



retention

SMART HEART FAILURE MANAGEMENT

Horizon 2020 Project RETENTION

“HEART FAILURE PATIENT MANAGEMENT AND INTERVENTIONS USING CONTINUOUS PATIENT MONITORING OUTSIDE HOSPITALS AND REAL-WORLD DATA”

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Document information and history

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This deliverable will document the Clinical Trial Protocol, along with the refined set of KPIs, criteria and methodology to evaluate the RETENTION platform.

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* The project uses a multi-stage internal review and release process, with defined milestones. Milestone names include abbreviations/terms as follows:

TOC = "Table of Contents" (describes planned contents of different sections);

- Intermediate: Document is approximately 50% complete – review checkpoint;

ER = "External Release" (i.e. to commission and reviewers);

- Proposed: document authors submit for internal review;
- Revised: document authors produce new version in response to internal reviewer comments approved: Internal project reviewers accept the document.



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1 Executive Summary

This document is the Deliverable D8.2 entitled “RETENTION Clinical Trial Protocol & Evaluation Framework” of WP8. Includes the Clinical Protocol of the Trial and the Evaluation methodology to be followed. More specifically this deliverable describes the categories of included patients and the randomisation algorithm, the criteria of the participants’ recruitment, which data will be collected through the smart sensors and the smart devices and when this data will be collected. It also describes how and when the notifications and the interventions will be made using the continuous patient monitoring values. The statistical analysis plan of the trial study is also included.

Additionally to the statistical analysis, it presents an evaluation checklist associated to T8.5, that provides the fundamentals for the non-clinical (i.e., technical) evaluation of the RETENTION solution (i.e., the RETENTION Patient Edge instances – Edge or mobile app, the RETENTION Clinical Site Backend - CSB, and the RETENTION Global Insights Cloud – GIC), along with associated testing activities scheduled to be performed to validate the solution in terms of performance and intended usage. To this extent, usability of interaction elements (CSB-GIS Dashboards, mobile app interface) will be measured by monitoring end-users' performance on a given set of important tasks to certify that those met the end-users needs, while technical indicators associated with the execution of test scenarios (i.e., series of actions leading to a predefined/expected result) will reassert the satisfaction of the functional and non-functional requirements and the overall performance of the solution. The first and complete version of this evaluation framework will be presented in the forthcoming D8.4.



2 About this Document

Role of the deliverable

The role of this deliverable is to present the protocol that includes the study design, primary and secondary endpoints, relevant guidance documents, regulatory status and activities, the subjects/population of this study with a definition of sub-population if subgroup analysis is intended, the Inclusion and the exclusion criteria, the statistical analysis with the plan and the power calculation, the cumulative safety and efficacy information, the description of recruitment strategy, the description and the assignment of interventions and notifications and the study management, study monitoring, data and sample management. The Evaluation Framework, a tool used for associating relationships between the work to be performed in T8.5 and the rest of the project, establishes a range of methods and tasks appropriate for the purpose to establish primary evaluation targets and process.

Relationship to other RETENTION deliverables

This deliverable is related with most of the deliverables but more closely with D10.1-10.4, D5.1, D5.2, D1.1, D3.1, D3.2, D4.1, D4.2, D8.1 and D8.3-D8.6.

Structure of the document

The current deliverable provides the protocol of the RETENTION system.

The deliverable includes 4 sections and the Appendix. Thus, the structure of the D8.2 is as follows:

- Section 1: presents the executive summary
- Section 2: presents the purpose, scope, structure of this deliverable and the relation to the other deliverables
- Section 3: presents the protocol
- Section 4: presents the first version of the evaluation framework



3 Clinical study

3.1 Study Identifier

The full name of the study is: HEART FAILURE PATIENT MANAGEMENT AND INTERVENTIONS USING CONTINUOUS PATIENT MONITORING OUTSIDE HOSPITALS AND REAL-WORLD DATA. The study identifier is RETENTION.

3.2 Study design and endpoints

3.2.1 Study design

The aim of this study is to investigate the effect of introducing daily and environmentally aware patient monitoring protocols outside hospitals and interventions informed by it, on all-cause and cardiovascular mortality, heart failure hospitalisations or emergency room visits, and quality of life in patients with symptomatic chronic heart failure (HF), patients with implanted Left Ventricular Assist Device (VAD) and heart transplant (HT) recipients.

Patient specific measures related to the vitals (including weight, blood pressure, heart rate, peripheral capillary oxygen saturation), daily physical activity, quality of sleep (as expressed through heart rate variability), psychological state and nutrition intake will be collected. In addition, the study will collect real world data derived from non-medical sources regarding environmental factors in the living environment of patients participating in the study (i.e., ambient temperature, relative humidity, pollutants).

The data will be collected through a Randomised Clinical Trial (RCT) where the aforementioned groups of patients, between 18 and 75 years of age, will be observed in an outpatient setting through the remote monitoring platform of RETENTION, which will be created for this purpose, and the standard clinical practice. A total of 450 participants will be recruited to participate in the study. 30-35% of the recruited patients will be women. This is because up until now, women have been underrepresented in most heart failure clinical trials, despite the fact that disease prevalence remains generally the same between both sexes. When it comes in heart failure with reduced ejection fraction, subgroup analysis of several trials reveals that women were older, more likely to have pre-existing hypertension and less likely to have coronary artery disease. In addition, despite heavier symptom burden, women fared better in survival and hospitalisation risk. LVAD implantation has also been studied mainly on male patients with the added restriction of smaller ventricular dimensions rendering device support unavailable in women.

A control group of patients of similar age dispersion will also be set up and followed up only by the standard means and procedures currently employed as best practices. This will be a multi-centre RCT conducted at six clinical centres in Greece, Italy, Germany and Spain.

Randomisation: A total of 450 participants will be recruited to participate in the study, all of whom are treated according to standard heart failure care protocols. All patients will be provided with monitoring devices and home sensors to collect the data required by the study. Data will be collected continuously from all the participants. Half of the participants (Test group, n=225) data, collected through the provided devices, will be made available to treating physicians for review and additional interventions as determined by the analysis of these data may be done according to the judgement of the treating physician. In the rest of the participants (control group, n=225), treating physicians will be blinded to the data collected through the RETENTION platform and therefore no additional interventions will be done. Randomisation will be conducted centrally. Randomisation will be conducted centrally through the RETENTION platform.



Randomisation will be stratified by centre and type of patients (heart failure, LVAD and heart transplant) with a block size of 4.

Duration¹: It is re-estimated that instead of eight (8), fourteen(14) months will be required to collect all the essential documents from all participating sites, prepare the files for submission to Ethics and Regulatory authorities in all four countries in order to obtain the appropriate approvals later on, by M20, instead of M18 that was originally planned. Upon receipt of ethics approvals from all sites, sites will be activated within one (1) month. Patient recruitment will start in month 20 of the project and will last for ten (10) months. Following recruitment and randomisation, each participant will be monitored in an outpatient setting through the remote monitoring platform of RETENTION for a period of 18 months. Over this period, each participant will have regular follow ups with clinic visits (upon registration/randomisation, and at months 4,8,12 and 18) in addition to the clinic visits required by the standard heart failure management protocols. All clinic visits can be performed within ± 15 days from the expected date. Upon completion of patient monitoring period, three (3) months will be needed for activities related to the termination of the study (e.g., for final analysis of the data collected by the study).

Equipment and means of data collection: The RCT will be conducted based on the use of non-medical equipment including monitoring devices (e.g., smartphone, weight Scale, smartwatch, blood pressure monitor, oximeter, home sensors) that will be provided to the study participants (patients) of both the test and the control group by the project. The smart devices will be used for running the clinical study application (RETENTION smart application), during which they will generate patients-associated usage data (measurements) and data provided by patients (via questionnaires), later on to be transmitted, aggregated and analysed (see Sect 3.7.3 below). All the devices that will be handed to the patients will be set up and tested prior to the hand over to them. They will also receive the basic training required for using these devices.

3.2.2 Primary and secondary endpoints

The **primary study outcome** will be the days lost (%) due to unplanned cardiovascular hospitalisations or all-cause death, comparing remote patient monitoring and interventions (RPMI) group with remote patient monitoring and usual care (RPMUC) group only during the individual follow-up time.

As additional measure of this primary outcome we will report the freedom from the combined occurrence of death or unplanned hospitalisation/ambulatory administration of intravenous (IV) diuretics, IV antibiotics, or intravenous (IV) steroids.

The **secondary end-points** include:

- a. All-cause mortality during the individual follow-up time (to a maximum of 575 days, i.e., the 547 days of the patient monitoring period plus 28 days from the final study visit)
- b. Cardiovascular mortality during the individual follow-up time (to a maximum of 575 days, i.e., the 574 days

¹ A delay of 5+ months was encountered in the completion of the present document D8.2, in relation to the study protocol and the evaluation framework. This delay inevitably affects the progress of the next project phases and will eventually result in a time shift for platform completion. At the time of submission of the present deliverable, the estimated minimum shift is ~3 months, therefore the onset of the trial study is shifted from the originally planned M19 to M22, and will end at M48 instead of 45, at the earliest. Accordingly, all trial internal phases are shifting as well, following the new estimated plan.



of the patient monitoring period plus 28 days from the final study visit)

- c. Time to first unplanned HF hospitalisation
- d. Time to first unplanned cardiovascular hospitalisation
- e. Total unplanned HF hospitalisations (recurrent event analysis)
- f. Total unplanned cardiovascular hospitalisations (recurrent event analysis)
- g. Days (%) lost due to HF hospitalisations during the individual follow-up time.
- h. Number of smart device alarm notifications.
- i. Change in the Kansas City Cardiomyopathy Questionnaire score between baseline (i.e., when a patient enters the study) and month 18.
- j. Change in the levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) between baseline and month 18.
- k. Change in the Depression Score Patient Health Questionnaire 9 (PHQ-9) score between baseline and month 18.
- l. Change in the Heart Failure Caregiver Questionnaire (HF-CQ version 5.0) between baseline and month 18.
- m. Rejection needing treatment in HT
- n. Driveline infection needing antibiotic in LVAD patients
- o. Unplanned visit for HF requiring intravenous (IV) Diuretic
- p. Number of visits outside the protocol

Measurements for the primary endpoint and secondary outcomes will be collected upon registration, at every clinic visit and at the end of the study.

