BMJ Open

Efficacy, Efficiency and Safety of a Cardiac Telerehabilitation Program Using Wearable Sensors (TELE WEAR): Rationale and Design of a Supervised Randomized Controlled Clinical Trial.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-059945
Article Type:	Protocol
Date Submitted by the Author:	07-Dec-2021
Complete List of Authors:	Antoniou, Varsamo; University of Thessaly School of Health Sciences, Clinical Exercise Physiology and Rehabilitation Laboratory, Department of Physiotherapy Xanthopoulos, Andrew; University of Thessaly Faculty of Medicine, Cardiology Giamouzis, Gregory; University of Thessaly Faculty of Medicine, Cardiology Davos, Constantinos ; Biomedical Research Foundation of the Academy of Athens, Cardiovascular Research Stavrou, Vasileios; University of Thessaly Faculty of Medicine, Laboratory of Cardio-Pulmonary Testing, Department of Respiratory Medicine Batalik, Ladislav; University Hospital Brno, Rehabilitation; Department of Rehabilitation, University Hospital Brno, Czech Republic Kapreli, Eleni; University of Thessaly School of Health Sciences, Clinical Exercise Physiology and Rehabilitation Laboratory, Department of Physiotherapy Gourgoulianis, Konstantinos; University of Thessaly Faculty of Medicine, Laboratory of Cardio-Pulmonary Testing, Department of Respiratory Medicine Skoularigis, John; University of Thessaly Faculty of Medicine, Cardiology Pepera, Garyfallia; University of Thessaly School of Health Sciences, Department of Physiotherapy, Clinical Exercise Physiology and Rehabilitation Laboratory
Keywords:	Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS, REHABILITATION MEDICINE, Cardiology < INTERNAL MEDICINE

TITLE PAGE

Efficacy, Efficiency and Safety of a Cardiac Telerehabilitation Program Using Wearable Sensors (TELE WEAR): Rationale and Design of a Supervised Randomized Controlled Clinical Trial.

Authors

Varsamo Antoniou, PT, BSc, MSc[a],PhD(c) [a]
Andrew Xanthopoulos, MD, PhD[b]
Gregory Giamouzis, MD, PhD[b]
Konstantinos Davos, MD, PhD, FESC[c]
Vasileios Stavrou, BSc, MSc, PhD[d]
Ladislav Batalik, PT, MSc, PhD[e,f]
Kapreli Eleni, PT, BSc, MSc, PhD[a]
Konstantinos I. Gourgoulianis MD, PhD[d]
John Skoularigis, MD, PhD[b]
Garyfallia Pepera, PT, BSc, MSc, PhD[a]

[a] Clinical Exercise Physiology and Rehabilitation Laboratory, Department of Physiotherapy, School of Health Sciences, University of Thessaly, Lamia, Greece
[b] Department of Cardiology, Faculty of Medicine School of Health Sciences, University of Thessaly Larissa Greece.
[c] Cardiovascular Research Laboratory, Biomedical Research Foundation, Academy of Athens, 4 Soranou Ephessiou Street, 115 27, Athens, Greece
[d] Laboratory of Cardio-Pulmonary Testing, Department of Respiratory Medicine, Faculty of Medicine, University of Thessaly, Larissa, Greece
[e] Department of Rehabilitation, University Hospital Brno, Jihlavska 20, Brno, 62500, Czech Republic
[f] Department of Public Health, Masaryk University Brno, Zerotinovo nam. 617/9, Brno, 601 77, Czech Republic

Corresponding author:
Varsamo Antoniou

PhD student in Cardiac Rehabilitation, Physiotherapy, Clinical Exercise Physiology & Rehabilitation Research Laboratory, Physiotherapy Department, Faculty of Health Sciences, University of Thessaly, Lamia, Greece. 3rd km of Old National Road, GR-35100 Lamia, Greece Tel: +306944635309 e-mail: varsamoantoniou@uth.gr

Xanthopoulos A. e-mail: andrewvxanth@gmail.com
Giamouzis G. e-mail: grgiamouzis@med.uth.gr
Davos C. e-mail: cdavos@bioacademy.gr
Stavrou V. e-mail: vasileiosstavrou@hotmail.com
Batalik L. e-mail: Batalik.Ladislav@fnbrno.cz
Kapreli E. e-mail: ekapreli@uth.gr
Gourgoulianis K. e-mail: kgourg@med.uth.gr
Skoularigis J. e-mail: iskoular@med.uth.gr
Pepera G. e-mail: gpepera@uth.gr

Word count: 3.337

Abstract

Introduction: Exercise – based cardiovascular rehabilitation is a beneficial tool for the secondary prevention of cardiovascular diseases with, however, low participation rates. Telerehabilitation, intergrading mobile technologies and wireless sensors, may advance the cardiac patients' adherence. This study will investigate the efficacy and safety of a telerehabilitation program based on objective exercise telemonitoring and evaluation of physical activity.

Methods and Analysis: A supervised, parallel-group, single-blind, randomized controlled trial will be conducted. One hundred and twenty four coronary disease patients will be randomized at a 1:1 ratio into two groups: intervention telerehabilitation group (TELE-CR) (n=62) and control, center – based cardiovascular rehabilitation group (CB-CR) (n=62). Participants will receive a 12 – week exercise based rehabilitation program; remotely monitored for the telerehabilitation group and

standard supervised for the center – based group. All participants will train at 70% of their maximal heart rate, as obtained from cardiopulmonary exercise testing (CPET) for 60'', three times/ week. The primary outcomes will be the assessment of cardiorespiratory fitness, expressed as peak oxygen uptake assessed by the CPET test or the 6 minute walking test (6MWT). Secondary outcomes will be the physical activity, the safety of the exercise intervention, (number of adverse events that may occur during the exercise), quality of life, training adherence, and cost – effectiveness. Assessments will be held at baseline, end of intervention (12 weeks) and follow up (36 weeks).

Ethics and dissemination: The study protocol has been reviewed and approved by the Ethics Committee of the University of Thessaly and by the Ethics Committee of the General University Hospital of Larissa. The results of this study will be disseminated through manuscript publications and conference presentations.

Keywords: cardiovascular rehabilitation; telerehabilitation; wearable sensors; physical fitness; physical activity

Trial registration: Clinical Trial.gov, Identifier: NCT05019157. Registered 24 August 2021. https://clinicaltrials.gov/ct2/show/NCT05019157?cond=cardiac+telerehabilitation&country=GR&draw=2&rank=1

Strengths and limitations of this study

- Telelerehabilitation as an alternative tool to contemporary centre/community based cardiac rehabilitation.

- Intergrading real-time supervision of the exercise sessions in cardiac telerehabilitation.
- Group – based exercise sessions in cardiac telerehabilitation.
- Objective monitoring and evaluation of physical activity and exercise intensity in cardiac rehabilitation interventions.
- Inability, by study design, to blind participants to treatment allocation

INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of morbidity and premature mortality globally.[1-5] Coronary artery diseases (CAD) account for the largest proportion of CVD mortality.[6] A systematic review by the Global Public Health Burden (GBD) reveals an increase of 11.8% in the mortality rates due to ischemic CVDs in Greece [6] with cardiac risk factors[7] being very common among Greek patients and without signs of future decline.[8] The increased rates of CVDs put additional pressure on the health care systems, especially under the ongoing austerity climate across Europe.

