



HAL
open science

Home- versus clinic-based EXercise InTervention in patients with Heart Failure (EXIT-HF trial): a pragmatic randomized controlled trial

Cristine Schmidt, Sandra Magalhães, Priscilla Gois Basilio, Marisol Gouveia, Manuel Teixeira, Cláudio Santos, Aida Isabel Tavares, João Pedro Ferreira, Fernando Ribeiro, Mário Santos

► To cite this version:

Cristine Schmidt, Sandra Magalhães, Priscilla Gois Basilio, Marisol Gouveia, Manuel Teixeira, et al.. Home- versus clinic-based EXercise InTervention in patients with Heart Failure (EXIT-HF trial): a pragmatic randomized controlled trial. *Revista Portuguesa de Cardiologia*, 2023, 10.1016/j.repc.2023.05.013 . hal-04212451

HAL Id: hal-04212451

<https://hal.univ-lorraine.fr/hal-04212451v1>

Submitted on 20 Sep 2023

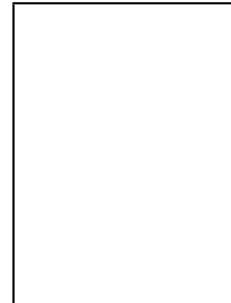
HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Journal Pre-proof

Home- versus clinic-based EXercise InTervention in patients with Heart Failure (EXIT-HF trial): a pragmatic randomized controlled trial

Cristine Schmidt Sandra Magalhães Priscilla Gois Basilio Marisol Gouveia Manuel Teixeira Cláudio Santos Aida Isabel Tavares João Pedro Ferreira Fernando Ribeiro Mário Santos



PII: S0870-2551(23)00402-X

DOI: <https://doi.org/doi:10.1016/j.repc.2023.05.013>

Reference: REPC 2253

To appear in: *Revista Portuguesa de Cardiologia*

Received Date: 5 May 2023

Accepted Date: 6 May 2023

Please cite this article as: Schmidt C, Magalhães S, Basilio PG, Gouveia M, Teixeira M, Santos C, Tavares AI, Ferreira JP, Ribeiro F, Santos M, Home- versus clinic-based EXercise InTervention in patients with Heart Failure (EXIT-HF trial): a pragmatic randomized controlled trial, *Revista Portuguesa de Cardiologia* (2023), doi: <https://doi.org/10.1016/j.repc.2023.05.013>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2023 Published by Elsevier.

Home- versus clinic-based EXercise InTervention in patients with Heart Failure (EXIT-HF trial): a pragmatic randomized controlled trial

Cristine Schmidt^{1,2,3}, Sandra Magalhães⁴, Priscilla Gois Basilio², Marisol Gouveia⁵, Manuel Teixeira⁵, Cláudio Santos², Aida Isabel Tavares^{6,7}, João Pedro Ferreira^{8,9}, Fernando Ribeiro¹⁰, Mário Santos^{11,12,3,*}

¹Surgery and Physiology Department, Faculty of Medicine, University of Porto, Portugal

²Research Center in Physical Activity, Health and Leisure, Faculty of Sport, University of Porto, Portugal

³Laboratory for Integrative and Translational Research in Population Health (ITR), Porto, Portugal

⁴Cardiac Rehabilitation Unit, Hospital Santo António, Centro Hospitalar Universitário do Porto, Portugal

⁵iBiMED - Institute of Biomedicine, Department of Medical Sciences, University of Aveiro, Portugal

⁶CEISUC - Centre for Health Studies and Research, University of Coimbra, Coimbra, Portugal.

⁷ISEG, UL - Lisbon School of Economics and Management, University of Lisbon, Portugal

⁸Cardiovascular R&D Centre - UnIC@RISE, Department of Surgery and Physiology, Faculty of Medicine of the University of Porto, Portugal.

⁹Université de Lorraine, Inserm, Centre d'Investigations Cliniques, Plurithématique 14-33, and Inserm U1116, CHRU Nancy, F-CRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists), Nancy, France.

¹⁰iBiMED - Institute of Biomedicine, School of Health Sciences, University of Aveiro, Aveiro, Portugal

¹¹Cardiology Service, Hospital Santo António, *Centro Hospitalar Universitário do Porto*, Portugal

¹²UMIB, *Instituto de Ciências Biomédicas Abel Salazar*, University of Porto, Portugal

*Corresponding author.

E-mail address: mariosantos001@gmail.com (M. Santos)

Exercício físico no domicílio *versus* hospitalar em doentes com insuficiência cardíaca (EXIT-HF): um ensaio randomizado controlado pragmático

Introdução: A acessibilidade limitada e a baixa adesão explicam, em parte, a reduzida proporção de doentes com insuficiência cardíaca (IC) que participam em programas de reabilitação cardíaca (RC). Os programas no contexto domiciliário podem contornar alguns desses obstáculos e mostraram-se tão eficazes e menos dispendiosos do que os programas hospitalares. Contudo, ainda não está claro se as evidências de estudos internacionais se podem aplicar à realidade portuguesa.

Objetivos: Comparar o impacto clínico e económico de um programa de RC no domicílio *versus* hospitalar em doentes com IC.