3.2.3 Relevant guidance documents

The following guidelines have also been considered in connection with the conduct of the RETENTION study:

- (a) Health Technology Assessment agencies / EUnetHTA: This is not applicable for this study.
- (b) Regulatory bodies (e.g., the European Medicines Agency, EMA¹): No medicine development is included in the study.
- (c) Clinical efficacy and safety guidelines for the evaluation of medicines in disease areas- e.g., diabetes (CPMP/EWP/1080/00 Rev. 1) or oncology (EMA/CHMP/EWP/205/95/Rev.4): Not applicable.
- (d) General guidelines e.g., addressing clinical pharmacology and pharmacokinetics (e.g. bioanalytical methods validation EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2 or pharmacokinetics in paediatric population EMEA/CHMP/EWP/147013/2004): Not applicable.
- (e) Methodological guidelines - e.g., statistical principles for clinical trials (CPMP/ICH/363/96) or clinical trials in small populations (CHMP/EWP/83561/2005): The clinical study will be conducted according to Good Clinical Practice (GCP), EU regulation (No 536/2014) and country specific legislations. Initially, the required RCT protocol files will be prepared and customised for each country. Informed Consent (ICF) will be



particularly emphasised to ensure compliance with the EU's General Data Protection Regulation (GDPR, 2016/679).

3.3 Regulatory status and activities

The randomised clinical study protocol will be designed and finalised according to current EU regulations, and ethics approvals will be obtained for all three clinical sites. The clinical protocol has been finalised at M13 (and is being delivered in the present document) instead of M8, approved by all sites, and in line with the Quality Assurance procedures of the RETENTION consortium. These procedures mostly entail peer reviewing amongst the members of the consortium and, if needed, from external actors. The actual protocol document will be formally submitted through Sygma EU platform. The list of deliverables for the clinical evaluation of RETENTION has been formulated taking into consideration the H2020 Guidelines on Clinical Trials. Compliance is mandatory for the call DTH-12-2020 under which RETENTION is submitted.

Additionally, all Principal Investigators from clinical centres will establish contact with relevant authorisation bodies to obtain approvals. The RETENTION study will be consistent with existing ethical and legal standards in relation to multi-centre trials. Processes within the project will ensure continual ethical scrutiny of activities throughout the lifetime of the project, as well as regulatory compliance.

3.3.1 Scientific advice / protocol assistance

Not applicable, no advice has been asked from a regulatory authority.

3.3.2 Qualification advice

This is a clinical study which will not involve any drug prescriptions other than those that would be required by established guidelines for the follow up and care of the recruited patients. The novelty in the study arises from the use of continuous patient monitoring outside hospitals collecting and analysing the aggregated data with state-of-the-art machine learning techniques. Their results provide the treating physician with better knowledge on the patient's daily status hence the decisions made on his/her behalf result in improved outcomes.

3.4 Subjects / Population(s)

3.4.1 Definition of sub-populations if subgroup analysis is intended

There will be two groups of patients. The first group will be subject to remote monitoring through the RETENTION platform but no additional intervention will be given other than the standard follow-up practice as it has been performed in the participating clinical centres during the last decade. The second group will be monitored and followed up on using the remote monitoring platform, and additional interventions will be provided as the system evolves with time based on the data analytics. All participants will take part in the clinical study after detailed explanation of the project's aims and their participation requirements. They will receive an information leaflet and will sign an informed consent form. They will be able to leave the clinical study at any point without any kind of explanation necessary. All participants will be assessed at baseline, and at months 4,8,12 and 18.

A total of 450 patients across the six hospitals will participate in the project. These patients will include:

- 200 patients with HF not enlisted for transplant at the time of their recruitment (approximately 44% of the total number of patients)
- 150 LVAD patients (approximately 34% of the total number of patients)

- 100 heart transplant recipients (approximately 22% of the total number of patients)

Of these patients 225 patients will be the test group, referred to as remote patient monitoring and interventions group (RPMI group), and 225 patients will be the control group, referred to as remote patient monitoring and usual care (RPMUC group). The control and the test group for each site will have equal numbers of recruits in each of the above three categories of patients. Of the recruited patients 30-35% will be women. This is because up until now, women have been underrepresented in most heart failure clinical trials, despite the fact that the disease prevalence remains generally the same between both sexes. The individual clinical units which will participate in the study are expected to recruit the numbers of patient shown in Table 1.

Table 1: Recruitment targets for individual clinical partners and countries

Partner	Clinical Unit	No of Patients	Country
OCSC	OCSC	100	Greece
NKUA	NKUA	80	Greece
UNIBO	UNIBO	100	Italy
UKESSEN	UKESSEN	100	Germany
SERMAS	Hospital Universitario Ramón y Cajal (SERMAS-HURC) Hospital Universitario Puerta de Hierro (SERMAS-HUPH)	70	Spain

3.4.2 Inclusion criteria

In order to be eligible for participation in the study, the subject must fulfil all of the required inclusion criteria. These are classified as general criteria that apply to all subjects and criteria that apply specifically and solely to heart failure, VAD and heart transplant patients, respectively.

General inclusion criteria (applying to all subjects):

- Age of 18-75 years
- Ability to understand and provide consent to participate in the study
- Have a cognitive assessment score of > 22 as assessed by the Montreal Cognitive Assessment (MoCA), i.e., adults without or with mild cognitive impairment at most
- Have a depression score as assessed by Personal Health Questionnaire-9 (PHQ-9) score < 10
- Provide written informed consent

Inclusion criteria for Heart Failure patients:

- Have a diagnosis of symptomatic heart failure, class II or III according to the New York Heart Association (NYHA) Classification
- Have echocardiographically determined left ventricular ejection fraction (LVEF) $\leq 40\%$
- Have been hospitalised due to cardiovascular reasons or had urgent visit to the Emergency Department due to decompensated HF that required administration of intravenous diuretics within the last 12 months before randomisation.



Currently hospitalised patients can be included provided they do not fulfil exclusion criterion #1 that concerns current in-hospital administration of IV diuretics/vasoactive/inotropic drugs.

Inclusion criteria for patients with ventricular assist devices (VAD):

- Have left ventricular assist device (LVAD) implanted either as destination therapy or as bridge-to-transplantation, within at least 90 days and no longer than 48 months before randomisation

Inclusion criteria for heart transplant recipients:

- Have been discharged following heart transplantation within at least 30 days and no longer than 36 months before study randomisation.

3.4.3 Exclusion criteria

The subject must be excluded from participating in the study if fulfils any of the following criteria:

- Is clinically unstable at the time of randomisation as defined by:
 - Administration of IV diuretics during the last 12 hours or IV vasodilators or inotropes during the last 48 hours before randomisation
- Has acute coronary syndrome within the last 30 days before randomisation
- Has acute inflammatory heart disease, e.g. acute myocarditis, within 90 days prior to randomisation
- Has a planned revascularisation, cardiac resynchronisation therapy (CRT) implantation or any valvular procedures within 3 months after randomisation
- Has known current alcohol or illicit drug abuse
- Has end-stage renal disease requiring haemodialysis
- Shows significant impairment or unwillingness to use the telemonitoring equipment (e.g., dementia, impaired self-determination, lacking ability to communicate)
- Has any severe non-cardiovascular disease limiting life expectancy to less than 1 year
- Is pregnant
- Participates currently in other telemonitoring programs/studies using smart devices

3.5 Statistical analysis plan and power calculation

The power analysis for the clinical study of RETENTION is based on a similar analysis performed for the TIM-HF-2 evaluating a telemonitoring intervention² with similar endpoints and considering similar inclusion criteria:

- Chronic heart failure New York Heart Association (NYHA) class II or III
- Echocardiographically determined left ventricular ejection fraction (LVEF) $\leq 45\%$
- Hospitalisation due to decompensated HF within the last 12 months before randomisation
- Depression score PHQ-9 < 10

For the sample size calculation, TIM-HF-2 used data for specific subgroups from the TIM-HF trial for sample size calculations. For the patient subgroup that mirrored the population they did include in the TIM-HF-2 trial, 19 days were lost due to all-cause death or unplanned cardiovascular hospital admissions at 12 months

² Koehler F, Koehler K, Deckwart O et. al. Lancet. 2018 Sep 22;392(10152):1047-1057. doi: 10.1016/S0140-6736(18)31880-4. Epub 2018 Aug 25. PMID: 30153985.



in the usual care group, and 12 days were lost for patients in the remote patient management group, which corresponds to a 38% reduction. The estimated standard deviation (pooled) was 48 and based on that they calculated that 750 patients would be required in each group to detect this difference with a power of 80% and a two-sided α of 5%.