Cardiovascular rehabilitation (CR) can play a key role as a multidisciplinary secondary intervention aiming to the reduction of CVDs' risk factors, the adoption of healthy lifestyle behaviors and the minimization of disability among CVD patients.[9] Recent guidelines on CVD prevention recommend a multifaceted approach addressing exercise training, dietary counseling, smoking cessation, risk factor modification and psychosocial support.[10-12] A number of meta-analysis confirm the effectiveness of exercise training in reducing cardiovascular mortality, morbidity, re-

hospitalizations rates,[13 14] physical inactivity and all CVD risk factors including blood pressure, blood lipid profile, glucose metabolism and weight status.[15 16] Despite global recommendations, patients' participation in CR programs is low, mainly due to insufficient medical referral, travel distance, low self-efficacy, perceived body image and lack of time.[17-19] Moreover, during the COVID-19 pandemic, new barriers have arisen, such as the suspension of centre-based CR and in-person sessions, travelling and circulation restrictions.[20 21] Thus the need to avoid the downgrading of CR is imperative.[22]

Rapid development in information and communication technologies (ICTs) may help to overcome the barriers to CR. [23-25] Telerehabilitation is proposed as a feasible, [26 27] safe and cost – effective intervention, [28 29] leading to long-term improvement of CVD risk factors, reduced healthcare costs and increased CR participation adherence. [30].Recent systematic reviews advocate to the use of telehealth interventions as an adjunct to CR [31-33] for the continuance of CR through pandemic circumstances. [20 21]

A recent review proclaims the integration of remote technologies and wearable sensors in the telerehabilitation, mentioning though the need for further investigation. [34] Another systematic review indicates that, software-enabled systems reduce timing-related barriers to patients' participation.[32] The feasibility and safety of cardiac telerehabilitation need further investigation since most relevant studies are not addressing safety matters and a formal cost - effectiveness analysis.[32 34]

Our study focuses on the objective recording and monitoring of the exercise implementation and physical activity, through the use of wearable sensors (heart rate monitors, accelerometers). Based on thorough literature review, it is the first study to

integrate real time supervision (use of videoconference platforms) and a group based design for home exercising (up to 5 participants).

The primary aims of this study are to compare the effect between telerehabilitation and regular outpatient CR methods, related to cardiorespiratory fitness (CRF) and functional capacity. Whilst possible effects in physical activity, training adherence, anxiety and stress management, safety and cost – effectiveness are considered as secondary aims.

The hypothesis of the study will be that the telerehabilitation intervention will have at least the same efficiency with the regular, centre - based rehabilitation and that it will be as safe as and even more cost-effective than the centre - based rehabilitation intervention.

METHODS

Study design

A supervised, parallel-group, single-blind, randomized controlled trial with 6 months follow-up will be employed. The study includes CAD patients, enrolled in a telerehabilitation group (TELE-CR) and a control group undertaking regular outpatient CR rehabilitation (CB-CR) for comparison reasons. Three assessments will take place at baseline (A_0), end of intervention (A_{12}) and follow up 36 weeks (A_{36}). A CONSORT (Consolidated Standard of Reporting Trials) flow diagram is shown in Fig. 1.

The study protocol complies with the SPIRIT 2013 statement guidelines[35] and the intervention procedures are described according to the CONSORT- E- HEALTH checklist.[36] We used the SPIRIT checklist when writing our report.[35] The trial is registered at ClinicalTrials.gov with registration number NCT05019157.

Table 1 presents a summary of the study schedule and assessments.

Table 1. Summary of study schedule

	Enrollment	Baseline (A_0)	End of Intervention(A_{12})	Follow Up (A_{36})
Eligibility screen	X			
Informed consent	X			
Randomization		X		
Allocation		X		
Interventions				
Center – based CR		◆———	———	———◆
Telerehabilitation		◆———	———	———◆
Assessments				
Demographic characteristics		X		

Spirometry, TTE	X		
Strength evaluation test	X		
Cardiac biomarkers (BNP, NT-proBNP, Troponines, CPK)	X	X	
CPET – 6MWT	X	X	X
HRQoL	X	X	X
HADS	X	X	X
IPAQ	X	X	X
FTND	X	X	X
Cost analysis		X	
Training Adherence		X	

TTE: Transthoracic echocardiography, CPET: cardiopulmonary exercise testing, 6MWT: 6 Minute Walking Test, BMP: B-type natriuretic peptide, CPK: Creatine phosphokinase, HRQoL: Health related quality of life, HADS: Hospital Anxiety and Depression scale, IPAQ: International Physical Activity Questionnaire FTND: Fagestrom Test for Nicotine Dependence

Patient population and eligibility

Patients will be recruited- prior to their hospital discharge- from the Cardiology Department of the General University Hospital of Larissa in Greece and will be screened for eligibility by the medical staff (cardiologists and medical physicians) of the corresponding hospital, according to the criteria shown in Table 2. Through risk stratification and pre – exercise assessment only low and moderate cardiac risk patients will be included in the study groups (Table 3). Those who consent to participation will be screened for eligibility and will be provided with a trial information sheet (explanation of the study design and scopes, participants' responsibilities, confidentiality of the collected data) and a consent form to be signed. Basic sociodemographic data including sex, age, weight, height, cardiac diagnosis, pharmacologic treatment, educational level, place of residence and profession will also be collected.

Table 2. Inclusion and exclusion criteria

Inclusion criteria	
i.	adults aged 40-70 years
ii.	diagnosed with coronary artery disease (CAD) (stable angina, myocardial infarction, patients after coronary revascularization or coronary artery bypass grafting) in the last 6 months, with left ventricular ejection fraction > 45%
iii.	current outpatients, stable for at least four weeks prior to the intervention enrollment
iv.	able to perform physical exercise,
v.	able to speak, read and write Greek
vi.	possession of a mobile phone/smartphone
vii.	internet access at home

Exclusion criteria
i. severe ventricular arrhythmia, with functional or prognostic significance or exercise – induced myocardial ischemia as assessed by CPET at baseline
ii. heart failure
iii. comorbidity precluding exercise training (e.g. orthopedic, neurological or cognitive conditions)
iv. unstable angina
v. uncontrolled atrial or ventricular arrhythmia
vi. acute pulmonary embolism
vii. acute myocarditis or pericardial effusion
viii. uncontrolled diabetes mellitus (Type I, II)
ix. severe obstructive respiratory disease (forced expiratory volume 1 (FEV1)<50%).

Table 3. Cardiac risk stratification

Low Risk	**Moderate Risk**	**High Risk**

-Absence of angina or other symptoms (eg unusual shortness of breath, mild headache or dizziness) -Functional capacity> 7 METs, left ventricular ejection fraction (LVEF) ≥ 50% -Absence of arrhythmia at rest -Absence of depression	- Presence of angina or other symptoms (eg unusual shortness of breath, mild headache or dizziness, dizziness occurring at high levels of exercise ≥ 7 METs) -Mild to moderate silent ischemia (ST eruption <2 mm) -Functional capacity> 5 METs -LVEF = 40-49%	-Presence of arrhythmias - Presence of angina or other symptoms (eg unusual breathlessness, mild headache or dizziness, dizziness occurring at high levels of exercise <5 METs) -Silent ischemia (ST stroke ≥ 2 mm) -Presence of abnormal hemodynamics during exercise (reduction of BP) or post-exercise hypotension -LEVF <40%

Randomization and blinding

One hundred and twenty four eligible patients will be randomized, via a computerized randomization system, in a 1:1 ratio (adjusted for age and gender) into two groups: center-based CR (CB-CR) and telerehabilitation group (TELE-CR). The allocation will be hidden until the completion of the baseline assessment in sequentially numbered, sealed, opaque envelopes. Due to the nature of the intervention, both the participants and the hospital's staff supervising the exercise programs are unable to be blinded to the treatment allocation. The researchers, responsible for all study assessments, will be blinded to the intervention allocation. Primer investigators will be unaware of the randomization allocation until the completion of the intervention and the collection of all study data.

Patient and public involvement

There was no patient or public involvement in the design of this study (setting of the research question or the outcome measures). The patients will not be asked to take part either in the interpretation or the writing procedures of the results of this study.