Métodos: Este é um ensaio randomizado controlado pragmático de não-inferioridade, unicêntrico, de grupos paralelos. Doentes adultos com IC (N=120) serão randomizados para um programa de RC no domicílio ou hospitalar. Em ambos os grupos, os doentes participarão de um programa RC com 12 semanas de duração, com duas sessões de treino por semana. O protocolo de exercício físico consiste numa combinação de treino aeróbio [(a 60%-80% do consumo máximo de oxigênio (VO_{2pico}))] e treino de resistência muscular (bandas elásticas). Os doentes alocados ao programa de RC no domicílio irão realizar 4 a 5 sessões de exercício físico supervisionadas para se familiarizar com o protocolo de treino e depois continuar com as restantes sessões em casa. O *outcome* primário do estudo é a variação no VO_{2pico} no final do programa. Os *outcomes* secundários incluem alterações em biomarcadores plasmáticos, aptidão física, atividade física, qualidade de vida, dieta, bem-estar psicológico, dispneia e custo-efetividade.

Resultados: Neste momento, o estudo está em fase de recrutamento. O estudo iniciou-se em novembro de 2019 e a recolha de dados está prevista para encerrar em dezembro de 2022. Este é o primeiro estudo em Portugal que compara o programa RC tradicional com um programa RC domiciliário em doentes com IC. Esperamos que os resultados deste estudo possam melhor informar as decisões dos profissionais de saúde sobre RC em doentes com IC.

PALAVRAS-CHAVE

Reabilitação cardíaca; Programa domiciliário; Insuficiência cardíaca

Declarations of interest: none

Trial Registration: ClinicalTrials.gov: NCT04334603.

<https://clinicaltrials.gov/ct2/show/NCT04334603>

Trial Funding: This work was financially supported by the project POCI-01-0145-FEDER-030011, funded by FEDER, through COMPETE2020-POCI, and by national funds, through FCT/MCTES (PTDC/MEC-CAR/30011/2017).

ABSTRACT

Introduction: The limited accessibility and the lack of adherence explain, in part, the low proportion of heart failure (HF) patients undergoing exercise-based cardiac rehabilitation (CR) programs. Home-based programs showed to be as effective and less costly than clinic-based ones and might address those obstacles. Whether the evidence from international studies can be applied to our population is still unclear.

Objectives: To compare the clinical and economic impact of a home-based versus clinic-based CR intervention in HF patients.

Methods: This is a single-center, single-blind, parallel groups, non-inferiority pragmatic randomized control trial. Adult HF patients (N=120) will be randomized to either a clinic-based or home-based CR program. In both groups' patients will participate in a 12-week combined CR program with 2 sessions per week. Exercise training (ExT) protocol consists of a combination of endurance [(at 60%-80% of peak oxygen uptake (VO_{2peak}))] and resistance training (elastic bands). Those allocated to the home-based program will start with 4 to 5 supervised ExT sessions to familiarize themselves with the training protocol and then will continue the remaining sessions at home. The primary endpoint is the change in VO_{2peak} at the end of the 12-week program. Secondary outcomes include alterations in circulating biomarkers, physical fitness, physical activity, quality of life, diet, psychological wellbeing, dyspnea, and cost-effectiveness analyses.

Results: Patients are currently being recruited for the study. The study started in November 2019 and data collection is anticipated to be completed by December 2022. This is the first study in Portugal comparing the traditional CR program with a home-

based program in HF patients. Our study results will better inform healthcare professionals who care for HF patients regarding CR.

Trial Registration: ClinicalTrials.gov: NCT04334603.

<https://clinicaltrials.gov/ct2/show/NCT04334603>

Keywords: cardiac rehabilitation, home-based, heart failure

1. INTRODUCTION

Heart failure (HF) affects approximately 64 million people worldwide, and accounts for an annual health care cost of \$31 billion¹. In Portugal, it is currently estimated that 380 000 people live with HF and more than 35 000 HF hospitalizations take place in our healthcare system every year². Despite the existence of a variety of pharmacological and device therapies for HF, patients still have poor long-term prognosis and quality of life (QoL)³. Exercise-based cardiac rehabilitation (CR) could reduce the risk of hospitalization by 30% and is a Class I Level A recommendation for the management of HF⁴. However, CR is still an underused treatment in HF patients. In Europe, less than 20% of HF-eligible patients have access to a CR program⁵. Several factors related to health services, physicians and patients' attitudes explain the current low utilization rates. The imbalance between supply (available CR units) and demand (increasing HF prevalence) is an important barrier to deliver this treatment. In addition, adherence is a relevant and well-recognized problem in CR interventions⁶. Time and costs associated with the transportation, lack of time and motivation have also a negative impact on CR programs adherence⁶.

Home-based interventions might help to bypass two of the main barriers: accessibility and adherence. This allows for the treatment of patients living far away from CR units and to extend the usual short-term duration of the clinic-based intervention; the flexibility of the home-based interventions is also a factor that may help improving the levels of CR participation and adherence⁷. Home-based CR programs have promisingly demonstrated to increase participation rates and short-term exercise capacity⁸. Technological advances made possible and increasingly affordable to monitor at distance the frequency and intensity of exercise; telemonitoring allows the individual tailoring of exercise prescription and distance coaching, as well as enhancing

adherence^{8,9}. Moreover, home-based CR has been reported to be a safe, beneficial⁹ and cost-effective intervention¹⁰.

The heterogeneity of the populations and exercise prescriptions previously studied limits the external validity of available evidence to our national context. Contextual differences such as the type of health system organization and reimbursement policies, and patient characteristics and literacy may significantly influence the clinical effectiveness of a home-based exercise standardized delivery provision. Therefore, further evidence is needed to better inform physicians and health policy makers regarding the beneficial effects and cost-effectiveness of home-based CR programs in Portugal.