For RETENTION we expect a slightly higher decrease in the endpoint (40%). If we apply the same rate of losses TIM-HF trial for control group (19 days per year) to a follow up period of 18 months, we expect a mean of 29 (19+10) days lost due to all-cause death or unplanned cardiovascular hospital admissions in the usual care group and 17 days lost in the test group (-40% of 29). Under these assumptions, the number of patients for each group of the study should be 199 (398 in total). Hence, accounting for about 10% of attrition rate and loss to follow up, the recruitment target for the study has been set to 450 patients.

Group sample sizes of 199 and 199 achieve 80% power to reject the null hypothesis of equal means difference with a standard deviation for both groups of 48 and with a significance level (alpha) of 0,05 using a one-sided test.

Statistical analysis plan

- Demographic, clinical, and device data, and treatment results will be summarised using descriptive summary statistics. Data collected in the trial will be summarised overall and by treatment groups. Continuous variables will be presented with the numbers of observations, means, standard deviations, minimums, and maximums. For comparisons, the difference between the groups will be summarised with the difference of the two means together with 95% confidence intervals and tested using the two-sample t-test. These calculations will be done under the assumption that the data for the two groups are independent and approximately gaussian in distribution. If asymptotic assumptions fail, nonparametric summary statistics (medians, 25th and 75th percentiles) may be displayed. In addition, more appropriate non-parametric tests will be considered if the assumptions for the parametric tests are violated. For the comparison of two independent samples, if the data are not normally distributed, Mann-Whitney rank sum test will be performed instead of the parametric t-test,
- For categorical variables results will be summarised with subject counts, percentages. The differences between the two treatment groups will be summarised with the difference in percent and compared using the chi-square test or Fisher's exact test as appropriate.
- Survival analysis techniques will be used to analyse the time-to-event variables.

The primary analyses will compare the days lost due to unplanned cardiovascular hospitalisations or all-cause death and the survival free from death or unplanned hospitalisation/ambulatory administration of intravenous therapy between interventions group and usual care group by the means of the parametric t-test or non-parametric rank sum test as mentioned above.

To evaluate the additional measure of the primary outcome, the survival free from the combined endpoint, survival curves will be constructed using Kaplan-Meier estimates. Log-rank test results will also be computed for comparison of survival distributions between intervention and usual care groups.

Pre-specified subgroup analyses include:

- The three patient categories (HF, LVAD and HT)
- Males and Females
- Patients with a hospitalisation less than three months from the enrolment



- Patients older than 60 years

3.6 Cumulative safety and efficacy information

This is a clinical study which will not involve any drug prescriptions other than those that would be required by established guidelines for the follow up and care of the recruited patients.

3.6.1 Cumulative efficacy information

Not applicable. There is no previous study combining real world data on Heart Failure with data derived from medical devices.

3.7 Conduct

3.7.1 Schedule for study conduct including timelines for key study milestones

The RETENTION clinical study will be conducted according to the following timeline:

- Study subject approvals package: M14
- Ethics approvals for the different clinical units: M20
- First Patient, First Visit (FPFV): M22
- First Patient, Last Visit: M39
- Last Patient, First Visit: M31
- Last Patient, Last Visit: M48 and end of follow ups

3.7.2 Description of recruitment strategy

Candidates for the study are already available from the existing pools of patients available in each of the participating hospitals. The target number of recruited patients for each of the hospitals is shown in Table 1. The recruitment target ratios for the different types of patients will be preserved across the clinical units of each country.

The pool of patients already available will be thoroughly screened based on the last clinical evaluation and the patients considered as potential candidates will be informed about the purpose of the study. Their positive response to the expression of interest will be followed by a new clinical evaluation to assess their current clinical status and obtain their base line for further evaluation.

An informed consent form will be signed prior to the clinical evaluation required for the participation to the study.

3.7.3 Description of the clinical protocol

The RCT will involve the remote monitoring of all patients who will participate in it. This will be enabled through the RETENTION platform, which will be developed to collect data obtained from the smart devices (smartphone, weight scale, pulse oximeter, digital blood pressure monitor, tracker-smartwatch, home sensor for temperature and humidity, home gateway) and the RETENTION mobile application running on the smartphone. All the above will be given to the patients participating in the study by the project. These data will be amalgamated with clinical tests and assessments of the participants of the study as well as real world data obtained from external resources (e.g., environment data from the Copernicus service or other similar).

The following types of data will be collected and analysed.



Data collected upon registration/randomisation:

Demographics:

- Date of birth, age
- Sex (male, female)
- Ethnicity (European, North African, Middle East, Sub-Saharan African, Central Asia, East and South)
- Marital status(single/widow with no family support, single/widow with other family members, living with a partner/spouse)
- Country of residence (Greece, Germany, Italy, Spain)
- Home address (Country, zip code, city, address number)
- Level of education (Up to and including high school, Above high school education, No education, Other)
- Employment status (Working (full or part time), Not currently working, Full-time homemaker, Retired, Student, Other)
- ABO Blood Group (A,B,O,AB)
- Height

Medical cardiovascular History:

- Primary aetiology of heart failure (ischemic: post-ACS, post-MI, post-CABG, post-PCI; non-ischemic: hypertensive, cardiomyopathy, valvular, other; unknown)
- Cardiac transplantation
- Ventricular assist device
- Coronary artery disease (acute coronary syndrome, percutaneous coronary intervention, coronary artery bypass surgery)
- Ventricular tachycardia/Ventricular fibrillation/Resuscitated sudden death
- Brady-arrhythmias/AV block
- Valvular surgery or percutaneous valvular procedures
- Venous thromboembolism / pulmonary embolism
- Carotid Artery Disease
- Stroke / Transient ischemic attack (TIA)
- Atrial Fibrillation
- Diabetes mellitus (type 1 or type 2)
- Arterial hypertension
- Dyslipidaemia
- Peripheral vascular disease
- Permanent Pacemaker (PPM)
- Implantable Cardioverter-Defibrillator (ICD)
- Cardiac Resynchronisation Therapy, with defibrillator (CRT-D) or without defibrillator (CRT-P)
- Aortic Aneurysm
- Heart Transplant
- LVAD Implant
- HF & CV medical therapies (ACEI/ARNI/ARB, BB, MRA, SGLT2i, diuretic, anticoagulant, antiplatelet, statin, amiodarone)



Non-cardiovascular history

- Smoker [never, current, past (meaning >6 months)]
- Severe alcohol intake [never, current, past (meaning >6 months)]
- Thyroid disease (if yes, define hyper- or hypo-thyroidism)
- Cancer
- Anaemia
- Chronic Obstructive Pulmonary Disease (COPD)
- Chronic Kidney Disease
- Benign Prostatic hyperplasia
- Other than HF & CV medical therapies
- Recent HF hospitalisation discharge date, or recent urgent ED visit due to HF date
- Number of HF hospitalisations within the last 12 months
- Caregiver data (if caregiver available):
- Sex
- Date of birth, age
- Children (yes/no)
- Living situation (Living alone /Living with the person that cares for only /Living with the person cared for and other family members/ Other)
- Highest level of education (Up to and including high school/ Above high school education/ Other)
- Employment status (Working (full or part time) /Not currently working / Full-time homemaker / Retired /Student or other)
- Caregiver condition (Cardiovascular Disease/ Hypertension/Diabetes mellitus/ High cholesterol)

Data collected at every clinic visit (upon registration and at months 4,8,12 and 18):

- Weight
- Vital signs: Blood pressure, heart rate, Peripheral capillary oxygen saturation, Temperature
- ECG
- Rhythm
- Heart rate
- Conduction delay(LBBB,RBBB, LAH, LPH, incomplete RBBB or LBBB)
- QRS duration
- QTc
- PQ/PR
- Blood tests at months 4,8,12 (Urea, Creatinine, Potassium, Sodium, SGOT, SGPT, LDH, INR, CPK, Troponin, Uric Acid, CRP, White blood cells, Haemoglobin, Platelets and NT-proBNP)
- Blood tests at months 0(registration) and 18(Urea, Creatinine, Potassium, Sodium, SGOT, SGPT, LDH, INR, CPK, Troponin, Uric Acid, CRP, White blood cells, Haemoglobin, Platelets and NT-proBNP, Glucose, Magnesium, Cholesterol, Triglycerides, HDL, LDL, γ GT, ALP, Total proteins, Albumin, Total Bilirubin, D-Dimers, Fibrinogen, Calcium, Phosphorus, CRP, Procalcitonin, TSH, FT3, FT4, B12, Fe, Ferritin)
- Depression score PHQ-9
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Six-minute walk test
- Cardio-pulmonary exercise testing (upon registration and at month 18)



- VE/VCO₂
- VO₂max
- RER
- Echocardiography (upon registration and at months 8 and 18)
- Left Ventricular Ejection Fraction (LVEF)
- Left Ventricular End Diastolic Diameter (LVEDD)
- Left Ventricular End Systolic Diameter (LVESD)
- Left Ventricular Posterior Wall (PW) and Interventricular Septum (IVS) Thickness at diastole
- Left Atrium diameter (LA)
- Right Atrium diameter (RA)
- Aortic Root diameter
- Basal right ventricle diameter
- Fractional area change
- Tricuspid Annular Plane Systolic Excursion (TAPSE)
- Right Ventricular Systolic Pressure (RVSP)
- Inferior Vena Cava (IVC)
- Aortic Valve Regurgitation (*if yes: trace/mild or moderate or severe*)
- Aortic Valve Stenosis (*if yes: mild or moderate or severe*)
- Mitral Valve Regurgitation (*if yes: trace/mild or moderate or severe*)
- Mitral Valve Stenosis (*if yes: mild or moderate or severe*)
- Tricuspid Valve Regurgitation (*if yes: trace/mild or moderate or severe*)
- Tricuspid Valve Stenosis (*if yes: mild or moderate or severe*)
- Interrogation of defibrillator (upon registration and at months 8 and 18)