Interventions

Individually determined CR programs will be implemented in both study groups based on the participants' referral diagnosis, physical fitness level and expected training goals. All participants will undertake a 12 – week, exercise - based CR program, including 3 training sessions of 60'/week. Exercise will be prescribed individually, according to the results of the baseline CPET and to the FITT [frequency, intensity, time (duration), and type of exercise] model.[37] Participants will exercise with an intensity of 70% of their maximal heart rate (HR_{max}), as assessed during baseline CPET or 6MWT assessment and at a level of 12/20–14/20 of Borg scale.[10] Each exercise circuit will consist of 20 structured stations for aerobic, strength and balance training of 2' duration/station (Tables 4, 5). Aerobic progression will go through the duration, followed by an increase of 5–10% / week in the exercise intensity.[38] [39] Progression in the resistance training involves, primarily, the achievement of the desired volume (number of training sets), followed by the gradual increase in intensity (amount of load lifted) and adaptations in density (rest periods).[38] [40] Resistance training will follow a low pace, rest/recovery to work/contraction ratio: 2:1.[37] Participants in the CB-CR group will use free weights or machines for their resistance training, whilst participants in the TELE – CR group will exercise using their body weight or resistance bands. At the completion of the intervention, the effectiveness of the training program will be assessed and patients will be encouraged

to maintain a physically active lifestyle. However, no specific exercise prescription or face - to - face feedback will be provided until the follow - up assessment.

Table 4: CB-CR exercise program

Warm Up			
*Cycling or mild treadmill walking			5’
*Stretching activities	*Upper back stretch *Chest stretch *Lower back, waist mobility *Calf stretch *Hamstring stretch *Quadriceps stretch		5’

Aerobic Training		**Strengthening Training**		**Balance Training**	
* Cycling or treadmill walking	Exercise with an intensity of 70% of their maximal heart rate (HR_{max}) at a level of 12/20–14/20 of Borg scale	*Biceps curls *Shoulder press *Triceps *Lateral fly *Front deltoid raise *Mini squats *Hamstring curls *Plantar flex *Side leg raise	12 repetitions 1 set/ exercise, starting at 30 and 70% of one-repetition maximum (1RM) for the upper body and lower body respectively increasing gradually to 70% of 1RM and 80% of 1RM for the upper and lower body, respectively	*Standing on one foot *Walking heel to toe *Reaching - front -Lateral -back	Starting with their own body weight and later including unstable surfaces

Duration 40’

1RM: the maximum weight a patient can lift in one complete repetition for a given exercise in a controlled way through a full range of motion with good posture

Cool Down		
*Cycling or mild treadmill walking *Moving hands slowly *Stretching exercises		10’

Table 5: TELE-CR exercise program

Warm Up		
*Marching on the spot		5’
*Stretching activities	*Upper back stretch *Chest stretch *Lower back, waist mobility *Calf stretch *Hamstring stretch *Quadriceps stretch	5’

Aerobic Training	Strengthening Training	Balance Training

*Box stepping *Knee raises only -With hand to opposite knee -Hand to opposite ankle *Knee bends only -With swinging arms -With reaching arms *Side steps -Just tapping -With half arm lift -Reaching over *Marching -Heal lift only -With arms moving	10 repetitions 2 sets/ exercise	*Biceps curls *Shoulder press *Triceps *Lateral fly *Front deltoid raise *Mini squats *Hamstring curls *Plantar flex *Side leg raise	12 repetitions 1 set/ exercise, starting at 30 and 70% of one-repetition maximum (1RM) for the upper body and lower body respectively increasing gradually to 70% of 1RM and 80% of 1RM for the upper and lower body, respectively	*Standing on one foot *Walking heel to toe *Reaching - front -Lateral -back	Starting with their own body weight and later including unstable surfaces

Duration 40’

1RM: the maximum weight a patient can lift in one complete repetition for a given exercise in a controlled way through a full range of motion with good posture

Cool Down	
*Marching on the spot gently *Moving hands slowly *Stretching exercises	10’

Blood samplings will be taken, in all assessment endpoints, from all study participants to assess any effects of the intervention on the cardiac biomarkers' blood concentration (BNP, NT-proBNP, Troponines, CPK).

All patients will be receiving educational and informational videoconference sessions regarding issues of upright exercising, physical activity, diet/nutritional and smoking cessation counseling (based on recent guidelines)[10] and psychosocial support (via psychotherapy) on stress and anxiety management. Consultation sessions may include a family member or friend, especially for elderly patients.[41] Communication strategies such as motivational interviewing, during telephone calls or videoconferences, will be integrated, as they appear to be useful in helping promote patients' adherence and avoid incidents of early drop outs. Motivational interviewing will be based on the OARS (Open-ended questions, Affirmation, Reflective listening, and Summarizing) principle that helps patients to present their perceptions, and clinicians to summarize.

Any adverse effects that may occur during the intervention period will be reported for safety monitoring and future data interpretation analysis.[42] Adverse effects are defined as all-cause mortality, hospitalization for CVD or serious atrial or ventricular arrhythmia, musculoskeletal problems (muscle, tendon or joint problems) or other diseases preventing exercise participation. Constant supervision of the CB –CR exercise program and the existence of a defibrillator will ensure the participants' safety. Whilst for the TELE – CR group, real time exercise telemonitoring via videoconference platforms and exercise training within the prescribed HR zone will ensure safety. Table 6 summarizes the indications for dropping out training sessions.

Table 6. Indications for dropping out training session

• Exercise induced angina
• Fatigue, shortness of breath, dizziness, sweating, cyanosis, headache
• Orthostatic hypotension, drop in SBP> 20 mmHg during exercise
• SBP≥ 220 mmHg, DBP ≥ 110 mmHg
• HR drop (> 10 bpm) during exercise
• Ventricular tachycardia (> 120 bpm)
• When participant reaches the intensity limit of the exercise

SPB: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate

Participants who might withdraw from the study will consent for follow-up assessment of at least the primary outcomes and will be willing to continue with assessments for other outcomes, if they wish to.

Auditing of the study is planned to be performed by periodic- in person- visits of the trial investigator at the hospital facilities or via telephone conducts with the leading physiotherapist of the corresponding hospital.

Any substantive protocol amendments will be reviewed by the institutional review boards/research ethics committees (IRBs/RECs) of the UNIVERSITY OF Thessaly and will be will be communicated to all relevant stakeholders (REC/IRBs, trial registries)

Centre – based Cardiac Rehabilitation group (CB- CR group)

Participants will attend a supervised, individually tailored, exercise - based CR program at the hospital's facilities. CB-CR participants will be instructed to wear an accelerometer during the entire study period. Due to the accelerometer's storage capacity of 30 days, recorded data will be uploaded with a USB-connection and stored in the hospital server in an encrypted way on a monthly basis. Total training attendance rate will be documented by the hospital's staff

Telerehabilitation group (TELE - CR group)

Participants in the TELE-CR group will undertake three training sessions (or more if needed) in the hospital's outpatient clinic for familiarization with the use of the wearable sensors, the uploading of the training data to the web application (Polar Flow) and the exercising within their individually determined exercise intensity.

Following the training period, TELE-CR participants will be lent a Polar H10 chest strap that records HR data and a wrist sports watch (Polar M430, Kempele, Finland) and will proceed with the telerehabilitation program at their homes. Both wearable sensors are validated and reliable tools, allowing effective assessment of exercise intensity[43] and will be used only during the exercise training sessions. The wrist sports watch will display continuous HR reading from the Polar H10 chest strap, enabling patients to exercise within their prescribed HR zone and exercise data (duration, training mode, physical activity tracking). Participants in the TELE-CR group will be exercising in groups of up to maximum 5 participants in each session. Real time supervision of this group – based exercise session by a specialized physiotherapist will be implemented via videoconference web platforms or applications. At the end of every training session, patients will upload training data to the web platform (Polar Flow) via Bluetooth or USB connection. Each patient will have his/her username and login account and can check his/her training data graphically and correlate it to his/her personal goals. CR specialized staff from the corresponding hospital will have access to all patients' accounts so as to monitor successful data uploading, assess the collected data and provide them with training feedback once a week via telephone video calls. Uploaded data will be further backed up to an external hard drive to be

processed and evaluated by the trial investigator after the completion of the intervention.

Additionally, all patients will be lent a tri-axial accelerometer (Actigraph wGT3X, Actigraph), that they will wear around their waist during the 12 week intervention period. Patients should visit the hospital's outpatient clinic on a monthly basis to upload the recorded data to a secure PC application in an encrypted manner. Training adherence will be monitored by the specialized physiotherapist supervising the telerehabilitation exercise sessions.

