left and right congestion).
- 12-lead ECG.
- Baseline echocardiogram (or the last available in the year before the current admission).
- Complete blood tests (renal and liver function, electrolytes, lipid profile, NTproBNP/BNP, CA125, blood count, and coagulation).
- Alternative methods for congestion analysis used by local clinical practice: lung ultrasound, VExUS, impedance, right heart catheterization.
- Measurement with the ReDS system.

**5.5.2. Follow-up visits (every day during admission):**
- Vital signs (blood pressure, heart rate, arterial saturation) and daily physical examination findings (weight, signs of left and right congestion).
- Measurement with the ReDS system
- Alternative methods for congestion analysis used by local clinical practice: lung ultrasound, VExUS, impedance, right heart catheterization.

**5.5.3. Visit at discharge (within 24 hours before hospital discharge):**
- Current NYHA functional class at discharge.
- Vital signs (blood pressure, heart rate, arterial saturation) and daily physical examination findings (weight, signs of left and right congestion).
- 12-lead ECG.
- Echocardiogram at discharge (not mandatory).
- Complete blood tests (renal and liver function, electrolytes, lipid profile, NTproBNP/BNP, CA125, blood count, and coagulation).
- Alternative methods for congestion analysis used by local clinical practice: lung ultrasound, VExUS, impedance, right heart catheterization.
- Measurement with the ReDS system
- Major interventions performed during the index admission: revascularization, electrical cardioversion, arrhythmia substrate ablation, device implantation, complications, etc.

**5.5.4. First visit at HF Clinic (14 +/- 3 days after hospital discharge):**
- Current NYHA functional class.
- Vital signs (blood pressure, heart rate, arterial saturation) and daily physical examination findings (weight, signs of left and right congestion).
- 12-lead ECG.

- Complete blood tests (renal and liver function, electrolytes, lipid profile, NTproBNP/BNP, CA125, blood count, and coagulation).
- Alternative methods for congestion analysis used by local clinical practice: lung ultrasound, VExUS, impedance, right heart catheterization.
- Measurement with the ReDS system.
- Clinical events.

**5.5.5. Final visit at HF Clinic (30 días+/-5 days after hospital discharge):**
- Current NYHA functional class.
- Vital signs (blood pressure, heart rate, arterial saturation) and daily physical examination findings (weight, signs of left and right congestion).
- 12-lead ECG.
- Complete blood tests (renal and liver function, electrolytes, lipid profile, NTproBNP/BNP, CA125, blood count, and coagulation).
- Alternative methods for congestion analysis used by local clinical practice: lung ultrasound, VExUS, impedance, right heart catheterization.
- Measurement with the ReDS system.
- Clinical events.

The information will be stored in a restricted-access online database developed by P INVESTIGA. Only designated researchers at each center will have access to this information.
After entering the data into the system, it will be automatically reviewed with monthly scheduled quality checks. Errors, discrepancies, missing data, and out-of-range entries will be resolved both automatically and manually (by the clinical monitor and data manager) generating data queries. The system will provide detailed query process control. Corrections to the electronic CRD can only be made by specially designated personnel and must be signed by the researcher. All changes will be automatically recorded in the system's audit trail. An authenticated user account will be created and maintained by P INVESTIGA for each authorized user once they have completed the corresponding training. Users must keep their passwords confidential. Depending on their role within the clinical study, users may be limited to viewing the information only or have additional permissions to enter and correct data, generate query resolutions, and provide electronic signatures. Only researchers will be able to sign clinical entries.
All electronic documents related to the study will be stored in the archive generated by P INVESTIGA, allowing storage under conditions protected from fire, flood, theft, or pests. Access to the archives will be controlled. After the database is closed, all data from the electronic CRF, as well as the change control performed, will be exported and electronically stored in the server archive. The research team will keep this information stored for at least 15 years after the completion of the study and will be obligated to make the information accessible upon request by the Ethics Committee, regulatory agencies, or monitoring and auditing company. At the end of this period, local laws and regulations will be considered to decide whether to extend the retention period or proceed with the destruction of the data.