The following data will be additionally collected for patients with VAD:

- Controller parameters
- Alarms
- RPMs
- Power consumption
- Flow
- Pulsatility index
- Driveline exit site evaluation (photographic evidence) as early signs of infection

Data collected on a daily basis through remote monitoring:

Data collected from smart sensors and devices on a daily basis will be:

- Weight(once per day)
- Blood pressure (morning)– excluding patients with LVAD
- Heart Rate (continuous)
- Peripheral capillary oxygen saturation (morning, evening)
- Sleep: deep and light sleep phases, sleep interruptions.
- Steps, distance, floors climbed, calories consumed

Data collected through self-reporting (via the RETENTION smart phone application):



- Symptoms (once a week or sooner if any worsening is observed by the patient. In patients reporting worsening, they will be asked to specify through the application e.g., swollen feet, shortness of breath, not being able to lie down due to shortness of breath, dizziness, rapid heartbeats).
- Timely adherence to prescribed medication (on the designated time an alarm will be set to remind the patient to take his/her medication – timely alarm deactivation will be reported to the platform as proof of adherence).
- Nutrition intake (MNA Score) every 4 months through automatic reminder.
- MOCA and PHQ9 questionnaires ±15 days from each clinic visit
- Heart Failure Caregiver Questionnaire (HF-CQ Version 5.0)(baseline and at month 18)

Data collected through smart environment sensors and the smart watch/phone:

- Patient living space data (temperature, humidity, GPS vicinity)
- Patient living environment data (extreme temperatures and weather conditions, pollutants obtained from Copernicus services)
- Patient outdoor movement

Table 2: Timeframe of patient assessments

Parameter	Registration/Randomisation	Month 4	Month 8	Month 12	Month 18	Daily	Once a week/per need
Age	✓						
Sex	✓						
Ethnicity	✓						
Marital Status	✓						
Country of Residence	✓						
Height	✓						
Level of education	✓						
Employment status	✓						
ABO Blood Group	✓						
Cardiovascular history	✓						
Non-cardiovascular history	✓						
Home Address	✓						
Caregiver data	✓						
Weight	✓					✓	



Parameter	Registration/Rand omisation	Month 4	Month 8	Month 12	Month 18	Daily	Once a week/per need
Body Temperature	✓					✓	
Blood Pressure	✓					✓	
Heart Rate	✓					✓	
Oxygen Saturation	✓					✓	
Sleep						✓	
Steps						✓	
Medication Alarm						✓	
Symptoms	✓	✓	✓	✓	✓		✓
Clinical examination	✓	✓	✓	✓	✓		
MNA Score		✓	✓	✓	✓		
HF-CQ v5	✓				✓		
MOCA	✓						
PHQ9	✓	✓	✓	✓	✓		
KCCQ	✓	✓	✓	✓	✓		
ECG	✓	✓	✓	✓	✓		
Blood Tests	✓	✓	✓	✓	✓		
6MWT	✓	✓	✓	✓	✓		
CPET	✓				✓		
ECHO	✓		✓		✓		
ICD Interrogation	✓		✓		✓		
VAD Parameters	✓	✓	✓	✓	✓		

3.7.4 Interventions

When there are changes in specific clinical characteristics of the patients, a notification will be created. The doctor will be informed for these notifications of the Test group through the RETENTION platform. After a notification pops-up, the doctor should contact the patient to confirm the parameters, check the factors that



may lead to the changes (e.g., salt intake, non-adherence to medical therapy), manage the clinical situation -if possible- remotely (e.g., Increase diuretic, adjust beta-blocker dose) or arrange an unscheduled visit if needed.

Table 3: Cut-off values for notifications and interventions in the RETENTION group

Clinical characteristics	Type of Notification	Definition of Notification	Type of Intervention	Clinical Intervention
Weight:	<i>Low level:</i>	Gain >2kg in one day or gain > 3 Kg in seven days	<u>1. Dismiss notification</u> <u>-measurement error</u> <u>-not clinically relevant</u> <u>2. Telephone visit</u> <u>3. Schedule in-person visit</u>	<u>- Reinforce dietetic plan</u> <u>- Increase diuretic dose</u>
	<i>Critical level:</i>	Gain ≥3kg in 2 days	<u>1. Dismiss notification</u> <u>-measurement error</u> <u>-not clinically relevant</u> <u>2. Telephone visit</u> <u>3. Schedule in-person visit</u>	<u>- Reinforce dietetic plan</u> <u>- Increase diuretic dose</u> <u>- Check if IV diuretic is needed</u> <u>- Consider visiting the emergency department (ED)</u>
Blood pressure:	<i>Low level:</i>	Systolic Blood Pressure (SBP) < 100 mmHg and a 10 mmHg reduction from the average of the previous 3 measurements) or SBP>140mmHg	<u>1. Dismiss notification</u> <u>-measurement error</u> <u>-not clinically relevant</u> <u>2. Telephone visit</u> <u>3. Schedule in-person visit</u>	<u>-Check for triggers: Temperature, hypovolemia...</u> <u>-Check if Hypovolemia (sweat, diarrhoea)</u> <u>-Consider reducing dose of diuretics, ARBs, B-blockers, MRAs, ARNIs etc</u>
	<i>Critical level:</i>	Systolic Blood Pressure (SBP)< 90 mmHg and a 10 mmHg reduction from the average of the previous 3 measurements mmHg or SBP>150mmHg	<u>-1. Dismiss notification</u> <u>-measurement error</u> <u>-not clinically relevant</u> <u>2. Telephone visit</u> <u>3. Schedule in-person visit</u>	<u>-Check for triggers: Temperature, hypovolemia...</u> <u>-Check Temperature</u> <u>-Check if Hypovolemia (sweat, diarrhoea)</u> <u>-Consider adjust dose of ARBs, B-blockers, MRAs,ARNIsetc</u> <u>-Consider visiting the emergency department (ED)</u>
Heart Rate:	<i>Low level:</i>	<50bpm or >110bpm and 10 bpm change from the average of the	<u>1. Dismiss notification</u> <u>-measurement error</u> <u>-not clinically relevant</u>	<u>-Check for triggers: Temperature, hypovolemia</u>



		3 previous measurements	<u>2. Telephone visit</u> <u>3. Schedule in-person visit</u>	<u>-Check Temperature</u> <u>-Check if Hypovolemia (sweat, diarrhoea)</u> <u>-Consider adjust dose of antiarrhythmic drugs (B-blockers, digoxin)</u> <u>-Check symptoms (dizziness, palpitations)</u>
	<i>Critical level:</i>	<40 bpm or >150bpm	<u>1. Dismiss notification</u> <u>-measurement error</u> <u>-not clinically relevant</u> <u>2. Telephone visit</u> <u>3. Schedule in-person visit</u>	<u>-Check for triggers: Temperature, hypovolemia...</u> <u>-Check Temperature</u> <u>-Check if Hypovolemia (sweat, diarrhoea)</u> <u>-Consider adjust dose of antiarrhythmic drugs (B-blockers, digoxin)</u> <u>-Check symptoms (dizziness, palpitations)</u> <u>-Consider visiting ED</u>
Peripheral capillary oxygen saturation:	<i>Low level:</i>	<95% and a 2% reduction from the average of the 3 previous measurements	<u>1. Dismiss notification</u> <u>-measurement error</u> <u>-not clinically relevant</u> <u>2. Telephone visit</u> <u>3. Schedule in-person visit</u>	<u>-Check for dyspnoea, oedema, cough or other symptoms</u> <u>-Check temperature</u> <u>-Advice to monitor promptly</u>
	<i>Critical level:</i>	<90%	<u>1. Dismiss notification</u> <u>-measurement error</u> <u>-not clinically relevant</u> <u>2. Telephone visit</u> <u>3. Schedule in-person visit</u>	<u>-Consider visiting ED-</u> <u>Advice medical evaluation</u>
Temperature:	<i>Low level:</i>	>37,2 °C	<u>1. Dismiss notification</u> <u>-measurement error</u> <u>-not clinically relevant</u> <u>2. Telephone visit</u> <u>3. Schedule in-person visit</u>	<u>-Check for LVAD driveline exit</u> <u>-Other symptoms</u>
	<i>Critical level:</i>	>37,8 °C	<u>1. Dismiss notification</u> <u>-measurement error</u> <u>-not clinically relevant</u>	<u>-Check for LVAD driveline exit</u> <u>-Other symptoms</u>