OUTCOME MEASURES

Primary outcome

The primary outcome will be the assessment of the cardiorespiratory fitness, at baseline, the completion of the intervention (A_{12}) and follow up (A_{36}) in all study groups (CB-CR, TELE-CR).

Secondary outcomes

Secondary outcomes will be the physical activity level, safety, health related quality of life (HRQoL), training adherence, depression and anxiety levels, nicotine dependence and cost effectiveness. Physical activity, HRQoL, nicotine dependence and psychosocial well-being will be measured and assessed at baseline, end of intervention (A_{12}) and follow up (A_{36}). Training adherence and cost evaluation will be assessed at the completion of the intervention (A_{12}).

MEASUREMENTS

Cardiorespiratory fitness

CRF will be assessed in all study groups by peak oxygen uptake (peak VO2), determined by CPET and a 6MWT at the corresponding hospital at baseline, at the completion of the intervention (A12) and follow up (A36). CPET will be set according to recommendations of ESC and the American Heart Association. [44 45] The test will be performed on a cycle ergometer, using an individual ramp protocol aiming at total test duration of 8'–12'. Patients will be instructed to maintain a pedalling frequency of 60-70 rounds per minute. A twelve lead ECG and blood pressure will be recorded continuously during the test. Peak VO2 will be defined as the average value during the last 30" of exercise. Patients will be encouraged to exercise until they reach respiratory exchange ratio (RER) ≥1.15. If a participant fails to achieve a RER≥1.15, he/she will be excluded from the study. A cardiologist will be present while testing to deal with any emergencies that may arise.

Physical Activity

Daily physical activity (PA) will be measured via a tri-axial accelerometer (ActiGraph wGT3X, ActiGraph) at baseline and at the completion of the intervention (A_{12}). The ActiGraph will be worn continuously and has been previously identified as a reliable PA tool [46 47] validated, in healthy and cardiac patients. [48 49]

The self-reported PA will be assessed at all three assessments endpoints, by the offline international physical activity questionnaire, adopted in the Greek language (IPAQ-Gr) that presents acceptable reliability and high repeatability values.[50]

Cost-effectiveness

The cost-effectiveness analysis will be performed using the assessment of Quality-adjusted life years (QALYs) at baseline (A_0) and end of intervention (A_{12}).Patients will complete the EQ-5D questionnaire (EuroQol-5D) individually[51]and their final scores will be converted into QALYs. The cardiovascular readmission costs (as derived from the invoices from the hospital's financial department), the cardiologist follow-up visits and the diagnostic tests will constitute the healthcare costs. The CB-CR costs will be calculated based on the price list of medical expenses provided by hospital regarding professional wages (physiotherapist, cardiologist), exercise testing assessment costs, and transportation costs to and from the patients' homes to the hospital. In the TELE-CR group the costs will include the purchase of the necessary equipment and consumables (internet connection subscription, telephone communication cost).

The cost / benefit analysis will result from the calculation of the incremental cost-effectiveness ratio (ICER):

$$ICER = (cost_{\text{intervention group}} - cost_{\text{control group}}) / (effectiveness_{\text{intervention group}} - effectiveness_{\text{control group}}).$$

Incremental cost refers to the difference/patient, in the total average cost between the intervention (TELE-CR) and the control group (CB-CR). Incremental effectiveness is defined as the difference in the mean change in QALYs between the study groups**.**

Anxiety and depression/Smoking cessation

Anxiety/depression rates and nicotine dependence will be assessed at all three assessment points. Anxiety levels will be evaluated through the Greek version of the Hospital Anxiety and Depression Scale (HADS) that comprises of 7 items, each for

anxiety and depression subscales.[52] HADS is a validated measure to assess anxiety and depression symptoms, recommended for CAD patients.[53 54] Nicotine dependence will be assessed through the Fagestrom Test for Nicotine Dependence.

Training adherence

Patients' training adherence is defined as a percentage of the total number of completed training sessions (100%=36). Patients' adherence in both study groups will be recorded by the supervising hospital outpatient clinic's staff and will be evaluated at the end of intervention (A_{12}).

STATISTICAL ANALYSIS

Normality of data will be examined with Kolmogorov-Smirnov tests. Descriptive statistics will be used to report demographics and baseline characteristics. Between-group and within group differences in the outcome measures will be evaluated using multivariate analysis of variance (MANOVA). The effectiveness of the control (CB-CR) and intervention (TELE-CR) group will be examined with dependent t-test for each group (pre- and post-scores). All participants will be included in an intention to treat analysis, regardless of adherence, for at least the assessment of the primary outcomes. Significance level will be set at P=0.05. Statistical Package for Social Sciences (SPSS), version 25, will be used for all data analysis.

Sample size calculation

The calculation of the sample size was performed with G * Power 3.1.9.4 software. For test F, h detection of moderate effect size (f = 0.3) after the interaction test (α level = 0.05, 80%) a total of 111 participants were required to examine the recurrent MANOVA. After adjusting for potential drop-outs (estimated attrition rate ≤ 10%) a

minimum sample of 124 participants is required. Therefore, at least 62 participants will be recruited in each group.

ETHICS AND DISSEMINATION

The study protocol is approved by the Ethics Committee of the University of Thessaly (#1108/01-12-2021) and by the Ethics Committee of the General University Hospital of Larissa. Written informed consent will be obtained from all study participants prior to their enrollment to the study intervention.

The findings of this study will be disseminated at a local, national and international level through publications in peer-reviewed journals, national and international conference presentations, social, broadcast and print media. Additionally all study participants will receive the study findings through electronic and postal mail.

DISCUSSION

This trial is aiming to evaluate the efficacy, the efficiency and the safety of an exercise-based telerehabilitation program using wearable sensors and web applications compared to a traditional supervised center - based CR.

The objective assessment of functional capacity through CPET and the objective monitoring and recording of exercising and physical activity via the use of wearable sensors are the main features of this study that increase its reliability. Objective measurement of PA and training intensity, using accelerometer and heart rate data is suggested to be more reliable than using questionnaires than self-reported PA[55-57] or than the perceived rate of exertion on its own.[55]

Although a cost-effectiveness analysis is almost prerequisite for any novel intervention, only a few telerehabilitation studies have performed one. Frederix et al. have showed the cost - effectiveness of an internet-based telerehabilitation program.[28] Whilst Kidholm et al. outlined the non-cost effectiveness of a telerehabilitation program compared to center-based CR.[58] In our study, we intent to include a comprehensive cost- effectiveness analysis to evaluate any possible economic gains.

Moreover, the geographical features of Greece, with many islands and remote areas, contribute to the care inequality being observed, combined with the high variability of access to primary care professionals.[59] CR is almost absent from the Greek public health system, partly owing to the lack of clinics and training in its delivery. Furthermore, while some studies have already investigated the implications of telerehabilitation in other diseases, such COPD, with favorable outcomes,[60] no similar study, to our knowledge, has not yet been carried out for CAD patients, leaving a great gap open. In accordance to these statements recent guidelines support the implementation of home-based CR, telehealth, and mHealth interventions, with the use of wearable activity trackers to increase cardiac patients' participation rates and long-term adherence to healthy behaviors.[11]

Therefore, there is an urgent need for innovative, safe, more cost-effective CR strategies. If an exercise based telerehabilitation program, using wearable sensors, meets these prerequisites, it can act as a supplementary and/or substitutional (according to the needs) to traditional center - based CR in CAD patients of low to moderate cardiac risk, thus allowing more patients to have access to CR with the least possible economic burden.

FOOTNOTES

Contributorship statement

VA, GP conceived the study design, and AX,GG,KG,JS, KD, EK contributed to the conception of the design. LB, KD drafted the manuscript, and all authors reviewed several drafts of the manuscript. All authors approved the final manuscript to be published.

Conflicts of interests

The authors declare that they have no conflicts of interests.

Funding statement

This work was supported by the Ministry of Health of the Czech Republic project for conceptual development in research organizations, ref. no. 65269705 (University Hospital Brno, Brno, Czech Republic).