This study aims to compare the clinical and economic impact of a home-based versus clinical-based CR intervention in HF patients. The powered primary outcome is the change in peak oxygen consumption (VO_{2peak}). Secondary outcomes are alterations in physical fitness, physical activity, QoL, adherence to the Mediterranean diet, psychological wellbeing, dyspnea, selected disease-related biomarkers, and cost-effectiveness indicator. We hypothesised that the home-based intervention would result in a similar improvement in VO_{2peak} and other secondary outcomes and would be cost-effective compared with a clinical-based intervention.

2. METHODS

This study protocol was registered on 6 April 2020 in the database of clinical trials (clinicaltrials.gov) under the registration number NCT04334603 (Protocol version 2) (<https://clinicaltrials.gov/ct2/show/NCT04334603>). Trial registration includes all components of the World Health Organization Trial Registration Data Set, as recommended by the International Committee of Medical Journal Editors. A SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist¹¹.

2.1. Trial design and setting

The study is a single-center, single-blind, parallel groups, non-inferiority pragmatic randomized controlled trial. Patients with HF will be randomized into two groups: clinic-based (standard CR) and home-based CR. Figure 1 shows a schematic representation of the study protocol. The study will be conducted at *Centro Hospitalar Universitário do Porto - Hospital de Santo António*, a tertiary university public hospital in Porto, Portugal.

2.2. Participants

One hundred and twenty patients (men and women) diagnosed with HF [(HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF)] according to the criteria of the European Society of Cardiology (ESC)⁴ will be evaluated and randomized. Inclusion and exclusion criteria are listed in Table 1. Individual participants will be discontinued from the trial, in agreement with their physician where appropriate, if any major surgery or health condition arises that will significantly affect their safety to participate in exercise for a duration of >one month, or if the participant elects to withdraw their consent for any reason.

2.3. Recruitment

Patients will be consecutively recruited at the Unit of CR of Cardiology Department of *Centro Hospitalar Universitário do Porto - Hospital de Santo António*, Portugal between November 2019 and December 2022. Eligible participants will receive the participant information sheet and sign the participant consent form in the first day of evaluations.

2.4. Randomization

Following the cardiopulmonary exercise testing (CPET), patients will be randomized to a clinic-based or home-based CR program. Although we started the study with a randomization ratio of 1:1, we had to adjust to a 1:2 ratio due to the COVID pandemic. The clinic-based program required the patient to travel to the hospital and have contact with many people, which put patients at an increased risk of SARS-CoV-2 infection. Therefore, we decided to favour the home-based group to be able to continue the study. To ensure between group balance, it performed a covariate adaptive randomization using the method of minimization. The minimization criteria were HF phenotype (HFrEF vs HFpEF) and baseline VO_{2peak} (<17.5 vs 17.5-24.5 vs >24.5 mL/Kg/min). An independent research officer performed the randomization (software minimPy®). The allocation group was communicated to the patients by a researcher after the CPET. Patients were not blinded owing to the nature of the intervention. Except for those delivering the intervention, the staff was kept blinded to allocation. A blinded researcher conducted the CPET before and after the intervention, and another blind researcher collected the data into a database.

2.5. Interventions

The design of the ExT program follows the exercise recommendations for patients with established chronic HF, regardless of left ventricular ejection fraction¹². In both groups' patients participate in a 12-week combined ExT program with 2 training sessions per week, for a total of 24 sessions. ExT protocol consists of 5-10 minutes of warm-up with calisthenic and stretching exercise, 25 minutes of resistance exercises using elastic bands with 2 sets of 12-15 repetitions of ten exercises (squat, leg curl, leg abduction, leg adduction, standing calf raise, bench press sitting, seated row, biceps, triceps, lateral raises), 30 minutes of moderate to vigorous aerobic training at 60%-80% of VO₂peak (11-14 Borg's scale), and 5 minutes of cool down with stretch exercises. In both groups, patients are encouraged to walk at home at least a third time, a minimum of 30 minutes.

2.5.1 Clinic-based group

The clinic-based group will receive a CR program at the hospital, which includes 24 supervised ExT sessions and counselling for lifestyle modification. ExT will be monitored with real-time ECG and heart rate monitor (model Polar M200; Polar Electro Ltd). During aerobic training, the speed and inclination of the treadmill will be adjusted to ensure that every training session were carried out at the assigned heart rate level. The resistance training intensity will be progressively increased according to rated perceived exertion scale. When patients performed the set comfortably (11-14 Borg's scale) and would be able to perform more two repetitions than the prescribed ones, the intensity will be increased. Adherence, defined as the total exercise sessions during the intervention, will be evaluated by measuring sessions attendance.

2.5.2. Home-based group

The home-based group participates in a technology-enabled (computer or mobile phone application linked to a wearable smartwatch) program following the same ExT prescription of the clinical-based program. The structure of the program is like most trials included in the Cochrane meta-analysis comparing home to clinical-based CR¹³ and consists of unsupervised exercise sessions (walking), weekly phone calls and counselling for lifestyle modification. At the beginning of the program, those allocated to the home-based program will undergo 4 to 5 supervised ExT sessions (equal to those

in the clinical-based program) in the CR Unit to familiarize themselves with the training protocol and learn how to use the wearable smartwatch (heart rate monitor, model Polar M200; Polar Electro Ltd, Kempele, Finland) and fill out the exercise logs. After these sessions, patients will start training in their home environment (20 exercise sessions). Every exercise session completed by the participant will be recorded by the smartwatch and uploaded to the Polar Flow application (Polar Flow, Polar Electro Ltd, Kempele, Finland). Participants will be telephoned every week to monitor progress. During phone calls, a semi-structured interview will be conducted with the following objectives: to verify adherence to the exercise prescription (crossing self-reported information with data gathered from the heart rate monitor of the smartwatch), to identify problems/barriers to achieving the exercise goals, to provide training-specific advice for the adaptation of the exercise program on the patient's home environment, adjust ExT intensity and accomplish the recommended prescription, and to provide counselling for lifestyle modification. Patients will be instructed to contact the rehabilitation center staff if they experience any symptoms during and after exercising. Adherence will be evaluated by the smartwatch, exercise logs, and telephone.