			<p><u>2. Telephone visit</u> <u>3. Schedule in-person visit</u></p>	<p><u>-Consider take antipyretics/antibiotics</u></p>
Symptoms:	<i>Low level:</i>	1 day of deterioration	<p><u>1. Dismiss notification</u> <u>-measurement error</u> <u>-not clinically relevant</u> <u>2. Telephone visit</u> <u>3. Schedule in-person visit</u></p>	<p><u>-Re-evaluate</u> <u>-Consider adjustment of medical therapy</u></p>
	<i>Critical level:</i>	More than 3 days of deterioration	<p><u>1. Dismiss notification</u> <u>-measurement error</u> <u>-not clinically relevant</u> <u>2. Telephone visit</u> <u>3. Schedule in-person visit</u></p>	<p><u>-Consider visiting ED</u></p>
Activity:	<i>Low level:</i>	30% weekly decrease in activity	<p><u>1. Dismiss notification</u> <u>-measurement error</u> <u>-not clinically relevant</u> <u>2. Telephone visit</u> <u>3. Schedule in-person visit</u></p>	<p><u>-Discuss with patient reasons for low activity (symptoms, fatigue, boredom, other reasons)</u> <u>-If not due to change in symptoms, advice to increase activity</u></p>
	<i>Critical level:</i>	70% weekly decrease in activity	<p><u>1. Dismiss notification</u> <u>-measurement error</u> <u>-not clinically relevant</u> <u>2. Telephone visit</u> <u>3. Schedule in-person visit</u></p>	<p><u>-Check symptoms</u> <u>-Consider medical evaluation</u> <u>-Consider specialist advice (depression?)</u></p>
Sleep:	<i>Low level:</i>	More than 14 days sleeping \leq 5 hours	<p><u>1. Dismiss notification</u> <u>-measurement error</u> <u>-not clinically relevant</u> <u>2. Telephone visit</u> <u>3. Schedule in-person visit</u></p>	<p><u>-Check if it is because of Symptoms?</u> <u>-Inform again the need for a normal sleeping pattern</u> <u>-Consider specialist advice (neurologist-psychologist etc.)</u></p>
Adherence to treatment		\geq 3 days without treatment adherence	<p><u>Telephone visit</u></p>	<p><u>-Check reasons for non-adherence</u> <u>-Reinforce importance of medication</u> <u>-Schedule an in-person visit</u></p>



				-Consider ED
Pulsatility index:	<i>Critical Level:</i>	Profound reduction below 2 (<2)	<u>1. Dismiss notification</u> <u>-measurement error</u> <u>-not clinically relevant</u> <u>2. Telephone visit</u> <u>3. Schedule in-person visit</u>	<u>-Check for Hypovolemia</u> <u>-Consider changing medication</u>
Flow:	<i>Low Level:</i>	Progressive flow reduction every day	<u>1. Dismiss notification</u> <u>-measurement error</u> <u>-not clinically relevant</u> <u>2. Telephone visit</u> <u>3. Schedule in-person visit</u>	<u>-Check symptoms</u> <u>-Check hypovolemia/hypertension</u> <u>-Consider changing medication (diuretics/ antihypertensive drugs)</u> <u>-Visit VAD clinic</u>
	<i>Critical Level:</i>	Flow below 2.5	<u>1. Dismiss notification</u> <u>-measurement error</u> <u>-not clinically relevant</u> <u>2. Telephone visit</u> <u>3. Schedule in-person visit</u>	<u>-Check symptoms</u> <u>-Check hypovolemia/hypertension</u> <u>-Consider changing medication (diuretics/ antihypertensive drugs)-</u> <u>Visit VAD clinic</u>
Watts:	<i>Critical Level:</i>	Watts above 6	<u>1. Dismiss notification</u> <u>-measurement error</u> <u>-not clinically relevant</u> <u>2. Telephone visit</u> <u>3. Schedule in-person visit</u>	<u>-Check symptoms</u> <u>-Visit VAD clinic</u> <u>-Check INR levels</u>
Driveline:	<i>Critical Level:</i>	Change in the colour of the driveline	<u>1. Dismiss notification</u> <u>-measurement error</u> <u>-not clinically relevant</u> <u>2. Telephone visit</u> <u>3. Schedule in-person visit</u>	<u>-Check Temperature</u> <u>-Consider antibiotics</u> <u>-Visit VAD Clinic</u>

3.7.5 Receiving Notifications

Patients will be advised that the clinical team will only receive notifications in the RETENTION group, and that the RETENTION is not an alarm system. In case of severe symptoms, the patient will be instructed to contact the emergency services.



Notifications will be created through the RETENTION platform for both study groups, however the clinicians will be informed only for notifications from the intervention group. Once a notification appears on the clinician's interface on the platform, he/she will communicate with the patient to obtain further information regarding patient's clinical condition. If, based on type of notification and information obtained through contact with patient, the notification is considered clinically relevant, the physician will provide specific advice/ instructions to the patient through either remote consultation or by arranging an unscheduled clinic visit with the patient. All consultations and medical instructions/advice will be made by clinicians according to their clinical judgement and based on the 2021 European Society of Cardiology Guidelines for the Diagnosis and Management of Heart Failure.

3.7.6 Study management, study monitoring, data and sample management

Both clinicians and patients / carers will have access to the RETENTION platform under different roles and privileges albeit sharing a secure authentication scheme. On registration to the study, patients and caregivers will also be registered in the RETENTION platform and be given access credentials. Reporting and statistics facilities will be provided. All recruited patients and caregivers will go through the standard education and training regarding their condition, as well as on using the RETENTION platform.

It should also be noted that RETENTION will abide to all principles of GDPR including the principles of lawfulness, fairness and transparency, purpose limitation, and data minimisation. Towards the realisation of these principles, RETENTION has adopted a layered architecture in which non-anonymised personal patient data will only be stored at the components of the platform operating at the clinical sites involved in the clinical study of the project and be accessible only to local clinicians, having responsibility for the follow ups of patients and making appropriate interventions for them. These personal data will be transmitted only in a fully anonymised form to the cloud of the platform for analysis using AI techniques (data mining and machine learning). It should also be noted that any processing operations on non-anonymised personal data held at the clinical sites of the project shall be limited strictly to what is absolutely necessary, e.g., having the minimal reports necessary for authorised clinical personnel to perform their duties for the purposes of the project (e.g., conducting follow ups in the context of a visit and approving suggested interventions or otherwise). And beyond these notes, it should be stressed that any data processing in the RETENTION platform will be done in such way to ensure demonstrable compliance with the GDPR.

Study management, study monitoring, data and sample management will be in line with the regulatory requirements that have been described above in section 3.3. The clinical coordinator of the RETENTION consortium and the principal investigators of the clinical sites will be overseeing the execution and progress of the study, in regular monthly meetings.

3.7.7 Sponsor coordinating centre(s) and committees

The sponsor of the clinical study will be the OCSC. The sponsor will be responsible as per EU regulation (No 536/2014) defines.

3.7.8 Study medication

No additional medications included apart from the already prescribed per patient.

3.7.9 Clinical centres

The clinical sites which will participate in the study are shown in Table 1. These centres were selected on their previous experience on this field and on the number of patients they treat.



3.8 Orphan designation (if needed)

No orphans included.

3.9 “Unit cost per patient” for clinical trial, studies, investigations

RETENTION uses actual costs.



4 Organisational issues

For each Pilot set-up, a set of activities will be carried out in anticipation of study participants, at technical, clinical, and administrative level, that are described in through this section.

- In order for the equipment to be delivered in the time required per study participants' category, the acquisition of complete sets of devices must have been concluded well in advance to the pilot start.
- Each host organisation (Greek Pilot: OCSC and NKUA, German Pilot: UKESSEN, Italian Pilot: UNIBO, Spanish Pilot: SERMAS-HURC and SERMAS-HUPH) associated to a RETENTION pilot, should have designated the team members (registered end-users of the CSB@Dashboard):
 - Clinical team, responsible for the clinical study (i.e., recruitment, clinical protocol adherence, monitoring), including organisational procedures and communication with the participant on medical issues;
 - The head of the clinical study along with his/her communication info will be referred to the accompanying information material of the study that will be handed to each participant.
 - Technical team, who will handle the initial installation and monitoring of the smooth operation of associated with each patient's devices.
- User guide and troubleshooting instructions will include communication info for providing guidance in cases of technical difficulties or for triggering actions for maintenance/repairing in case of malfunctions.
- Several dissemination activities using the different RETENTION materials (e.g., leaflets, posters, website, social media accounts, etc.) can be used for gathering expressions of interest.
- The start date for the recruitment defined in section 3.

4.1 Phase A: Pre-recruitment

During the pre-recruitment, the Clinical team checks the participants' condition in accordance with the inclusion and exclusion criteria (defined in section 3) and assess their willingness to participate in the RETENTION study. In some cases, additional examinations for participants with a recent history of what could become exclusion criteria can be requested. Those best meeting the requirements and who could benefit from this project through remote monitoring, will be informally approached by the Pilot Clinical team to be informed about the project objectives, the involved activities, their tasks upon participation and the advantages and disadvantages according to their health condition that they could obtain.

Subsequently, those who are willing, without a shadow of a doubt, to participate (and meet the selection criteria) form a list whose members will be later contacted at the start of the recruitment procedures. The list contains personal data (i.e., full names, contact details, other PII, desire to participate), and will be under the supervision of the head of the Pilot Clinical team. For those that have met the selection requirements and are keen to participate, still have expressed some doubts or concerns, additional explanations could be provided, and their concerns are collected for future evaluation.



The list containing personal data of potential RETENTION study participants is kept in a safe place. This information is not part of the one collected by the RETENTION platform.

Information will be erased once the pre-recruitment phase is over.



4.2 Phase B: Recruitment

For those who want to participate without a doubt and met selection criteria, complementary diagnostic exams will be held to validate in certainty that they do not meet exclusion criteria relating to recent illness that could compromise their participation in the study, or to reveal a previously unspotted condition (exclusion criteria) making their participation unfeasible. Considering that these initial selections are based on the willingness of each participant that may change until the “Recruitment day” (e.g., loss of interest, significant change in daily life, personal reasons), or the established medical conditions change, participants will be asked again about their interest in participating in the study prior to the baseline assessment. Those who have expressed second thoughts will be placed on a separate play-off list.