Data sharing statement

The trial protocol, the full study report and the statistical code for generating the results will be made publicly available through publications in peer reviewed journals and trial registries

.

References

1. Bansilal S, Castellano JM, Fuster V. Global burden of CVD: focus on secondary prevention of cardiovascular disease. *International journal of cardiology*

2015;201 Suppl 1:S1-7. doi: 10.1016/s0167-5273(15)31026-3 [published Online First: 2016/01/10]

2. Kyu HH, Abate D, Abate KH, et al. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet* 2018;392(10159):1859-922. doi: 10.1016/S0140-6736(18)32335-3

3. Cook C, Cole G, Asaria P, et al. The annual global economic burden of heart failure. *International journal of cardiology* 2014;171(3):368-76. doi: 10.1016/j.ijcard.2013.12.028 [published Online First: 2014/01/09]

4. Savarese G, Lund LH. Global Public Health Burden of Heart Failure. *Card Fail Rev* 2017;3(1):7-11. doi: 10.15420/cfr.2016:25:2 [published Online First: 2017/08/09]

5. Abreu A, Pesah E, Supervia M, et al. Cardiac rehabilitation availability and delivery in Europe: How does it differ by region and compare with other high-income countries?: Endorsed by the European Association of Preventive Cardiology. *European journal of preventive cardiology* 2019;26(11):1131-46. doi: 10.1177/2047487319827453 [published Online First: 2019/02/21]

6. Vos T, Lim SS, Abbafati C, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet* 2020;396(10258):1204-22. doi: 10.1016/S0140-6736(20)30925-9

7. Kotseva K, De Backer G, De Bacquer D, et al. Lifestyle and impact on cardiovascular risk factor control in coronary patients across 27 countries: Results from the European Society of Cardiology ESC-EORP EUROASPIRE

V registry. *European journal of preventive cardiology* 2019;26(8):824-35. doi: 10.1177/2047487318825350 [published Online First: 2019/02/12]

8. Touloumi G, Karakosta A, Kalpourtzi N, et al. High prevalence of cardiovascular risk factors in adults living in Greece: the EMENO National Health Examination Survey. *BMC Public Health* 2020;20(1):1665. doi: 10.1186/s12889-020-09757-4
9. Piepoli MF, Hoes AW, Brotons C, et al. Main messages for primary care from the 2016 European Guidelines on cardiovascular disease prevention in clinical practice. *The European journal of general practice* 2018;24(1):51-56. doi: 10.1080/13814788.2017.1398320 [published Online First: 2017/11/24]
10. 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. *European journal of preventive cardiology* 2021;28(5):460-95. doi: 10.1177/2047487320913379
11. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC). *European heart journal* 2021 doi: 10.1093/eurheartj/ehab484
12. Sandercock GR, Cardoso F, Almodhy M, et al. Cardiorespiratory fitness changes in patients receiving comprehensive outpatient cardiac rehabilitation in the

UK: a multicentre study. *Heart* 2013;99(11):785-90. doi: 10.1136/heartjnl-2012-303055 [published Online First: 2012/11/28]

13. Anderson L, Oldridge N, Thompson DR, et al. Exercise-Based Cardiac Rehabilitation for Coronary Heart Disease: Cochrane Systematic Review and Meta-Analysis. *Journal of the American College of Cardiology* 2016;67(1):1-12. doi: 10.1016/j.jacc.2015.10.044 [published Online First: 2016/01/15]
14. Salzwedel A, Jensen K, Rauch B, et al. Effectiveness of comprehensive cardiac rehabilitation in coronary artery disease patients treated according to contemporary evidence based medicine: Update of the Cardiac Rehabilitation Outcome Study (CROS-II). *European journal of preventive cardiology* 2020;27(16):1756-74. doi: 10.1177/2047487320905719 [published Online First: 2020/02/23]
15. de Vries H, Kemps HM, van Engen-Verheul MM, et al. Cardiac rehabilitation and survival in a large representative community cohort of Dutch patients. *European heart journal* 2015;36(24):1519-28. doi: 10.1093/eurheartj/ehv111 [published Online First: 2015/04/19]
16. Long L, Mordi IR, Bridges C, et al. Exercise-based cardiac rehabilitation for adults with heart failure. *The Cochrane database of systematic reviews* 2019;1(1):Cd003331. doi: 10.1002/14651858.CD003331.pub5 [published Online First: 2019/01/30]
17. Neubeck L, Freedman SB, Clark AM, et al. Participating in cardiac rehabilitation: a systematic review and meta-synthesis of qualitative data. *European journal of preventive cardiology* 2012;19(3):494-503. doi: 10.1177/1741826711409326 [published Online First: 2012/07/11]

18. Dunlay SM, Witt BJ, Allison TG, et al. Barriers to participation in cardiac rehabilitation. *American heart journal* 2009;158(5):852-9. doi: 10.1016/j.ahj.2009.08.010 [published Online First: 2009/10/27]

19. Ruano-Ravina A, Pena-Gil C, Abu-Assi E, et al. Participation and adherence to cardiac rehabilitation programs. A systematic review. *International journal of cardiology* 2016;223:436-43. doi: 10.1016/j.ijcard.2016.08.120 [published Online First: 2016/08/25]

20. Sari DM, Wijaya LCG. Cardiac rehabilitation via telerehabilitation in COVID-19 pandemic situation. *The Egyptian Heart Journal* 2021;73(1):31. doi: 10.1186/s43044-021-00156-7

21. Besnier F, Gayda M, Nigam A, et al. Cardiac Rehabilitation During Quarantine in COVID-19 Pandemic: Challenges for Center-Based Programs. *Arch Phys Med Rehabil* 2020;101(10):1835-38. doi: 10.1016/j.apmr.2020.06.004 [published Online First: 2020/06/27]

22. Ambrosetti M, Abreu A, Cornelissen V, et al. Delphi consensus recommendations on how to provide cardiovascular rehabilitation in the COVID-19 era. *European journal of preventive cardiology* 2021;28(5):541-57. doi: 10.1093/eurjpc/zwaa080

23. Batalik L, Dosbaba F, Hartman M, et al. Long-term exercise effects after cardiac telerehabilitation in patients with coronary artery disease: 1-year follow-up results of the randomized study. *European journal of physical and rehabilitation medicine* 2021 doi: 10.23736/s1973-9087.21.06653-3 [published Online First: 2021/02/24]

24. Batalik L, Pepera G, Papathanasiou J, et al. Is the Training Intensity in Phase Two Cardiovascular Rehabilitation Different in Telehealth versus Outpatient

Rehabilitation? *Journal of Clinical Medicine* 2021;10(18) doi: 10.3390/jcm10184069

25. Batalik L, Konecny V, Dosbaba F, et al. Cardiac rehabilitation based on the walking test and telerehabilitation improved cardiorespiratory fitness in people diagnosed with coronary heart disease during the covid-19 pandemic. *International Journal of Environmental Research and Public Health* 2021;18(5):1-11. doi: 10.3390/ijerph18052241
26. Kraal JJ, Peek N, Van den Akker-Van Marle ME, et al. Effects of home-based training with telemonitoring guidance in low to moderate risk patients entering cardiac rehabilitation: short-term results of the FIT@Home study. *European journal of preventive cardiology* 2014;21(2 Suppl):26-31. doi: 10.1177/2047487314552606 [published Online First: 2014/10/31]
27. Piotrowicz E, Piotrowicz R, Opolski G, et al. Hybrid comprehensive telerehabilitation in heart failure patients (TELEREH-HF): A randomized, multicenter, prospective, open-label, parallel group controlled trial—Study design and description of the intervention. *American heart journal* 2019;217:148-58. doi: 10.1016/j.ahj.2019.08.015
28. Frederix I, Solmi F, Piepoli MF, et al. Cardiac telerehabilitation: A novel cost-efficient care delivery strategy that can induce long-term health benefits. *European journal of preventive cardiology* 2017;24(16):1708-17. doi: 10.1177/2047487317732274 [published Online First: 2017/09/20]
29. Maddison R, Rawstorn JC, Stewart RAH, et al. Effects and costs of real-time cardiac telerehabilitation: randomised controlled non-inferiority trial. *Heart* 2019;105(2):122. doi: 10.1136/heartjnl-2018-313189