***Data safety***

The study will be carried out while always maintaining confidentiality in accordance with current legislation (Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on Data Protection (GDPR), Organic Law 3/2018 of 5 December on the Protection of Personal Data and guarantee of digital rights, and the provisions in this regard contained in Law 41/2002 of 14 November, the basic law regulating patient autonomy and rights and obligations in the matter of information and clinical documentation, as well as any applicable and relevant regulations).

## 5.6. Sample size estimation and data analysis

The sample size estimation is based on the two previous studies by the group with this technology (references 19 and 20, which observed a Hazard ratio of 0.20 and 0.10 for the primary efficacy event respectively for ReDS-guided treatment) and on the average rate of the primary efficacy event (15%) of the participating hospitals during 2023. For an 80% power, a 5% alpha error, and considering a 10% subject loss rate during follow-up, 507 patients per group (1014 in total) are needed to detect a 50% reduction in the primary efficacy event (conservative estimate).

To evaluate the efficacy of the randomization process, a descriptive analysis will be performed using the chi-square test, Student's t-test, or Wilcoxon rank-sum test, as appropriate. All comparisons will be conducted according to the intention-to-treat principle. The time to the primary endpoint will be evaluated using Kaplan-Meier estimates and Cox proportional hazards models. A hierarchical analysis of the primary event with the win ratio method will also be performed. The number of patients needed to treat to prevent an efficacy event (NNT), and a safety event (NNH) will be calculated. For secondary outcomes, differences in plasma biomarker levels will be evaluated with chi-square, Fisher's exact test, t-test, and Wilcoxon rank-sum test, as appropriate. A p-value <0.05 will be considered statistically significant. The Stata program (StataCorp, Texas, USA) will be used.

Two interim analyses of the results are planned when 30% (risky estimate) and 60% (average estimate) of the sample size is reached. In addition, a steering committee of the clinical trial will be created, comprising members of recognized prestige (Dr. Jose Luis Zamorano, Dr. Marisa Crespo Leiro, Dr. Toni Bayés-Genís, Dr. Stefan Anker, Dr. Anu Lala, Dr. William Abraham, Mr. Tomás Fajardo), independent of the research team, who will ensure strict compliance with the protocol and have access to real-time event rates to detect potential futility of the intervention.

## 5.7. Ethics

The study will be conducted in accordance with the principles of good clinical practice expressed in the Declaration of Helsinki. All patients will provide their informed consent, and the protocol will be approved by the Ethics Committee of the coordinating hospital (Ramón y Cajal) and each participating center. It will be registered at www.clinicaltrials.gov.

### 5.8. Study limitations

The main limitations are listed below, followed by the planned compensatory mechanisms:
1) Insufficient sample size. There is a possibility that the effect intensity of the "ReDS-guided strategy" might be lower than observed in the two previous studies (reference 19, observational, HR 0.18; reference 20, randomized trial, HR 0.09). Therefore, a conservative sample size calculation with an HR of 0.50 was chosen.
2) Futility of the intervention. In case the "ReDS-guided strategy" proves to be futile, an interim analysis of efficacy and safety variables is planned at 30% and 60% of the sample size. It is relevant to consider that in the previous clinical trial (reference 20), there were no significant differences in safety events (arterial hypotension, worsening of renal function, or electrolyte disturbances).

### 5.9. Execution risks and contingency plan

1) Unmasking of the single blind: to minimize this risk, the researchers at each center will be individuals separate from the clinical team responsible for patient care, and the randomization process will be conducted telematically via a mobile application.
2) Assignment and validation of clinical events: an ad hoc committee will be formed to review all reported efficacy and safety events, blinded to the study group.

### 5.10. Patient participation

In order to incorporate the perspective of the patient community throughout the design, execution of the study, and its analysis, the executive committee of the clinical trial includes one representative (Mr. Tomás Fajardo) from the Spanish Patient Association CARDIOALIANZA, which brings together 48 patient associations with heart diseases from all over Spain and has shown its support for the project through a letter signed by its president.

### 5.11. Gender perspective

Within the methodology and data analysis, three aspects related to the gender perspective have been included:
1) A quota of at least 30% female patients included in the total population.
2) Analysis of the main and secondary efficacy and safety variables by sex.
3) Nearly 50% of the researchers from the 25 hospitals involved in the study are women, aiming for parity in representation.