2.5.3. Nutritional and psychological consultation

During the CR consultation, all patients that are identified in need of nutrition counselling will be sent to the nutritional consultation (for all patients in general and specifically for diabetic, obese, frail, hypertensive and dyslipidemic patients). In addition, patients will be sent to psychology and/or psychiatry consultations according to the clinical indication.

2.5.4. Socioeconomic support

Financial support from a social worker will be provided in cases of economic difficulties in obtaining essential medication and transport to the CR center.

2.6. Assessments

2.6.1. Demographic and clinical data

Sociodemographic and clinical data (including lipid profile, hemoglobin A_{1c} smoking status, and office blood pressure) will be captured from patients' files and/or during the CR consult. Clinical files might also be used to complete and/or confirm the

patient's profile. The following information will be recorded: age, gender, marital status, educational level, HF diagnosis (etiology, left ventricular ejection fraction, and New York Heart Association functional class), medication and comorbidities. Changes in medication throughout the study will be recorded.

2.6.2. *Anthropometric*

Body height will be measured standing upright against a stadiometer (Seca 213). Weight and body mass index will be measured with patients lightly dressed, using a body composition monitor (Tanita, Inner Scan BC 532). Waist circumference will be measured at the umbilical level.

2.6.3. *Outcome measurements*

Assessment of the outcome's measures is depicted in table 2. All evaluations will be conducted at CR Unit, at CHUP-HSA, at baseline and after 12 weeks.

2.6.3.1. Primary outcome

2.6.3.1.1. *Peak oxygen consumption (VO_{2peak})*

The primary outcome of the study is the change in VO_{2peak} after 12 weeks. VO_{2peak} is the gold standard for assessing cardiovascular fitness and is a strong prognostic indicator in HF patients¹⁴. VO_{2peak} will be evaluated through the maximal CPET testing on a treadmill (Medisoft, Model 870C). The testing protocol will be chosen according to the patient's physical activity (PA) level and orthopedic/musculoskeletal condition (modified Naughton or Bruce). The CPET will be conducted under medical supervision, with electrocardiography continually monitored throughout the protocol. Using a stationary metabolic cart system (Geratherm® Respiratory Ergostik, under BLUE CHERRY®), respiratory gas exchange measurements will be obtained breath-by-breath and recorded every 30 seconds. Heart rate and blood pressure will be recorded at regular intervals throughout the test. During CPET testing, patients will be strongly encouraged to achieve a 16 in the Borg rating of perceived exertion (6 to 20 scale), and a respiratory exchange ratio >1.10 . Peak VO_2 will be determined as the highest VO_2 achieved during exercise.

2.6.3.2. Secondary outcomes

2.6.3.2.1 *Disease-related biomarkers*

All subjects will undergo venous blood sampling drawn from an antecubital vein at baseline and after 12 weeks. Alterations in disease-related biomarkers, such as N-terminal pro b-type natriuretic peptide (NTproBNP), high-sensitivity C-reactive protein (hsCRP) and Troponin T (TnT) will be assessed using the standard protocol of our hospital laboratory. The circulating levels of other important functional biomarkers in HF, including galectin-3 (Gal-3), fibroblast growth factor 21 (FGF-21), and angiotensin-2 (Ang2), will be quantified using commercially available ELISA kits. Nitric oxide (NO) will be indirectly measured by the quantification of nitrate and nitrite using a total NO assay kit. All the measurements will be performed in duplicate according to the respective manufacturer's instructions.

NTproBNP has great prognostic significance in these patients⁴. Hs-CRP is a nonspecific marker of the inflammatory response; in HF patients, higher levels are associated with a worst outcome¹⁵. Elevation in TnT is a predictor of adverse outcomes in hospitalized as well as stable ambulatory patients with HF¹⁶. Gal-3 can be used as a prognostic biomarker to monitor the progression and risk of mortality in chronic HF patients¹⁷. Despite the mechanisms underlying the effects of FGF21 in HF are not fully understood, it has been shown that FGF-21 levels are elevated in HF, and have good predictive values for adverse cardiac events within 1 year¹⁸. Ang2 had been mostly associated with acute cardiovascular events¹⁹. However, higher levels of Ang2 in serum were also seen in chronic HF patients of increasing severity²⁰. In HF, endothelial function is compromised due to higher levels of inflammation and oxidative stress, which will impair NO production²¹.

2.6.3.2.2. *Physical fitness*

Changes in physical fitness levels will be evaluated by the *Senior Fitness Test* battery²². Physical fitness in HF patients is related with better QoL and, an improvement in physical fitness may be associated with a reduction in cardiac rehospitalization and all-cause mortality²³.

Six-minute walking test (6MWT): it will be performed in an indoor corridor with a course of 25 m, marked every 5 m with cones. Baseline oxygen saturation, heart rate, brachial arterial blood pressure and the Borg scale rating will be recorded. During the test, the participants must walk as fast as they can, and they are allowed to stop or slow down if they feel like doing it. At the end of the test, the Borg scale and heart rate will be measured. It will be recorded the number of laps and the additional distance covered.