The recruitment (procedure that has previously obtained local ethics approval) of each study participant that takes place at the premises of the host organisation (participating to a Pilot), depends on a framework of mandatory activities and ancillary procedures, supported primarily by the Clinical Site Backend (CSB) of the RETENTION platform (CSB@Dashboard), and the required documentation and its evaluation in accordance with the GDPR, namely the paper-based informed consent form (ICF) (in English and in pilot’s language, two copies for each edition to be signed) and the Data Protection Impact Assessment (DPIA) (English), along with study-relevant information documents (pilot language), and other material (e.g., informative leaflet in pilot language, end-user guide for the devices to be handed).



The (paper-based) signed informed consent form (ICF) containing personal data of the recruited RETENTION study participant is kept in a safe place. In relation to this, data that later on (all the eligibility conditions are confirmed) will be stored within the CSB are the PseudoID-1 (unique identifier created automatically), home details, contact phone, (1 up to 3) person(s) and contact details who can be notified in case of an emergency, and the date of signature.

The signed ICF is the only element that captures the correlation of the PseudoID-1 and the real identity of the participant.

In case of - for any reason - withdrawal of the consent, the CSB@Dashboard record will capture the new status (withdrawn participant) and date of the withdrawal. From that moment onwards, device/sensor usage data will not be digested.

During the recruitment phase, the baseline assessment (i.e., clinical assessment activities during 1st visit) will be conducted in the context of the host organisation, providing all patients with the necessary safety measurements in agreement with the National/Regional Health Authorities.

The recruitment starts with a phone call (by the Clinical team) scheduling appointment for participants that were previously enlisted in the pre-recruitment list. At the time and date of the appointment, the participant is informed by a member of the Clinical team where additional clarifications for RETENTION project are given. In this moment, the ICF and informative material are presented to the participant (2 copies for each language, for host organisation and participant), but is not signed by him/her yet.

After presenting this information, personal health record information (presented in section 3) is collected and two important questionnaires are applied firstly, since their results can imply exclusion criteria in RETENTION clinical study. It is only after the analysis of the results of these questionnaires and the gathering of information in accordance with the inclusion and exclusion criteria that it is possible to confirm whether the potential participant meets the medical criteria and has the necessary fine motor skills to use the

equipment and devices to be provided by the project. These are important requirements that attest to the capacity of the participant and the benefit of his/her participation in a project of this nature. Once all the eligibility conditions are confirmed, the participant is considered recruited, and then is invited to sign the ICF (signifies the “Recruitment day” timestamp) and begin the baseline assessment (initial RETENTION patient record is about to be created, while answers (values) of questionnaires’ questions will be inputted as well).



Designated member of the Clinical team (CSB@Dashboard end-user role: Clinician or clinical expert), creates the patient record. It is then when the unique identifier PseudoID-1 for him/her is created. This identifier is entered in the signed ICF.

All members of the Clinical team have access to the full medical record of the recruited study participant (associated to the host organisation).

4.3 Phase C: Baseline assessment of a recruited study participant

Having the copies of the signed ICF securely stored and finishing entering its details (excluding the full name) within patient’s RETENTION platform record, the baseline assessment starts (note: this activity can be performed on a later day than the confirmation of participation). During the baseline assessment, personal health record parameters (presented in section 3.7.3, “Data collected upon registration/randomisation”) will be collected to make the best possible evaluation of the study participant. Nonetheless, parameters to be presented to each of the recruited participants will always vary according to the clinical history of each of them and the group (i.e., HF patients not enlisted for transplant, VAD patients, heart transplant recipients) (approximately) they belong in.

During this baseline assessment the participant goes through 3 steps, to maximise assessment and assess more people in the shortest possible time. In each office, different members of the Clinical team carry out the procedures and necessary activities for the assessment:

- In the first step, a patient record (i.e., Data collected upon registration/randomisation) is made via the CSB@Dashboard, encapsulating contact details and PII, along with medical parameters for the recruited participant. This profile establishes not only the associated to a specific group equipment that will later be provided, but also the activities that will be performed in the following assessments.
- During the second step, some parameters of the participant's physical assessment (i.e., Non-cardiovascular history) are acquired. At this point the participant's evaluation starts by filling questionnaires associated to his/her group and specific condition.
- Only participants with VAD need to proceed with the last step (i.e., data will be additionally collected for patients with VAD), where a certified clinician awaits them in order to measure VAD Controller parameters (e.g., Alarms, RPMs, power consumption, flow, pulsatility index, driveline exit site evaluation). In order not to make this process exhaustive, the participant of this group can be assessed on a different day (but in a short time) and time that is originally scheduled upon completing the second step.



In case of technical failure, or in case of internet availability/connectivity problems, assessments and questionnaires presented to the participants are performed on paper, and later inputted via the CSB@Dashboard, to reduce the assessment duration. The member of the Clinical team performs this activity keeps the paper-based records safely.



- Upon completion of step 2 (and 3), the participant returns to an office where an appointment is scheduled to deliver the equipment kit and fills-out the equipment-related forms (format as with ICF) and informative material on how to operate them. This form (containing PseudoID-1, and contact details) is later collected by the technical team and used as a proof of delivery (on scheduled day and time range) of the device kits.



The (paper-based) equipment-related signed forms considered annexes to the ICF. In case of equipment changes, they are replenished.

4.4 Phase D: Clinical visit of a recruited study participant

In the case of scheduled 2nd, 3rd, 4th and 5th clinical visits, the same procedures are performed as before, except for the initial entry of the patient details.

4.5 Phase E: Withdrawal of consent by a study participant

Study participants may withdraw their consent to participate in the RETENTION study at any time without providing reasons. Still, in such cases they will be asked for what leads them to leave the study. Information as to when the study participant withdrew consent will be retained (in both the relevant form to be signed by the participant and in the system), and this is the point in time onwards that any data collected will not be considered in any analysis. Participants will be informed that the withdrawal of consent will not affect the results of analytics activities already carried out, since those utilised data obtained before and have been fully anonymised.

5 Evaluation Framework

This section presents an evaluation checklist associated to T8.5, that provides the fundamentals for the non-clinical (i.e., technical) evaluation of the RETENTION solution (i.e., the RETENTION Patient Edge instances – Edge or mobile app, the RETENTION Clinical Site Backend - CSB, and the RETENTION Global Insights Cloud – GIC), along with associated testing activities scheduled to be performed to validate the solution in terms of performance and intended usage. To this extent, usability of interaction elements (CSB-GIS Dashboards, mobile app interface) will be measured by monitoring end-users' performance on a given set of important tasks to certify that those met the end-users needs, while technical indicators associated with the execution of test scenarios (i.e., series of actions leading to a predefined/expected result) will reassert the satisfaction of the functional and non-functional requirements and the overall performance of the solution. The first and complete version of this evaluation framework will be presented in the forthcoming D8.4.

5.1 Basic elements of the technical evaluation

As aforementioned, the RETENTION study involves 2 groups of study participants (450 patients in total across 6 hospitals and 4 countries who will be randomly divided into two groups, Test group n=225, and Control group n=225). The Control group will be subject to remote monitoring and standard follow-up practice, while members of the Test group will be the ones to be monitored and followed up on using the RETENTION platform and supplementary interventions will be provided to them.

RETENTION entails a Big Data analytics study. The collected data consist of demographics and personal health records (including clinical data, medications, ECG, Labs results, VAD measurements), along with devices/sensors usage Big data (in terms of variety, volumes, and velocity) to be collected in massive volumes on a predefined periodic (e.g., daily, weekly, biweekly) basis automatically, along with questionnaires' records through self-reporting. All in a pseudonymised fashion (within CSB), may be subjected (previously anonymised prior to their transmission to the GIC) to different types of analysis, including statistical analysis techniques (e.g., descriptive statistics, regression, hypothesis testing) and AI techniques (e.g., data mining and machine learning), in such way to ensure demonstrable compliance with the GDPR, and as required by the clinical questions and scenarios in mind.

Within this context, the evaluation of the technical activities (associated to the T8.5 “non-clinical RETENTION platform validation”) has a goal to assess RETENTION project’s technical results against the use cases, technical and non-technical requirements defined in D3.1, along with the actual utilisation (e.g., usability, performance) of the overall functionality to be delivered. As such, and relevant to the technical evaluation KPIs to be documented in forthcoming deliverables (mainly D8.5 and D8.6), the following table (Table 4) provides a summary of how those KPIs (defined in GA) will be measured.