### 5.12. Adverse events and management

#### 5.12.1. Definition of adverse event related to the device

An adverse event related to the device (AED) is an AE that is related to the use of the investigational device. This includes any AE from inadequate or insufficient information in the instructions for use or any malfunction of the investigational device and any event resulting from erroneous use or intentional misuse of the investigational device (see ISO14155 3.1). Adverse events resulting from the necessary medical procedures for the use of the investigational device, even if not directly related to the device (e.g., moving

the patient to place the device before taking a measurement), will be considered AE related to the procedure.
There are three categories for classifying the relationship of the adverse event of the investigational device:
*Clearly unrelated:* A relationship between the AE and the investigational device and/or the procedure can be ruled out.
*Possibly related*: A potential relationship between the investigational device and/or the procedure cannot be ruled out.
*Clearly related:* It is almost certain that the AE is related to the investigational device and/or procedure.

#### 5.12.2. Definition of deficiency device

A device deficiency (DD) is defined as a failure of the medical device concerning its identity, quality, longevity, reliability, safety, or performance, including failures, misuse errors, and inadequate packaging (see ISO14155 3.15).
The DDs of the investigational device should be reported throughout the study. DDs that caused an adverse event will be reported in the respective adverse events form. If the DD did not cause an adverse event, it should be reported in the adverse events form as a "non-medical" event.

#### 5.12.3. Serious adverse event definition

AEs are classified as serious if one or more of the following consequences are met:

- Led to the death of the patient
- Led to a serious deterioration of the health of the subject, which resulted in:
- An illness or injury with potential life risk, or
- A permanent deficiency of a body structure or function, or
- An extended hospitalization of the patient, or
- A medical or surgical intervention to prevent a life-threatening illness or a permanent disability or deficiency of a body structure or function.

#### 5.12.4. Serious adverse definition of device

An AE that results in any of the characteristic consequences of a serious adverse event will be considered severe (see ISO14155 3.6).

#### 5.12.5. Non expected serious adverse event

These are defined as unanticipated if by their nature, incidence, severity, or outcome, they have not been identified in the current version of the risk analysis report (see ISO14155 3.42). These events should be reported by the sponsor immediately. An analysis will be conducted to determine the cause, and the immediate possibility of recurrence will be evaluated.

#### 5.12.6. Report responsibility

***From the investigator to sponsor***
The investigator must document all events in the corresponding CRFs available in the system. The timelines for initial case reports and possible revisions must be strictly followed.

All serious adverse events (SAEs) and serious device adverse events (SDAEs) must be reported along with a justification by completing the SAE-CRF as stipulated in ISO 14155:2011.
For device deficiencies, the DD-CRF must be filled out. Reports must be made considering all available information, even if this involves incomplete reporting. The investigator must follow up on the evolution of AEs if the patient remains in the study, or until the event has been resolved, whichever comes first.
The investigator must categorize each event with a single primary diagnosis. The primary diagnosis can describe the event using various recognizable clinical variables, symptoms, or with secondary diagnoses. Note: Observed symptoms and secondary diagnoses must be appropriately documented in the respective CRF.
Multiple events may occur in the same subject. An individual report must be made for each independent medical event based on the primary diagnosis.
Additionally, the action taken/treatment should also be included along with any available supporting documentation.
The investigator must ensure that all relevant information is available. This also includes information to third parties (family, other hospitals, etc.).
If a patient dies during the study, the investigator must document the cause of death, its circumstances, and place of death. All actions taken, which were initiated to obtain additional information, must be documented in writing and sent to P INVESTIGA.

***From the investigator to third parties***
According to international and national laws, some of the competent authorities (CAs) and ethics committees may require the reporting of SAEs and device deficiencies with potential for SADEs while the study. Investigators must ensure that they comply with their responsibilities towards their competent authorities and ethics committees.

***From the CRO***
P INVESTIGA will report all Serious Adverse Events (SAEs)/Serious Device Adverse Events (SDAEs) and all Device Deficiencies with the potential for SDAEs to the competent authorities, as required by local regulatory authorities. Furthermore, P INVESTIGA ensures that safety reports are forwarded to research centers and ethics committees as per local requirements. P INVESTIGA will periodically inform investigators of all reported AEs and DDs that could have generated an SDAE.