30-second chair stand: this test assesses lower body strength. To perform the test, patients will be required to stand up and sit down quickly and as safely as possible. The number of repetitions performed in 30 seconds, with the arms crossed over the chest, will be registered.

30-second arm curl: this test assesses upper body strength. Sitting in a chair, the patient should flex the forearm with a 2.27 kg weight for women and 3.63 kg for men for 30 seconds. The number of repetitions performed during the 30s will be registered.

Chair sit-and-reach: this test assesses lower body flexibility. From a sitting position in front of a chair, the patient tries to reach the toes with the leg straight in the knee joint. The distance between extended fingers and the tip of the toe (+or-), in centimeters, will be recorded and the best value will be taken for analysis.

Back scratch: this test assesses upper body (shoulder) flexibility. The patient tries to join the hands behind the back, leading one hand from the top, and the other from the bottom. The result is the distance between the middle fingers (+or-), in centimeters. The best value of two repetitions will be taken for analysis.

Eight-foot up-and-go test (8FUG): the test assesses agility and dynamic balance. The patient starts the test in a sitting position. After a signal, the patient must stand up, walk 2.44 meters, make a turn around a cone, and return to the initial position as fast as possible. The patients will perform the test twice and the best time will be considered.

Handgrip strength: strength (kg) will be measured with an isometric hand dynamometer (Lafayette Model 78010,78011, Indiana, USA). Both arms will be measured 3 times while patients were seated, with the shoulder adducted and neutrally rotated, the elbow flexed at 90°, and the forearm and wrist in a neutral position. The best attempt will be used as the final score.

2.6.3.2.3. *Daily physical activity*

Physical activity will be measured through a questionnaire and a triaxial accelerometer copulate to the POLAR M200. Self-reported PA will be assessed with the short form of the International Physical Activity Questionnaire (IPAQ-SF)²⁴ through a personal interview to identify time spent in specific behaviours. Total weekly PA in METs will be estimated using the instrument's scoring protocol (3.3 METs to walking, 4.0 METs to moderate, and 8.0 METs to vigorous activity).

PA will be evaluated objectively using the Polar M200 (Polar Electro Ltd) to measure time spent in light, moderate and vigorous physical activity, time spent sitting

and lying, and the number of daily steps. Minutes spent in each activity type will be summed to a total day score. Patients will be instructed to wear the watch device during 24 hours for a period of 7 consecutive days.

2.6.3.2.4. *Quality of life*

Changes in QoL will be evaluated through the Minnesota Living with HF Questionnaire (MLHFQ)²⁵, a disease-specific questionnaire for patients with HF. The MLHFQ encompasses 21 questions, whose purpose is to determine how the disease affects the physical, psychological, and socioeconomic conditions of the patients during the previous month. The MLHFQ total score range from 0 to 105 (no impairment to maximum impairment). Higher MLHFQ score means worse QoL. Two other scores can be determined: the physical dimension (8 items, 0–40), and the emotional dimension (5 items, 0–25). Answers options range from 0 (none) to 5 (very much), where 0 represented no limitation and 105 represented maximal limitation.

2.6.3.2.5. *Psychological wellbeing*

This will be evaluated by the Hospital Anxiety and Depression Scale (HADS)²⁶. The questionnaire is composed of 14 questions on a four-point (0-3) scale. The possible scores ranged from 0 to 21 for anxiety and 0 to 21 for depression. A score of 0 to 7 for either subscale will be regarded as being in the normal range, a score of 11 or higher indicates the probable presence of the mood disorder and a score of 8 to 10 is just suggestive of the presence of the respective state.

2.6.3.2.6. *Diet/dietary habits*

The dietary habits will be evaluated by the 14-Item Mediterranean Diet Assessment Tool (MEDAS-14) questionnaire²⁷. The answer to each of the 14 items is scored with 1 in the case of meeting the criteria defined as typical of this type of food (range of possible variation 0-14 points). A total score ≥ 10 represents a good adherence to the Mediterranean diet.

2.6.3.2.7. *Dyspnea*

Dyspnea symptoms will be evaluated by the Dyspnea-12 (D-12) questionnaire²⁸. It provides an overall score for breathlessness severity that incorporates seven physical items and five affective items. The D-12 consists of 12 descriptor items on a scale of

none (0), mild (1), moderate (2), or severe (3) symptoms. Total scores from the D-12 range from 0 to 36, with higher scores corresponding to greater severity.

2.6.3.2.8. Percentage of protein aggregates

Protein aggregates will be analysed using a diagonal two-dimensional (D2D) SDS-PAGE assay with mass spectrometry to identify and characterize detergent-resistant protein aggregates in plasma pre-cleared from albumin and immunoglobulin in a subgroup of 20 patients. Protein homeostasis (proteostasis) is frequently impaired in HF. The overload of protein degradation pathways and collapse of protein quality control will halt protein turnover and is associated with the formation of toxic protein aggregates and misfolded/dysfunctional proteins that contribute to the pathophysiology of the disease²⁹.