Table 4: KPIs associated to the technical evaluation and means for assessing them

KPI	Measures	Tools/Evidence
KPI-1.1: Integration of at least five (5) heterogeneous devices sensing and actuating IoT/IoMT devices (smart home devices/RFID sensors/hubs, wearable devices, smartphones, smart pillboxes, blood glucose meters etc.; see Table 2) to	Annotated and timestamped usage data	FHIR (medical measurements) and non-FHIR (home sensors) usage data stored in smartphone and (later on) in CSB



KPI	Measures	Tools/Evidence
effectively demonstrate its general applicability		
KPI-1.3: Data points collected through devices > 100 per patient	Descriptive analytics to measure number of measurements	Integrated analytics
KPI-1.4: Number of medical data points collected > 50 GB	Descriptive analytics to measure number of measurements	Integrated analytics
KPI-2.1: Delivery of basic analytics to infer high level parameters regarding the (i) functional, (ii) physiological, and (iii) behavioural state of each participant, as well as their (iv) safety, (v) risk, (vi) social interactions, (vii) cognitive, and (viii) sensory profiles	Definitions of descriptive and ML analytics	Integrated analytics
KPI-2.2: Delivery of advanced data analytics and learning capabilities for large scale analysis of the comprehensive datasets collected from all clinical trial and participants, capable of dealing with the volume and velocity of data collected by the various devices used for monitoring participants	ML analytics associated to clinical primary and secondary endpoints	Integrated analytics
KPI-3.1: The privacy-preserving and secure by design data handling capabilities delivered will ensure the key properties of: (i) anonymity, (ii) confidentiality, (iii) privacy, and (iv) integrity of data	Encrypted repository to manage personal data and PII	Integrated Security Component
KPI-3.2: The privacy-preserving and secure by design data handling capabilities delivered will ensure the afore-mentioned key properties for data: (i) in transit, (ii) at-rest, and (iii) in processing	Assessments to monitoring availability, privacy and integrity	Integrated security/privacy platform
KPI-3.3: The privacy-preserving and secure by design data handling capabilities delivered will have demonstrable security monitoring policy compliance and auditability for all properties	Assessments to monitoring availability, privacy and integrity	Integrated security/privacy platform



KPI	Measures	Tools/Evidence
contained in respective security policies.		
KPI-4.1: Development of a RETENTION Gateway for smart home devices federation	Annotated and timestamped usage data	non-FHIR usage data stored in CSB
KPI-4.2: Development of a RETENTION Mobile Application for end users participating in the clinical trials	Mobile app usage	Successful transmissions of usage data, reception of personalised notifications
KPI-5.1: Demonstration and validation of the RETENTION integrated platform at TRL7	Integration test procedures to verify that the RETENTION solution satisfies its functional requirements Installation/end user manuals	Test plan structured around critical/important use cases, to validate that the solution conforms to its technical specification and the intended use. Plan will define tests (to be performed automatically or semi-automatically) an end-user (mainly CSB::clinicians, and smartphone app::study participants) expected to perform without difficulties Production of manuals
KPI-5.2: Five (5) healthcare providers validating RETENTION solution	Number of CSB to be deployed	Use cases to validate that the solution conforms to its technical specification and the intended use
KPI-5.3: At least 450 patients recruited in the RETENTION clinical trials	Number of recruited study participants	Total number of recruited study participants by 6 different hospitals (5 Pilots)
KPI-5.4: At least 80% of the participants will evaluate the usability/accessibility of the platform, as greater than or equal to 8 in a range of 1-10 in at least 80% of the questions in the evaluation questionnaires	Usability/Effectiveness: ability of end-users to complete tasks using the system and the quality of the output of those tasks	a) Expert usability evaluation b) Task-based evaluation: end-users to carry out specific tasks. Performance will be quantitatively measured: i) effectiveness (e.g., n of solved tasks) and efficiency (e.g., n of actions to complete the task) c) Post-task rating: PSSUQ (Post-Study System Usability Questionnaire) ³

³<https://uiuxtrend.com/pssuq-post-study-system-usability-questionnaire/>



KPI	Measures	Tools/Evidence
KPI-5.5: At least 90% of the participants will be using the platform for the whole duration of the clinical trials, indicating a drop-out rate of less than 10%.	Usage: fine usage metrics (e.g., number of sessions, frequently used functionalities)	CSB logs, GIC logs Number of dropouts due to technical difficulties

In addition to those specific KPIs, the following technical questions will be thought through:

- What is the critical/important functionality to be tested? (note: 1st version of the test plan will define important use cases)
- Critical/important (for the kick-off of the Pilots) functionality has been deployed within the 1st version of the integrated RETENTION platform?
- Did all the integration tests succeed?
- Did all the baseline security/privacy assessments pass without identifying potential vulnerabilities?
- Did usability/effectiveness evaluation pass? If not, did the development cycle incorporate changes based on those usability test results (e.g., issues identified, corrections to the design needed)?
- Does any of the issues identified require change(s) to the RETENTION Architecture?
- Repeat all the above for version 2.

Based on the critical test use cases to be defined, a set of actions will be associated with trying to emulate user behaviour by using realist and varied inputs (i.e., dashboard/mobile app utilisation), or machine2machine tasks performed in the background (e.g., usage data/notifications/trained models' transmissions, notifications generation, personal data/FHIR and non-FHIR data backups). The description of each test use case (roles: i) CSB::clinicians, ii) smartphone app::study participants, iii) i) CSB/GIC::admins) should provide a detailed description, all basic actions needed to be triggered, and expected results based on given input. Each case will be described by using the following test use case template:

- Test Use case ID: unique identifier of each test
- Test Use case Name: user friendly name
- Objective: short description of CSB/GIC/Mobile app functionalities to be tested
- Prerequisite Tests: identifier(s) of test(s) that must have been previously and successfully executed
- Involved Components: CSB/GIC components and or mobile app functionality associated with
- Procedure: basic steps to be performed
- Input: (IFF) values to be used
- Expected Result: anticipated successful result
- Outcome: (S)uccess/(F)ailure/(PS)Partially Successful

Following this, four (4) phases are planned:

- Phase A: Generic identification of tasks (e.g., use cases, baseline analytics considering synthetic data, (semi-)automated testing routines) and KPIs for the evaluation of the under-development functionality;
- Phase B: Early usability and functional evaluation of interaction elements and implemented functionality based on synthetic and/or real data (early MVP version), that will allow the consortium to consider this early feedback, in order to repair/adjust/enhance technical elements accordingly.



Several KPIs will be evaluated (including: KPI-2.1 definition, creation and execution of basic descriptive analytics, KPI-2.4 and KPI-2.5 based on synthetic data, KPI-4.1, KPI-4.2);

- Phase C: Usability and functional evaluation involving end-users of the RETENTION platform to provide an assessment on whether the first implemented version (ver. 1.0: first version of the integrated RETENTION platform) fulfils the objectives of the project, effectiveness, impact and sustainability. Main technical KPIs will be evaluated (i.e., KPI-1.1, KPI-1.3, KPI-1.4, KPI-2.2, KPI-3.1, KPI-3.2, KPI-4.3, KPI-4.4, KPI-5.1, KPI-5.2, and KPI-5.4);
- Phase D: Assessing the full list of KPIs to provide an assessment on whether the final version (ver. 2.0: final version of the integrated RETENTION platform) fulfils the objectives of the project, effectiveness, impact and sustainability (KPI-5.1, KPI-5.2, KPI-5.4, KPI-5.5).

Business (model) benchmarking

The RETENTION stakeholders, apart from clinicians and patients, are policy makers and patient organisations. These stakeholders will mainly be interested in analysing the aggregated data from the GIC, so the purpose of engaging them in the platform evaluation will focus on assessing the dashboard that supports policy decisions. For this purpose, a selected number of policy makers (with previous or current involvement in cardiovascular policy) from each of the 4 countries of the study and from the United Kingdom (to include one of the biggest 5 countries of Europe), as well as representatives of Heart Failure/Cardiovascular patient associations, at European and national level, will be invited to engage with RETENTION starting from the early stages of the conceptual design of the policy dashboard. Through workshops and focus groups scheduled at critical points of the design, these stakeholders will provide feedback on the research and insights into their requirements from such platforms. Once the policy dashboard design is completed and implemented (incorporating the collected feedback), the same identified stakeholders will be invited for an evaluation workshop where they can test the platform through performing policy analytics, based on synthetic data and/or real data collected from the study patients. Their feedback, gathered through a questionnaire, will form the basis for troubleshooting and fine-tuning the platform, as well as understanding the impact RETENTION will have on the management of Heart Failure.

Synthetic data generation

In order to test both the procedures for administering the raw data stored in all repositories (FHIR and non-FHIR repositories, Security Component Repository), and technical capacity for defining models and associating them to analytics, a testing proof of concept based on synthetic data will allow the experiment of reviewing the structure of the datasets, the basic mechanism for administering the raw data, the algorithms (mainly basic descriptive analytics defined during Phase A) to be utilised, and data visualisation techniques presenting their output. The RETENTION synthetic dataset (size estimated in Table 5) will be a repository of programmatically created data, flexible and rich enough to help identify technical flaws or bugs, and at the same time to support the definition, creation and execution of analytics (descriptive and ML such as classification, regression, and clustering) at a time when data collection from actual study participants has not yet been initialised. Desired properties for those will be:

- will concern 30 (at least) patients of the 3 categories of patients (HF, VAD, and HT recipients) and the 2 groups (Test, Control);
- will be numerical, binary, or categorical (ordinal or non-ordinal);
- the number of Demographics and Personal Health Record (PHR) features and length will be arbitrary, while their values by design will contain outliers and null values (to be spotted later on during analysis and visualisation);

- features and values will consider their relevant codes to be utilised (e.g., SNOMED, ICD-10);
- devices/sensors usage data will also consider a mixture of conditions corresponding to relevant scenarios that trigger interventions.

Table 5: Size estimations of RETENTION dataset

Synthetic dataset characteristics	Test Group			Control Group		
	HF	VAD	HT	HF	VAD	HT
# of Patients	5	5	5	5	5	5
Demographics & PHR data	<ul style="list-style-type: none">• for 60% of each subset, randomly generated values within the set limits;• to the remaining 40% of the subset, random noise can be interjected in a controllable manner.					
Usage data of ~5 heterogeneous devices (MVP version)	<ul style="list-style-type: none">• 1 smartphone for each participant;• 1.000 datapoints for each participant/device (30.000 datapoints in total).					

For the creation, a synthetic patient generator (such as Synthea⁴, or any other JSON compatible data generator) will be used that permits to model the medical history of patients. Synthetic data needs to be analysed and possibly combined with other data sets to get results for KPIs.