30. Brouwers RWM, van Exel HJ, van Hal JMC, et al. Cardiac telerehabilitation as an alternative to centre-based cardiac rehabilitation. *Netherlands heart journal : monthly journal of the Netherlands Society of Cardiology and the Netherlands Heart Foundation* 2020;28(9):443-51. doi: 10.1007/s12471-020-01432-y [published Online First: 2020/06/05]

31. Cavalheiro AH, Silva Cardoso J, Rocha A, et al. Effectiveness of Tele-rehabilitation Programs in Heart Failure: A Systematic Review and Meta-analysis. *Health Serv Insights* 2021;14:11786329211021668-68. doi: 10.1177/11786329211021668

32. Jin K, Khonsari S, Gallagher R, et al. Telehealth interventions for the secondary prevention of coronary heart disease: A systematic review and meta-analysis. *European journal of cardiovascular nursing : journal of the Working Group on Cardiovascular Nursing of the European Society of Cardiology* 2019;18(4):260-71. doi: 10.1177/1474515119826510 [published Online First: 2019/01/23]

33. Subedi N, Rawstorn JC, Gao L, et al. Implementation of Telerehabilitation Interventions for the Self-Management of Cardiovascular Disease: Systematic Review. *JMIR mHealth and uHealth* 2020;8(11):e17957. doi: 10.2196/17957 [published Online First: 2020/11/28]

34. Batalik L, Filakova K, Batalikova K, et al. Remotely monitored telerehabilitation for cardiac patients: A review of the current situation. *World J Clin Cases* 2020;8(10):1818-31. doi: 10.12998/wjcc.v8.i10.1818

35. Chan A-W, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Annals of internal medicine* 2013;158(3):200-07. doi: 10.7326/0003-4819-158-3-201302050-00583

36. Eysenbach G. CONSORT-EHEALTH: Improving and Standardizing Evaluation Reports of Web-based and Mobile Health Interventions. *Journal of medical Internet research* 2011;13(4):e126. doi: 10.2196/jmir.1923

37. 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. *European journal of preventive cardiology* 2020:2047487320913379. doi: 10.1177/2047487320913379 [published Online First: 2020/04/01]

38. Hansen D, Abreu A, Ambrosetti M, et al. Exercise intensity assessment and prescription in cardiovascular rehabilitation and beyond: why and how: a position statement from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology. *European journal of preventive cardiology* 2021 doi: 10.1093/eurjpc/zwab007

39. Hansen D, Mathijs W, Michiels Y, et al. Phase III multidisciplinary exercise-based rehabilitation is associated with fewer hospitalizations due to adverse cardiovascular events in coronary artery disease patients. *European journal of preventive cardiology* 2020 doi: 10.1093/eurjpc/zwaa038

40. La Scala Teixeira CV, Evangelista AL, Pereira PEA, et al. Complexity: A Novel Load Progression Strategy in Strength Training. *Front Physiol* 2019;10:839. doi: 10.3389/fphys.2019.00839 [published Online First: 2019/07/30]

41. Lee WW, Choi KC, Yum RW, et al. Effectiveness of motivational interviewing on lifestyle modification and health outcomes of clients at risk or diagnosed with

cardiovascular diseases: A systematic review. *Int J Nurs Stud* 2016;53:331-41. doi: 10.1016/j.ijnurstu.2015.09.010 [published Online First: 2015/10/24]

42. Pepera GB, Paul D;Sandercock, Gavin R H. A pilot study to investigate the safety of exercise training and testing in cardiac rehabilitation patients. *The British Journal of Cardiology* 2013;20:78. doi: http://dx.doi.org/10.5837/bjc.2013.012
43. Bethell HJ. Exercise-based cardiac rehabilitation. *Medicine (Baltimore)* 2006;34(5):195-96. doi: 10.1383/medc.2006.34.5.195
44. Guazzi M, Arena R, Halle M, et al. 2016 focused update: clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *European heart journal* 2018;39(14):1144-61. doi: 10.1093/eurheartj/ehw180 [published Online First: 2016/05/04]
45. Fletcher GF, Ades PA, Kligfield P, et al. Exercise standards for testing and training: A scientific statement from the American heart association. *Circulation* 2013;128(8):873-934. doi: 10.1161/CIR.0b013e31829b5b44
46. Santos-Lozano A, Santín-Medeiros F, Cardon G, et al. Actigraph GT3X: Validation and Determination of Physical Activity Intensity Cut Points. *Int J Sports Med* 2013;34(11):975-82. [published Online First: 22.05.2013]
47. Mâsse LC, Fuemmeler BF, Anderson CB, et al. Accelerometer data reduction: a comparison of four reduction algorithms on select outcome variables. *Medicine and science in sports and exercise* 2005;37(11 Suppl):S544-54. doi: 10.1249/01.mss.0000185674.09066.8a [published Online First: 2005/11/19]
48. Van Remoortel H, Raste Y, Louvaris Z, et al. Validity of six activity monitors in chronic obstructive pulmonary disease: a comparison with indirect calorimetry. *PloS one* 2012;7(6):e39198. doi: 10.1371/journal.pone.0039198 [published Online First: 2012/06/30]

49. Healy GN, Matthews CE, Dunstan DW, et al. Sedentary time and cardio-metabolic biomarkers in US adults: NHANES 2003-06. *European heart journal* 2011;32(5):590-7. doi: 10.1093/eurheartj/ehq451 [published Online First: 2011/01/13]

50. Papathanasiou G, Georgoudis G, Papandreou M, et al. Reliability Measures of the Short International Physical Activity Questionnaire (IPAQ) in Greek Young Adults. *Hellenic journal of cardiology : HJC = Hellēnikē kardiologikē epitheōrēsē* 2009;50:283-94.

51. Kontodimopoulos N, Pappa E, Niakas D, et al. Validity of the EuroQoL (EQ-5D) instrument in a Greek general population. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2008;11(7):1162-9. doi: 10.1111/j.1524-4733.2008.00356.x [published Online First: 2008/05/21]

52. Rishi P, Rishi E, Maitray A, et al. Hospital anxiety and depression scale assessment of 100 patients before and after using low vision care: A prospective study in a tertiary eye-care setting. *Indian journal of ophthalmology* 2017;65(11):1203-08. doi: 10.4103/ijo.IJO_436_17

53. Bjelland I, Dahl AA, Haug TT, et al. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *Journal of psychosomatic research* 2002;52(2):69-77. doi: 10.1016/s0022-3999(01)00296-3 [published Online First: 2002/02/08]

54. Michopoulos I, Kalkavoura C, Michalopoulou P, et al. [Hospital anxiety and depression scale (HADS): Validation in a Greek general hospital sample]. *Psychiatrike = Psychiatriki* 2007;18(3):217-24. [published Online First: 2007/07/01]

55. Butte NF, Ekelund U, Westerterp KR. Assessing physical activity using wearable monitors: measures of physical activity. *Medicine and science in sports and exercise* 2012;44(1 Suppl 1):S5-12. doi: 10.1249/MSS.0b013e3182399c0e [published Online First: 2011/12/23]

56. Warren JM, Ekelund U, Besson H, et al. Assessment of physical activity - a review of methodologies with reference to epidemiological research: a report of the exercise physiology section of the European Association of Cardiovascular Prevention and Rehabilitation. *Eur J Cardiovasc Prev Rehabil* 2010;17(2):127-39. doi: 10.1097/HJR.0b013e32832ed875 [published Online First: 2010/03/11]

57. Westerterp KR. Reliable assessment of physical activity in disease: an update on activity monitors. *Curr Opin Clin Nutr Metab Care* 2014;17(5):401-6. doi: 10.1097/mco.0000000000000080 [published Online First: 2014/08/12]