2.6.3.2.9. Cost-effectiveness analysis

To compare the cost-effectiveness of clinical-based versus home-based CR intervention, we will use a 5-dimension questionnaire, the EQ-5D, to measure health-related QoL. We will differentiate between cardiac health care costs, noncardiac health care costs, and non-health care costs. The following information related with the cost of the resources used will be collected: type and the number of visits (urgent and non-urgent visits), procedures and medication associated to the visits and length of stay in case of hospitalization. A survey will be conducted to estimate the patients travel time and costs, work status, hours of absenteeism from work, and the time that each health professional spends with the patients during the CR program. We intend to calculate the costs from a societal perspective, which include medical direct costs, non-medical direct costs, and indirect costs, mainly those related with losses in productivity. We will estimate the incremental cost-effectiveness ratio, that is, ratio between the difference of average costs for home-based exercise programs and the control exercise approach program and the difference between average quality-adjusted life years (QALYs) of the two exercise programs.

2.7. Data collection, management, and monitoring

The collection, storage, and use of data for the research purpose will be explicitly authorize by patients in the signed consent form. All documents will be stored securely in confidential conditions and will only be accessible only by the study investigators.

Patients will be identified at database and project specific documents by the study participant number. A cloud-based platform will be designed and open to all project members, to centralize data into a repository. All hard-copy files will be stored in a securely locked filing cabinet.

Research fundings will be disseminated through peer reviewed journals with impact to the scientific community, and public presentations (to clinicians, to academic audiences, and in national and international meetings).

Study-related monitoring, audits, and inspections of all study-related documents and facilities by the hospital ethic committee will be permit. Given the role of the hospital Ethical Authorities, an independent data monitoring committee will be not needed.

2.8. Ethics and dissemination

The study design conforms with the principles outlined in the Declaration of Helsinki and National Legislation, according to the Good Clinical Practices guidelines and respecting patients' confidentiality. The study was approved by the local research Ethics Committee [2019/123(103-DEFI/107-CE)].

2.9. Statistical analyses

Sample size calculation was performed for the primary endpoint: change in VO_2peak at 12 weeks. Based on a previous trial³⁰ and to accommodate a 10% attrition rate, 120 patients (60 per group) are required to test the hypothesis that the home-based intervention is not inferior to the clinic-based one, assuming a non-inferiority limit of 1.25 mL/Kg/min at the 2.5% significance level and 80% power.

The normality of data distribution will be evaluated with the Shapiro–Wilk test or by kurtosis and skewness test. Baseline patient characteristics will be summarized using the mean and standard deviation or median and interquartile ranges for continuous variables, as appropriate, and frequencies and percentages for categorical variables. Mean differences will be expressed with their two-sided 95% confidence interval. Between group differences at baseline and in the change from baseline to the end of the intervention will be tested with unpaired Student t tests or Mann-Whitney U test. Analysis of Covariance will be also employed to adjust for baseline differences between groups. Within-group comparisons from baseline to the end of the intervention will be analysed using the paired Student t tests or Wilcoxon signed-rank test. Between group

comparisons at baseline in categorical variables will be tested with the chi-square test. All statistical analyses will be performed considering the intention-to-treat analysis (using an 80% cut-point for adherence) and a per protocol basis to mitigate bias. Patients with missing values of primary outcome (VO_{2peak}), will be excluded from the analyses. A two-sided p-value <0.05 will be considered significant. There are no interim analyses planned or early trial termination guidelines.

3. DISCUSSION

This study will investigate the clinical and economic impact of a home-based versus clinic-based CR intervention in HF patients. Various studies performed in other countries showed that home-based CR programs are a safe and beneficial alternative to clinic-based CR, and they also tend to be a cost-effective intervention compared with traditional exercise programs^{9,10}. However, the differences in ecological characteristics such as the type of health system organization and reimbursement policies, and patient characteristics and literacy may significantly influence the clinical effectiveness of a home-based CR.

To test the hypothesis that the home-based CR intervention would result in a benefit like clinic-based intervention, and if it can be a cost-effective intervention in the Portuguese healthcare setting, we designed a pragmatic clinical trial. Pragmatic trials can test the same intervention as an explanatory trial, but they are conducted in real-world clinical practice settings, with typical patients and by qualified clinicians. For example, we will include patients with peripheral arterial disease, atrial fibrillation, cardiac implanted devices, and older patients, who are generally excluded from the CR studies.

To our knowledge, this is the first study performed in Portugal with HF patients, that will study a home-based CR program using accessible and low-cost technology. We expect that this study can contribute to increasing the awareness of the importance of CR in HF and to provide data on different modalities of delivering CR. Each of these options should be considered in the local practice healthcare unit and to the individual HF patient to address common barriers to delivering CR such as lack of resources, and geographical and travelling constraints.

This is the first pragmatic randomized clinical trial in Portugal comparing the traditional CR program with a home-based program in HF patients. Our study results

will contribute to provide better information to healthcare professionals and hospitals who care for HF patients and to policy makers deciding on reimbursement policy regarding CR.

Declaration of interest: The authors declare no conflicts of interest.

Author Contributions: Study concept and design: CS, FR and MS.; Acquisition, analysis, or interpretation of data: CS, SM, PGB, MG, MT, CS, AIT, FR and MS.; Drafting of the manuscript, CS, FR, JPF and MS. Critical revision of the manuscript: CS, SM, PGB, MG, MT, CS, AIT, FR and MS. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement: This protocol paper does not describe any data. However, the datasets analyzed during the described study will be available from the corresponding author on reasonable request.