Ranges for each measure are specific for each patient's condition; values within the ranges are randomly generated by Synthea at each observation time, according to its standard behaviour.

Usability Evaluation

The usability evaluation to be conducted has a goal to improve the usage of the RETENTION solution (mainly the CSB and the GIC Dashboards and the Mobile application) by the main end users (i.e., study participants, clinicians). Consequently, active participation of them in the evaluation process will ensure that their different perspectives and views of are considered. Following the initial deployment (i.e., early version of the CSB dashboard), 2 types of usability assessments are planned:

- Expert usability evaluation (Phase B) to be performed at an early stage to help eliminate factors that could affect the usefulness and to identify all usability issues.
- Qualitative validation of 1st (Phase B) and the final version (Phase C) of the Dashboard with small groups of end-users focusing on the basic functionality and the satisfaction levels via: (i) Task-based evaluation and (i) Post-task rating (use of Post-Study System Usability Questionnaire - PSSUQ).

The results of the expert usability inspections and of the qualitative validations will be considered during the implementation phase of the Dashboard, providing recommendations on the following:

- Effectiveness: To which degree did the implemented functionality meet the objectives and the needs set out during the requirement analysis.

⁴Synthea: <https://github.com/synthetichealth/synthea/wiki>

- Efficiency: Whether end-users were able to accomplish basic tasks smoothly and quickly once they have become familiarised with the design of the Dashboard.
- Learnability: to which degree the Dashboard considered easy to learn and use, with little to no instruction.

Baseline Analytics and Test Interventions

Data literacy will be considered as an integral focal point for the RETENTION, aiming to continuously improve both data quality (i.e. size of data, format and consistent format) and data utilisation (i.e. groupings, test-and-error modelling and analytics production). In parallel, forming and performing baseline analytics right from the initial stages of the project during which the systematic collection of real patient data has not been initialised, allows the test and improvement of visualisation techniques to be deployed. Considering also the primary and secondary clinical endpoints, RETENTION will continuously define and execute workflows and checklists not only to answer primary clinical questions, but also other to test the behaviour of the technical solution to be developed. In this context, the following table (Table 6) provides an initial set of analytics to be deployed.

Table 6: List of Baseline analytics

ID	Label	Description	Association to DSS rule
All-B-S-01	Active Patients	Sum of all active Patients (associated with Organisation that end-user belongs)	N/A
All-B-S-02	Active Patients per type	Sum of all active Patients per type (associated with Organisation that end-user belongs)	N/A
All-B-S-03	Resources	Sum of all resources per type for all Patients (associated with Organisation that end-user belongs)	N/A
All-B-S-04	Devices/Sensors Usage data	Sum of all usage data transmissions for all Patients (associated with Organisation that end-user belongs)	N/A
All-B-S-05	Dropouts	Sum of all Patients withdrawn from study (associated with Organisation that end-user belongs)	N/A
All-B-S-06	Dropouts per type	Sum of all Patients per type withdrawn from study (associated with Organisation that end-user belongs)	N/A
All-Des-S-07	Recruitment vs Active vs Dropouts	Sum of all Patients per participation status (associated with Organisation that end-user belongs)	N/A
All-Des-S-08	Profiling of patients	Age distribution of active participants (associated with Organisation that end-user belongs)	N/A
All-Des-S-11	MOCA records: 1st visit (per type)	Distribution of initial scores on MOCA of active study participants per age group per type (associated with Organisation that end-user belongs)	N/A



ID	Label	Description	Association to DSS rule
All-Des-P-13	Personalised : Blood pressure records	Daily distribution of blood pressure readings transmitted by active participants (associated with Organisation that end-user belongs)	If # of daily records < X, produce non-medical intervention (e.g., "It seems that you are not using your Blood pressure device as frequently as you should. Please provide your blood pressure measurement.")
All-Des-S-14	Personalised : Weight records	Daily distribution of weight readings transmitted by active participants (associated with Organisation that end-user belongs)	If # of daily records < X, produce non-medical intervention (e.g., "It seems that you are not using your weight device as frequently as you should. Please provide your weight measurement.")

5.2 Privacy concerns

5.2.1 Ethical Standards to be considered

In pursuing the project's main objectives, RETENTION will adhere to the highest ethical, fundamental rights and legal standards. Considering the scope of RETENTION per se and, in particular, the ethical and legal aspects associated to the design and use of AI (e.g., human oversight/intervention, decision making, protection of personal data), it is intended that the project looks into these aspects and address them in an appropriate manner. More specifically, RETENTION project will take into account a series of instruments of horizontal relevance, as well as sector specific. It will, therefore, consider the following regulations and soft law instruments linked both the performance of scientific research in the context of Horizon 2020 framework and to the scope of RETENTION per se:

- The Convention for the Protection of Human Rights and Fundamental Freedoms, European Convention on Human Rights, as amended (ECHR)



- The Charter of Fundamental Rights of the European Union (2012/C 326/02), specifically Article 8 concerning the protection of personal data
- The 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 on the free movement of such data (General Data Protection Regulation)
- The Regulation (EU) 2019/881 of the European Parliament and of the Council of 17 April 2019 on ENISA (the European Union Agency for Cybersecurity) and on information and communications technology cybersecurity certification and repealing Regulation (EU) No 526/2013 (Cybersecurity Act)
- The Directive (EU) 2016/1148 of the European Parliament and of the Council of 6 July 2016 concerning measures for a high common level of security of network and information systems across the Union (NIS Directive) and being mindful of its forthcoming amendment (NIS2)
- The Regulation (536/2014) of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC
- Good Clinical Practice standards of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, 'ICH-GCP', European Medicines Agency, 2002.
- The Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC
- The Ethics Guidelines for Trustworthy AI, High-Level Expert Group on Artificial Intelligence set up by the European Commission, of 8th April 2019.

All obligations stemming from European and international documents of medical deontology and ethics that frame biomedical research involving human subjects shall also be upheld, such as i) the Belmont Report,⁵ ii) the Standards and operational guidance for ethics review of health-related research with human participants (WHO)⁶, iii) the Universal Declaration on Bioethics and Human Rights(UNESCO)⁷, and iv) the Declaration of Helsinki – Ethical principles for medical research involving human subjects(WMA)⁸.

⁵ The Belmont Report, Office of the Secretary, Ethical Principles and Guidelines for the Protection of Human Subjects of Research, The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research: <https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html>

⁶ WHO, 2011, Standards and operational guidance for ethics review of health-related research with human participants: <https://www.who.int/publications/i/item/9789241502948>

⁷ UNESCO, 2006, Universal Declaration on Bioethics and Human Rights: <https://unesdoc.unesco.org/ark:/48223/pf0000146180>

⁸ WMA, 2018, Declaration of Helsinki – Ethical principles for medical research involving human subjects: <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>



Other soft law instruments governing scientific research, such as the European Code of Conduct for Research Integrity⁹, the Guidelines to rules on Open Access to Scientific Publications & Open Access to Research Data in Horizon 2020¹⁰, and the Guidelines on Data Management in Horizon 2020.¹¹

5.2.2 Means for monitoring access to personal data

The aforementioned list captures the applicable regulations that are of direct relevance to the project. It is, not, however, meant to be exhaustive. The latter holds true, also, in view of the current discussions within the European Commission concerning the proposal of an EU regulatory framework for AI and means for improving the level of protection of personal data. In this context, the following will be considered:

- The “Deploying Pseudonymisation Techniques”, report by ENISA¹², in which specific use cases demonstrate the applicability of the pseudonymisation in the healthcare sector.

It is of high relevance to note that RETENTION will abide to all principles of GDPR including the principles of lawfulness, fairness and transparency, purpose limitation, and data minimisation. Towards the realisation of these principles, RETENTION plans to adopt a layered architecture in which study participants’ data will only be stored in a pseudonymised form at the clinical site repository (Clinical Site Backend - CSB), hosted by ICCS, and be accessible only to ICCS and the corresponding “local” clinicians, having responsibility for the follow-ups of the specific segment of patients and making appropriate interventions for them. Personal data will be transmitted only in an anonymised form to the global cloud component (Global Insights Cloud - GIC) for analysis using AI techniques. It should also be noted that any processing operations on non-anonymised personal data held at the clinical site repository of the project shall be limited strictly to what is absolutely necessary, e.g., having the minimal reports necessary for authorised clinical personnel to perform their duties for the purposes of the project (e.g., conducting follow ups in the context of a visit and approving suggested interventions or otherwise). In order to verify the good use of the mechanisms allowing access to the personal data and PII, a log (i.e., record-keeping system for processing activities) will record access to these sensitive data and any GDPR-requests and their status, in a way that demonstrates compliance with the GDPR (compliance with timescales, maintained logs for audit, evidence to be requested by the supervisory authority).

⁹The European Code of Conduct for Research Integrity, 2018: https://ec.europa.eu/info/funding-tenders/opportunities/docs/2021-2027/horizon/guidance/guideline-for-promoting-research-integrity-in-research-performing-organisations_horizon_en.pdf

¹⁰ European Research Council, Guidelines on Implementation of Open Access to Scientific Publications and Research Data: https://ec.europa.eu/research/participants/data/ref/h2020/other/hi/oa-pilot/h2020-hi-erc-oa-guide_en.pdf

¹¹Guidelines on Data Management in Horizon 2020: https://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm

¹² ENISA, 2022, Deploying Pseudonymisation Techniques: <https://www.enisa.europa.eu/publications/deploying-pseudonymisation-techniques>