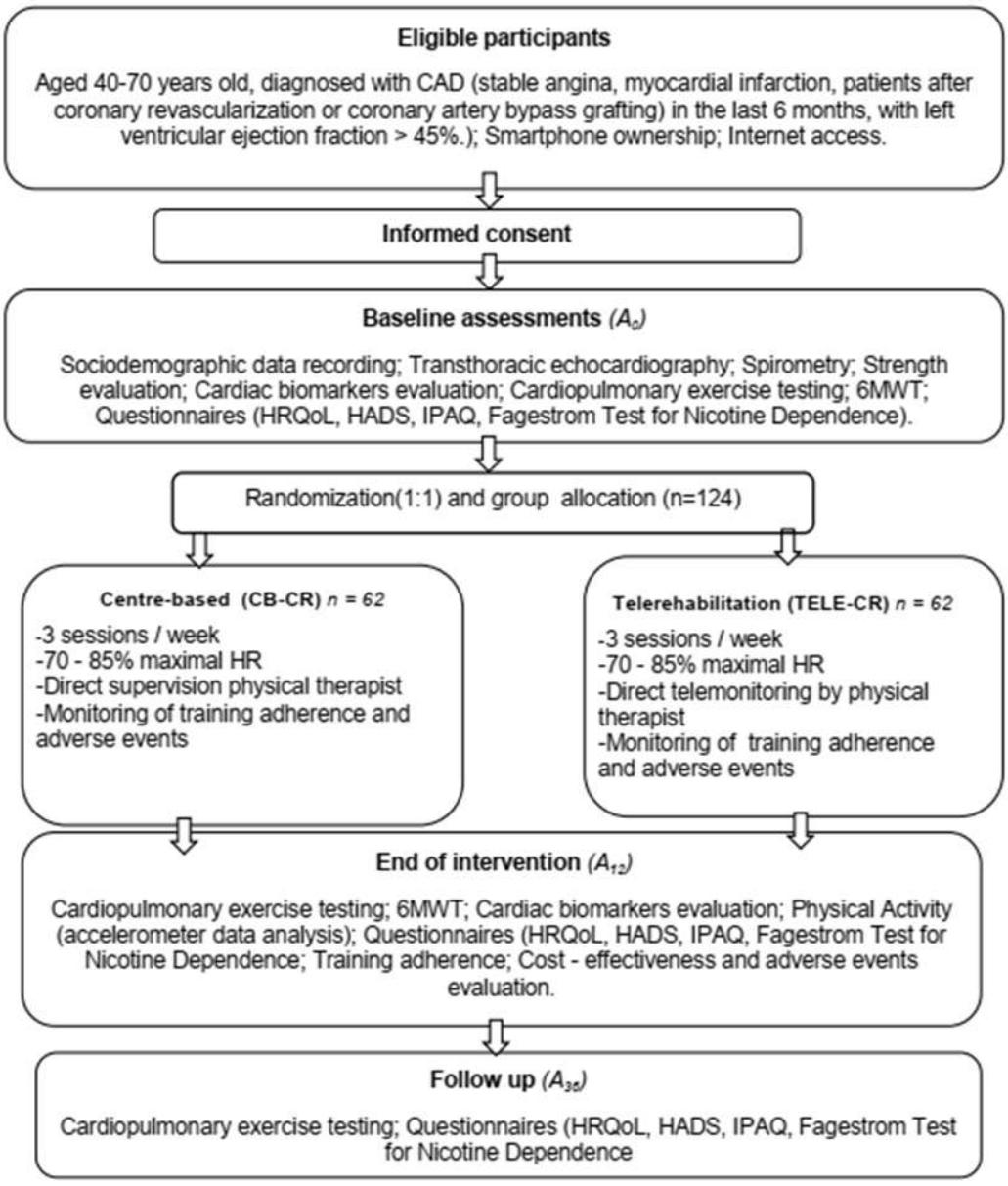
58. Kidholm K, Rasmussen MK, Andreasen JJ, et al. Cost-Utility Analysis of a Cardiac Telerehabilitation Program: The Teledialog Project. *Telemedicine journal and e-health : the official journal of the American Telemedicine Association* 2016;22(7):553-63. doi: 10.1089/tmj.2015.0194 [published Online First: 2015/12/30]

59. Network HFP. Heart failure policy and practice in Europe: Greece, 2020.

60. Vasilopoulou M, Papaioannou AI, Kaltsakas G, et al. Home-based maintenance tele-rehabilitation reduces the risk for acute exacerbations of COPD, hospitalisations and emergency department visits. *European Respiratory Journal* 2017;49(5):1602129. doi: 10.1183/13993003.02129-2016

.

Fig 1 Flowchart of the study design



HR: heart rate, HRQoL: Health related quality of life, HADS: Hospital Anxiety and Depression scale, IPAQ: International Physical Activity Questionnaire, CAD: Coronary Artery Disease

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered,	3,6

		name of intended registry	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	n/a
Funding	#4	Sources and types of financial, material, and other support	35
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 25
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	25
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a

Introduction

Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg,	9,10

		surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12-19
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	17
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	17,19
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	19-22
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7-8

Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	22
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	17,18, 20-22
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	17
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values).	17-19

		Reference to where details of data management procedures can be found, if not in the protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	22
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	22
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial	16-17

		conduct	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	23
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	17
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	9
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9,19
Declaration of	#28	Financial and other competing interests for principal	25

interests		investigators for the overall trial and each study site	
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	23
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	25
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

Notes:

- 18a: 15,16,18-20 The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons Attribution License CC-BY-NC. This checklist was completed on 05. December 2021 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Efficacy, Efficiency and Safety of a Cardiac Telerehabilitation Program Using Wearable Sensors in Coronary Heart Disease Patients: TELEWEAR-CR study protocol.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-059945.R1
Article Type:	Protocol
Date Submitted by the Author:	16-Mar-2022
Complete List of Authors:	Antoniou, Varsamo; University of Thessaly School of Health Sciences, Clinical Exercise Physiology and Rehabilitation Laboratory, Department of Physiotherapy Xanthopoulos, Andrew; University of Thessaly Faculty of Medicine, Cardiology Giamouzis, Gregory; University of Thessaly Faculty of Medicine, Cardiology Davos, Constantinos ; Biomedical Research Foundation of the Academy of Athens, Cardiovascular Research Batalik, Ladislav; University Hospital Brno, Rehabilitation; Department of Rehabilitation, University Hospital Brno, Czech Republic Stavrou, Vasileios; University of Thessaly Faculty of Medicine, Laboratory of Cardio-Pulmonary Testing, Department of Respiratory Medicine Gourgoulianis, Konstantinos; University of Thessaly Faculty of Medicine, Laboratory of Cardio-Pulmonary Testing, Department of Respiratory Medicine Kapreli, Eleni; University of Thessaly School of Health Sciences, Clinical Exercise Physiology and Rehabilitation Laboratory, Department of Physiotherapy Skoularigis, John; University of Thessaly Faculty of Medicine, Cardiology Pepera, Garyfallia; University of Thessaly School of Health Sciences, Department of Physiotherapy, Clinical Exercise Physiology and Rehabilitation Laboratory
Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS, REHABILITATION MEDICINE, Cardiology < INTERNAL MEDICINE

TITLE PAGE

Efficacy, Efficiency and Safety of a Cardiac Telerehabilitation Program Using Wearable Sensors in Coronary Heart Disease Patients: The TELEWEAR-CR study protocol

Authors

Varsamo Antoniou, PT, BSc, MSc, PhD$_{(c)}$[a]
Andrew Xanthopoulos, MD, PhD[b]
Gregory Giamouzis, MD, PhD[b]
Konstantinos Davos, MD, PhD, FESC[c]
Ladislav Batalik, PT, MSc, PhD[d,e]
Vasileios Stavrou, BSc, MSc, PhD[f]
Konstantinos I. Gourgoulianis MD, PhD[f]
Eleni Kapreli, PT, BSc, MSc, PhD[a]
John Skoularigis, MD, PhD[b]
Garyfallia Pepera, PT, BSc, MSc, PhD[a]

[a] Clinical Exercise Physiology and Rehabilitation Laboratory, Department of Physiotherapy, School of Health Sciences, University of Thessaly, Lamia**,** Greece
[b] Department of Cardiology, Faculty of Medicine School of Health Sciences, University of Thessaly Larissa Greece.
[c] Cardiovascular Research Laboratory, Biomedical Research Foundation, Academy of Athens, 4 Soranou Ephessiou Street, 115 27, Athens, Greece
[d] Department of Rehabilitation, University Hospital Brno, Jihlavska 20, Brno, 62500, Czech Republic
[e] Department of Public Health, Masaryk University Brno, Zerotinovo nam. 617/9, Brno, 601 77, Czech Republic
[f] Laboratory of Cardio-Pulmonary Testing, Department of Respiratory Medicine, Faculty of Medicine, University of Thessaly, Larissa, Greece

Corresponding author:

Garyfallia Pepera

Assistant Professor in Cardiac Rehabilitation, Clinical Exercise Physiology & Rehabilitation Research Laboratory, Physiotherapy Department, Faculty of Health Sciences, University of Thessaly, Lamia, Greece.