REFERENCES

1. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;**392**(10159): 1789-858. [www.doi.org/10.1016/s0140-6736\(18\)32279-7](http://www.doi.org/10.1016/s0140-6736(18)32279-7)
2. Gouveia MRA, Ascencao R, Fiorentino F, et al. Current costs of heart failure in Portugal and expected increases due to population aging. *Rev Port Cardiol*. 2020;**39**(1): 3-11. www.doi.org/10.1016/j.repc.2019.09.006
3. Packer M, Metra M. Guideline-directed medical therapy for heart failure does not exist: a non-judgmental framework for describing the level of adherence to evidence-based drug treatments for patients with a reduced ejection fraction. *European Journal of Heart Failure*. 2020;**22**(10): 1759-67. www.doi.org/https://doi.org/10.1002/ejhf.1857
4. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;**42**(36): 3599-726. www.doi.org/10.1093/eurheartj/ehab368
5. Bjarnason-Wehrens B, McGee H, Zwisler AD, et al. Cardiac rehabilitation in Europe: results from the European Cardiac Rehabilitation Inventory Survey. *Eur J Cardiovasc Prev Rehabil*. 2010;**17**(4): 410-8. www.doi.org/10.1097/HJR.0b013e328334f42d
6. Sérvio TC, Britto RR, de Melo Ghisi GL, et al. Barriers to cardiac rehabilitation delivery in a low-resource setting from the perspective of healthcare administrators, rehabilitation providers, and cardiac patients. *BMC Health Serv Res*. 2019;**19**(1): 615. www.doi.org/10.1186/s12913-019-4463-9
7. Thomas RJ, Beatty AL, Beckie TM, et al. Home-Based Cardiac Rehabilitation: A Scientific Statement From the American Association of Cardiovascular and Pulmonary Rehabilitation, the American Heart Association, and the American College of Cardiology. *J Am Coll Cardiol*. 2019;**74**(1): 133-53. www.doi.org/10.1016/j.jacc.2019.03.008
8. Imran HM, Baig M, Erqou S, et al. Home-Based Cardiac Rehabilitation Alone and Hybrid With Center-Based Cardiac Rehabilitation in Heart Failure: A Systematic Review and Meta-Analysis. *J Am Heart Assoc*. 2019;**8**(16): e012779. www.doi.org/10.1161/jaha.119.012779
9. Rawstorn JC, Gant N, Direito A, et al. Telehealth exercise-based cardiac rehabilitation: a systematic review and meta-analysis. *Heart*. 2016;**102**(15): 1183-92. www.doi.org/10.1136/heartjnl-2015-308966
10. Scherrenberg M, Falter M, Dendale P. Cost-effectiveness of cardiac telerehabilitation in coronary artery disease and heart failure patients: systematic review of randomized controlled trials. *European Heart Journal - Digital Health*. 2020;**1**(1): 20-9. www.doi.org/10.1093/ehjdh/ztaa005
11. SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials. *Annals of Internal Medicine*. 2013;**158**(3): 200-7. www.doi.org/10.7326/0003-4819-158-3-201302050-00583 %m 23295957
12. Ambrosetti M, Abreu A, Corrà U, et al. Secondary prevention through comprehensive cardiovascular rehabilitation: From knowledge to implementation. 2020 update. A position paper from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology. *Eur J Prev Cardiol*. 2020. www.doi.org/10.1177/2047487320913379

13. Anderson L, Sharp GA, Norton RJ, et al. Home-based versus centre-based cardiac rehabilitation. *Cochrane Database Syst Rev.* 2017;**6**(6): Cd007130. www.doi.org/10.1002/14651858.CD007130.pub4
14. Swank AM, Horton J, Fleg JL, et al. Modest Increase in Peak VO₂ Is Related to Better Clinical Outcomes in Chronic Heart Failure Patients. *Circulation: Heart Failure.* 2012;**5**(5): 579-85. www.doi.org/doi:10.1161/CIRCHEARTFAILURE.111.965186
15. Anand IS, Latini R, Florea VG, et al. C-reactive protein in heart failure: prognostic value and the effect of valsartan. *Circulation.* 2005;**112**(10): 1428-34. www.doi.org/10.1161/circulationaha.104.508465
16. Perna ER, Macin SM, Canella JP, et al. Ongoing myocardial injury in stable severe heart failure: value of cardiac troponin T monitoring for high-risk patient identification. *Circulation.* 2004;**110**(16): 2376-82. www.doi.org/10.1161/01.Cir.0000145158.33801.F3
17. Ibrahim NE, Januzzi JL, Jr. Established and Emerging Roles of Biomarkers in Heart Failure. *Circ Res.* 2018;**123**(5): 614-29. www.doi.org/10.1161/CIRCRESAHA.118.312706
18. Zhang Y, Liu D, Long XX, et al. The role of FGF21 in the pathogenesis of cardiovascular disease. *Chin Med J (Engl).* 2021;**134**(24): 2931-43. www.doi.org/10.1097/CM9.0000000000001890
19. Chan MY, Efthymios M, Tan SH, et al. Prioritizing Candidates of Post-Myocardial Infarction Heart Failure Using Plasma Proteomics and Single-Cell Transcriptomics. *Circulation.* 2020;**142**(15): 1408-21. www.doi.org/10.1161/circulationaha.119.045158
20. Eleuteri E, Di Stefano A, Giordano A, et al. Prognostic value of angiotensin-2 in patients with chronic heart failure. *Int J Cardiol.* 2016;**212**: 364-8. www.doi.org/10.1016/j.ijcard.2016.03.005
21. Piatek K, Feuerstein A, Zach V, et al. Nitric oxide metabolites: associations with cardiovascular biomarkers and clinical parameters in patients with HFpEF. *ESC Heart Fail.* 2022. www.doi.org/10.1002/ehf2.14116
22. Rikli RE, Jones CJ. Development and validation of criterion-referenced clinically relevant fitness standards for maintaining physical independence in later years. *Gerontologist.* 2013;**53**(2): 255-67. www.doi.org/10.1093/geront/gns071
23. Sabbag A, Mazin I, Rott D, et al. The prognostic significance of improvement in exercise capacity in heart failure patients who participate in cardiac rehabilitation programme. *European Journal of Preventive Cardiology.* 2020;**25**(4): 354-61. www.doi.org/10.1177/2047487317750427
24. Craig CL, Marshall AL, Sjöström M, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc.* 2003;**35**(8): 1381-95. www.doi.org/10.1249/01.Mss.0000078924.61453.Fb
25. Rector TS, Cohn JN. Assessment of patient outcome with the Minnesota Living with Heart Failure questionnaire: reliability and validity during a randomized, double-blind, placebo-controlled trial of pimobendan. Pimobendan Multicenter Research Group. *Am Heart J.* 1992;**124**(4): 1017-25.
26. Pais-Ribeiro J, Silva I, Ferreira T, et al. Validation study of a Portuguese version of the Hospital Anxiety and Depression Scale. *Psychol Health Med.* 2007;**12**(2): 225-35; quiz 35-7. www.doi.org/10.1080/13548500500524088
27. Afonso L, Moreira T, Oliveira A. Índices de adesão ao padrão alimentar mediterrânico – a base metodológica para estudar a sua relação com a saúde. 2014.