***Report calendar***
The deadlines for reporting adverse events by the investigator to P INVESTIGA will depend on the seriousness of the event:

| Event | Report to | Schedule |
|---|---|---|
| Adverse Event (AE) / Serious Device Adverse Event (SDAE) | P INVESTIGATES: Document in the AE CRD | 2 weeks |

| | | |
|---|---|---|
| Serious Adverse Event (SAE) / Serious Device Adverse Event (SDAE) | P INVESTIGATES: Document in the AE CRD | Immediately, no later than 24 hours post event detection |
| Unanticipated Serious Device Adverse Events (USDAE) | P INVESTIGATES: Document in the AE CRD | Immediately, no later than 24 hours post event detection |
| Device Deficiencies | P INVESTIGATES: Document in the DD CRD | 14 days |
| Device Deficiency with potential for SDAE | P INVESTIGATES: Document in the DD CRD | 24 hours |

***Emergency contact***

The ReDS devices used in the study are CE-approved at the time the study begins and will be used according to their intended use. Patients will not receive additional invasive procedures, so there is no need to provide an emergency contact. The informed consent form includes a phone number for each research center where the patient can get medical advice during normal working hours.

## 5.13. Amendment procedure

If changes to the clinical investigation plan (CIP) are necessary during the study, a justification for the change must be prepared, including the reason for the change. The modification of the CIP can be summarized in a separate document as an appendix to the current version of the CIP or result in a new version of the CIP. If the changes impact procedures related to the study or data analysis, they are defined as substantial. New versions of the CIP or substantial amendments must be reviewed and confirmed by the Coordinating Investigator. All investigators must acknowledge receipt of the amendment through the signature of the approval form for the amendment. Before implementing any changes, substantial amendments must be approved by the ethics committee and, if applicable, by the competent authorities. Non-substantial amendments will only be submitted for notification.

The investigator must not implement any deviation from the CIP without the sponsor's approval and without prior review and documented approval from the EC (and competent authorities if necessary). The only exception would be the need to eliminate an immediate risk to patients or if the change involves logistical and administrative aspects of the study.

### 5.13.1. Compliance and exceptions

All sponsor personnel, all staff at the research center, as well as third parties involved in tasks described in this CIP must adhere to the CIP. A deviation is any failure, intentional or not, to follow the requirements of this CIP, including laws, guidelines, and other regulations, as well as applicable amendments. Deviations that could affect or have affected patient safety or the scientific integrity of the clinical investigation are considered major. Otherwise, they are considered minor deviations.

Incorrect, spurious, or lost data from the CRD are not considered deviations per se and are managed according to the queries procedures described in the data management section of this CIP. However, the underlying reason could be a deviation.
Under emergency conditions, deviations from the CIP can be undertaken without prior notice from the sponsor and the ethics committee if they are carried out to protect the rights, safety, and well-being of human subjects.

### 5.13.2. Storage, reporting and analysis of deviations

Research centers must automatically inform the monitor of any deviation they are aware of. Additionally, adherence to the CIP is verified by the sponsor through monitoring visits. Each specific deviation from the center is recorded by the monitors in the deviation log and analyzed to determine the necessary corrective or preventive actions. Additional information about the type of deviation, actions taken, and outcomes may be collected in the monitoring visit reports. All information in the deviation logs is consolidated by the sponsor in the study's global deviation log.
Deviations by sponsor personnel or third parties must be immediately reported to the sponsor by anyone who detects them. They are recorded in the study's deviation log and evaluated to determine the need for corrective or preventive actions.
Deviations are reported in the interim and final reports of the clinical investigation.
The sponsor adheres to the specifications of the ethics committees and competent authorities and ensures that timelines and schedules are met.