28. Simsic AA, Yorke J, Regueiro EG, et al. Validation of the dyspnoea-12 scale into Portuguese speaking COPD patients. *The Clinical Respiratory Journal*. 2018;**12**(5): 1942-8. [www://doi.org/https://doi.org/10.1111/crj.12762](http://doi.org/https://doi.org/10.1111/crj.12762)
29. Gouveia M, Xia K, Colón W, et al. Protein aggregation, cardiovascular diseases, and exercise training: Where do we stand? *Ageing Res Rev*. 2017;**40**: 1-10. [www://doi.org/10.1016/j.arr.2017.07.005](http://doi.org/10.1016/j.arr.2017.07.005)
30. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *Jama*. 2009;**301**(14): 1439-50. [www://doi.org/10.1001/jama.2009.454](http://doi.org/10.1001/jama.2009.454)

Journal Pre-proof

Table 1: Inclusion and exclusion criteria.

Inclusion and exclusion criteria.	
Inclusion criteria	Exclusion criteria
<ol style="list-style-type: none"> 1. Diagnosis of HFrEF or HFpEF according to criteria of the ESC (2016) 2. Age \geq18 years 3. Clinical stability for \geq 6 weeks 4. Optimal medical treatment for \geq 6 weeks 5. Patients that are able to understand and follow the exercise prescription 6. Written informed consent 	<ol style="list-style-type: none"> 1. Patients who have undertaken cardiac rehabilitation within the past 12 months 2. Patients who have received an ICD, CRT or combined CRT/ICD device implanted in the last 6 weeks 3. Myocardial infarction in the last 3 months 4. Signs of ischemia during CPET 5. Symptomatic and/or exercise-induced cardiac arrhythmia or conduction disturbances 6. Currently pregnant or intend to become pregnant in the next year 7. Inability to exercise or conditions that may interfere with exercise intervention 8. Expectation of receiving a cardiac transplant in the next 6 months 9. Participation in another clinical trial 10. Patients who are unable to understand the study information or unable to complete the outcome questionnaires

Table 2: Timeline of assessments.

Assessment	Assessment measure	TIMEPOINT	
		Baseline	12-week
Screening			
Participant eligibility	Eligibility criteria will be checked at cardiology appointment according to criteria showed in table 1	X	
Informed consent	Specific form will be signed by the patient (in duplicate) at the Cardiac Rehabilitation appointment	X	
Demographic and clinical data	With patient and clinical Records (e.g., lipid profile, blood pressure, smoking status)	X	X
Anthropometric	Weight	X	X
	Height	X	X
	Body mass index	X	X
	Abdominal circumference	X	X
Primary outcome			
Cardiorespiratory fitness	Peak oxygen consumption (VO ₂ peak)	X	X
Secondary outcomes			
Disease-related biomarkers	N-terminal pro b-type natriuretic peptide (NTproBNP)	X	X
	high-sensitivity C-reactive protein (hsCRP)	X	X
	Troponin T (TnT)	X	X
	Angiotensin-2	X	X
	Galectin-3 (Gal-3)	X	X
	Fibroblast Growth Factor 21 (FGF-21)	X	X
	Nitric Oxide (NO)	X	X
Physical fitness	6MWT	X	X
	30-Second Chair Stand	X	X
	30-second arm curl	X	X
	Chair sit-and-reach	X	X
	Back scratch	X	X
	8FUG	X	X
	Grip strength	X	X
Daily physical activity	International Physical Activity Questionnaire (IPAQ-SF)	X	X
	Accelerometer coupled to POLAR M200	X	X
Quality of life	Minnesota Living with Heart Failure Questionnaire (MLHFQ)	X	X
Psychological wellbeing	Hospital Anxiety and Depression Scale (HADS)	X	X
Diet/dietary habits	14-Item Mediterranean Diet Assessment Tool (MEDAS-14)	X	X
Dyspnea	Dyspnea-12 questionnaire	X	X
		X	X
		X	X

Percentage of protein aggregates	Diagonal two-dimensional SDS-PAGE assay with mass spectrometry	X	X
Cost-effectiveness analyses	Cost per quality-adjusted life year (QALY).		X

Journal Pre-proof

Figure 1: Flowchart of the study.