### 5.13.3. Corrective and preventive actions and disqualification criteria

Corrective actions will be taken to repair or prevent any negative consequences caused by a deviation. Preventive actions will be taken to ensure that the same type of deviation does not occur again. Each deviation will be individually assessed by the sponsor for the necessity of an immediate response. Additionally, the sponsor will regularly evaluate the global deviation log to determine the need for a global preventive action.
All persons involved in the deviation will need to cooperate with the sponsor, identifying and implementing appropriate actions. The performance and implementation of these actions will be documented by the sponsor and filed in the central file and, in the case of specific deviations, in the investigator's file.
Disqualification of study personnel is the last measure within possible preventive actions. This implies that in the case of significant deviations that substantially affect the safety and well-being of the subjects, or that lead to a high probability of data disqualification and doubts about the study results, and there is a probability of recurrence, the responsible person or the investigating center will be excluded from the study.

## 6. MONITORING PLAN

The sponsor will hire the company P INVESTIGA to carry out the study. Both the sponsor and P INVESTIGA will be responsible for ensuring compliance with the protocol and norms through proper monitoring. It is the sponsor's obligation, supervised by P

INVESTIGA, to ensure that the devices are used under the immediate supervision of the investigator. Like the investigator, the physician is responsible for conducting the study according to the signed research contract, the study protocol, applicable laws (including local regulations and the Declaration of Helsinki), and any conditions imposed by the study review committees.

The entries in the electronic CRF will be reviewed, and the source data will be verified at the hospital by the monitors to ensure that the investigator and the research team conduct the clinical investigation as stipulated in the protocol, the Declaration of Helsinki, ISO 14155, and local laws to guarantee adequate protection of the rights, safety of the subjects, and the quality and integrity of the resulting data.
A monitor will periodically visit the hospital during the study. All participating centers will be monitored throughout the study duration, with the frequency of these visits adjusted as necessary to ensure adherence to the procedures described in the protocol, as well as to ensure the highest possible data quality. A detailed monitoring plan previously developed by P INVESTIGA will be followed. Periodic monitoring will ensure, among other things, that the hospitals remain adequate, the protocol is being followed, the ethics committees have been informed of protocol changes, the files and data collection are complete and available, the reports have been made and submitted on time to the sponsor and authorities, and that the investigator is fulfilling all their obligations.

Periodic monitoring will include, but not be limited to:
1. Completing and delivering the necessary electronic CRFs and other relevant study documentation
2. Continuous evaluation of the centers, including the storage and maintenance of the investigational devices
3. Adherence to the clinical investigation plan
4. Adherence to the current version of ISO 14155 and local regulations.

If the monitor becomes aware that the investigator is not meeting the requirements mentioned above, the monitor will be obliged to notify the sponsor and P INVESTIGA staff, who will review the situation and proceed to implement corrective plans, suspend recruitment, or, as a last resort, close the research center.

## 7. RESPONSABILITIES.

The ReDS-SAFE HF II study will be coordinated and controlled by the principal investigator:
Dr. Jesús Álvarez García
*Hospital Universitario Ramón y Cajal*
*Department of Cardiology, Advanced Heart Failure Unit*
*Carretera Colmenar Viejo km 9,100, 28034*
*Madrid (Spain)*

The principal investigator, as well as the members of the executive committee, will be responsible for the following processes as described in ISO14155:2011:

• Creation/review of the research plan
• Control of the study's performance and progress
• Continuous monitoring of the risk/benefit ratio
• If necessary, making the decision to prematurely terminate the study after consulting with the sponsor
• Coordination of the publication and presentation of study results
• Advising all investigators on medical issues related to the study
• Reporting adverse events

The clinical coordinators of the study will be assisted in all described tasks by the Study Coordinator/Project Manager. Additionally, they have the same rights and obligations as the rest of the investigators.

### 7.1. Responsibility of investigator

This study will be conducted by qualified investigators whose participation has been approved by the sponsor after careful analysis and documented in a clinical contract detailing the tasks. The principal investigator specified in the contract will be considered the principal investigator for that specific center. The principal investigator may delegate some of their functions to co-investigators. However, the principal investigator retains primary responsibility for the correct execution of the study in their center according to the following responsibilities (as defined in ISO14155:2011):
• Register the study with the responsible authorities at their center (hospital administration)
• Communication with the ethics committee and obtaining its dated and signed approval
• Reporting adverse events
• Active recruitment of candidate patients and providing appropriate medical care to patients participating in the study
• Patient education and obtaining written informed consent as described in the protocol
• Safe and effective use of study devices
• Conducting the study as described in the protocol
• Completing the CRFs within the corresponding time windows
• Confidential treatment of all study-related documents and information
If an investigator does not comply with the signed contract or the protocol and it is not possible to reach an agreement between the investigator and the sponsor, the sponsor is authorized to exclude the investigator from the study.

### 7.2. Responsibility of Steering Committee

It is formed by relevant members in the field of heart failure and the president of the patient association with cardiovascular disease Cardioalianza. This committee will be available for consultation on the main objectives, promotion, publication, and presentation of the study results. The scientific committee advises especially during the design phase of the research plan, and with the continuous control of safety in the execution of the study.
The members of this committee are:
Dr. Anu Lala
Dr. María Generosa Crespo Leiro
Dr. Toni Bayés-Genís

Dr. Stefan Anker
Dr. William Abraham
Dr. José Luis Zamorano Gómez
Mr. Tomás Fajardo

### 7.3. Responsibility of Sponsor

The sponsor of this clinical study is
Fundación para la Investigación Biosanitaria Ramón y Cajal
*Hospital Universitario Ramón y Cajal*
*Carretera Colmenar Viejo km 9,100, 28034*
*Madrid (Spain)*
The sponsor ensures that all necessary documents, information, and human resources will be available at the start and during the study. Additionally, the sponsor will have the following tasks and obligations:

- Select appropriate research centers and investigators in accordance with the clinical coordinator.
- If necessary, report to all relevant authorities and provide reports according to national laws.

### 7.4. Responsibility of Clinical Coordinator

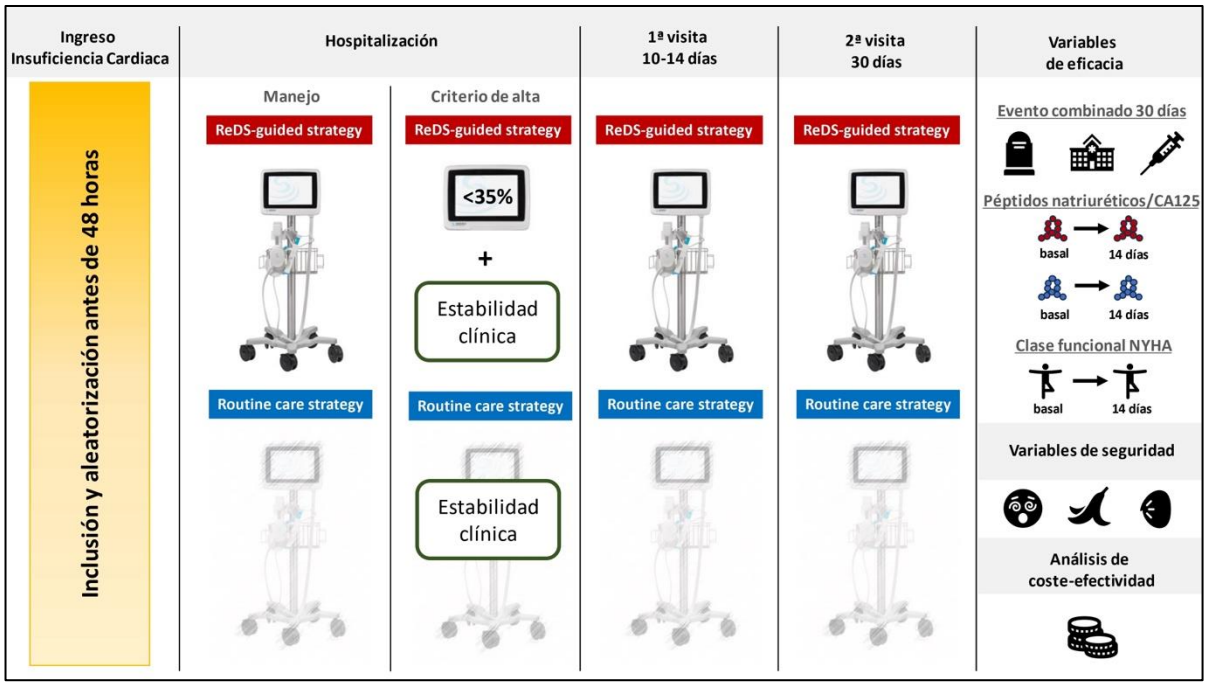
In case of any issues related to the clinical research plan and the medical devices used, the investigator should contact the clinical coordinator, who is responsible for the following:
• Assisting the Principal Investigator in the preparation of the protocol and its possible amendments.
• Assisting investigators during the study (securing the approval of research review committees/ethics committees and publication of study results, etc.),
• Providing regular information to the investigators about the progress of the study.
• Organizing the handling of inquiries.
• Handling data and analyzing it.
The sponsor appoints the person described below as the study coordinator:
Dr. Jesús Álvarez García
*Hospital Universitario Ramón y Cajal*
*Cardiology Department, Advanced Heart Failure Unit*
*Carretera Colmenar Viejo km 9,100, 28034*
*Madrid (Spain).*

### 7.5. Responsibility of Clinical Events Committee

All events related to the primary objective and secondary objectives will be reviewed by the Clinical Events Committee. This committee will consist of three physicians not participating in the study who will review all events recorded by the patients. Their function will be to assign the type of adverse event according to its severity and relevance to the study.
The members of this committee will be Dr. Marcelo Sanmartín, Dr. Pau Llàcer, and Dr. Milagros Fernández, from the Cardiology, Internal Medicine, and Nephrology departments of Hospital Universitario Ramón y Cajal.

## 5. ANNEX

### Annex 1: ReDS-SAFE HF II clinical trial




### Annex 2 List of participating centers and local PIs

| | |
|---|---|
| Hospital Universitario Ramón y Cajal | Jesús Álvarez García |
| Hospital Puerta de Hierro Majadahonda | Mercedes Rivas Lasarte |
| Hospital Universitario 12 de Octubre | Laura Morán Fernández |
| Hospital Clínico San Carlos | Josebe Goirigolzarri Artaza |
| Fundación Jiménez Díaz | Mikel Taibo Urquía |
| Hospital Universitario La Paz | Ángel Iniesta Manjavacas |
| Hospital Universitario de La Princesa | Pablo Díez Villanueva |
| Hospital Gregorio Marañón | Zorba Blázquez Bermejo |
| Hospital Clínic Barcelona | Eduard Solé González |
| Hospital Vall d'Hebron | Toni Soriano Colomé |
| Hospital Universitari de Bellvitge | Herminio Morillas Climent |
| Hospital del Mar | Sandra Valdivielso More |
| Hospital Moisés Broggi | Román Freixa Pamies |
| Hospital Dr. Josep Trueta | Aleix Fort Pal |
| Hospital Arnau de Vilanova | Ramón Bascompte Claret |
| Hospital Universitari Joan XXIII | Isabel Serrano Rodríguez |
| Hospital Virgen de la Arrixaca | Noelia Fernández Villa |
| Complejo Hospitalario Universitario de Santiago | Inés Gómez Otero |
| Hospital Clínico de Salamanca | David González Calle |
| Hospital Universitario de Toledo | Marta Flores Hernán |
| Hospital Virgen de la Macarena | Alejandro Recio Mayoral |

| | |
|---|---|
| Hospital Reina Sofía | Manuel Anguita |
| Hospital Virgen de la Victoria | Ainhoa Robles Mezcua |
| Hospital Marqués de Valdecilla | Gonzalo Martín Gorria |
| Hospital Clínico de Valencia | Julio Núñez Villota |
| CNIC | Borja Ibáñez Cabezas |

## Annex 3: ReDS guided diuretic protocol

| ReDS (%) | Diuretic Protocol |
|---|---|
| **Less than 20%** | *Discontinue diuretics.* |
| **20-35%** | *Maintain the prescribed diuretic dose. Consider switching from intravenous to oral administration if no significant edema is present. If significant edema persists, continue intravenous.* |
| **36-45%** | *Increase the diuretic dose. Switch to intravenous administration if given orally. Add a thiazide diuretic if the intravenous dose is equivalent to 200 mg.* |
| **Greater than 46%** | *Add a second diuretic. Administer all diuretics intravenously and aim for an hourly diuresis of at least 250 ml in the next 2 hours. If this is not achieved, double the prescribed dose.* |