3rd km of Old National Road, GR-35100 Lamia, Greece

Tel: +302231060207

e-mail: gpepera@uth.gr

Antoniou A. e-mail: varsamoantoniou@uth.gr

Xanthopoulos A. e-mail: andrewvxanth@gmail.com

Giamouzis G. e-mail: grgiamouzis@med.uth.gr

Davos C. e-mail: cdavos@bioacademy.gr

Batalik L. e-mail: Batalik.Ladislav@fnbrno.cz

Stavrou V. e-mail: vasileiosstavrou@hotmail.com

Gourgoulianis K. e-mail: kgourg@med.uth.gr

Kapreli E. e-mail: ekapreli@uth.gr

Skoularigis J. e-mail: iskoular@med.uth.gr

Pepera G. e-mail: gpepera@uth.gr

Word count: 3.435

Abstract

Introduction: Exercise – based cardiac rehabilitation (CR) is a beneficial tool for the secondary prevention of cardiovascular diseases with, however, low participation rates. Telerehabilitation, intergrading mobile technologies and wireless sensors, may advance the cardiac patients' adherence. This study will investigate the efficacy, efficiency, safety and cost-effectiveness of a telerehabilitation program based on objective exercise telemonitoring and evaluation of cardiorespiratory fitness.

Methods and Analysis: A supervised, parallel-group, single-blind, randomized controlled trial will be conducted. A total of 124 coronary disease patients will be randomized at a 1:1 ratio into two groups: intervention telerehabilitation group (TELE-CR) (n=62) and control, center – based cardiovascular rehabilitation group (CB-CR) (n=62). Participants will receive a 12 – week exercise based rehabilitation program; remotely monitored for the telerehabilitation group and standard supervised for the center – based group. All participants will train at 70% of their maximal heart rate, as obtained from cardiopulmonary exercise testing (CPET) for 40 minutes, three times/week. The primary outcomes will be the assessment of cardiorespiratory fitness, expressed as peak oxygen uptake assessed by the CPET test and the 6 minute walking test (6MWT). Secondary outcomes will be the physical activity, the safety of the exercise intervention, (number of adverse events that may occur during the exercise), the quality of life, the training adherence, the anxiety and depression levels, the nicotine dependence and cost – effectiveness. Assessments will be held at baseline, end of intervention (12 weeks) and follow up (36 weeks).

Ethics and dissemination: The study protocol has been reviewed and approved by the Ethics Committee of the University of Thessaly (1108/1-12-2021) and by the Ethics

Committee of the General University Hospital of Larissa (3780/31-12-2021). The results of this study will be disseminated through manuscript publications and conference presentations.

Keywords: cardiac rehabilitation; telerehabilitation; wearable sensors; cardiorespiratory fitness; functional capacity

Trial registration: Clinical Trial.gov, Identifier: NCT05019157. Registered 24 August 2021. https://clinicaltrials.gov/ct2/show/NCT05019157?cond=cardiac+telerehabilitation&country=GR&draw=2&rank=1

Strengths and limitations of this study

- Telelerehabilitation as an alternative tool to contemporary centre/community based cardiac rehabilitation.
- Intergrading real-time supervision and group-based exercise sessions in cardiac telerehabilitation.

  .
- Objective monitoring and evaluation of physical activity and exercise intensity in cardiac rehabilitation interventions.
- Inability, by study design, to blind participants to treatment allocation
- Possible selection bias, since only low and moderate cardiac risk patients will be recruited.

INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of morbidity and premature mortality globally.[1-5] Coronary artery diseases (CAD) account for the largest proportion of CVD mortality.[6] A systematic review by the Global Public Health Burden (GBD) reveals an increase of 11.8% in the mortality rates due to ischemic CVDs in Greece [6] with cardiac risk factors[7] being very common among Greek patients and without signs of future decline.[8] The increased rates of CVDs put additional pressure on the health care systems, especially under the ongoing austerity climate across Europe.

Cardiac rehabilitation (CR) can play a key role as a multidisciplinary secondary intervention aiming to the reduction of CVDs' risk factors, the adoption of healthy lifestyle behaviors and the minimization of disability among CVD patients.[9] Recent guidelines on CVD prevention recommend a multifaceted approach addressing exercise training, dietary counseling, smoking cessation, risk factor modification and psychosocial support.[10-12] A number of meta-analysis confirm the effectiveness of exercise training in reducing cardiovascular mortality, morbidity, re-hospitalizations rates,[13 14] physical inactivity and all CVD risk factors including blood pressure, blood lipid profile, glucose metabolism and weight status.[15 16] Despite global recommendations, patients' participation in CR programs is low, mainly due to insufficient medical referral, travel distance, low self-efficacy, perceived body image and lack of time.[17-19] Moreover, during the COVID-19 pandemic, new barriers have arisen, such as the suspension of centre-based CR and in-person sessions, travelling and circulation restrictions.[20 21] Thus the need to avoid the downgrading of CR is imperative.[22]

Rapid development in information and communication technologies (ICTs) may help to overcome the barriers to CR. [23-25] Telerehabilitation is proposed as a feasible, [26 27] safe and cost – effective intervention, [28 29] leading to long-term improvement of CVD risk factors, reduced healthcare costs and increased CR participation adherence. [30].Recent systematic reviews advocate to the use of telehealth interventions as an adjunct to CR [31-33] for the continuance of CR through pandemic circumstances. [20 21]

A recent review proclaims the integration of remote technologies and wearable sensors in the telerehabilitation, mentioning though the need for further investigation. [34] Another systematic review indicates that, software-enabled systems reduce timing-related barriers to patients' participation.[32] The feasibility and safety of cardiac telerehabilitation need further investigation since most relevant studies are not addressing safety matters and a formal cost - effectiveness analysis.[32 34]

Our study focuses on the objective recording and monitoring of the exercise implementation and physical activity, through the use of wearable sensors (heart rate monitors, accelerometers). Based on thorough literature review, it is the first study to integrate real time supervision (use of videoconference platforms) and a group based design for home exercising (up to 5 participants).

The primary aims of this study are to compare the effect between telerehabilitation and regular outpatient CR methods, related to cardiorespiratory fitness (CRF) and functional capacity. Whilst possible effects in physical activity, training adherence, health related quality of life (HRQoL), anxiety and depression levels , safety, nicotine dependence and cost – effectiveness are considered as secondary aims.

The hypothesis of the study will be that the telerehabilitation intervention will have at least the same efficiency with the regular, centre - based rehabilitation and that it will

be as safe as and even more cost-effective than the centre - based rehabilitation intervention.

METHODS

Study design

A supervised, parallel-group, single-blind, randomized controlled trial with 6 months follow-up will be employed. The study includes CAD patients, enrolled in a telerehabilitation group (TELE-CR) and a control group undertaking regular outpatient CR rehabilitation (CB-CR) for comparison reasons. Three assessments will take place at baseline (A_0), end of intervention (A_{12}) and follow up 36 weeks (A_{36}). A CONSORT (Consolidated Standard of Reporting Trials) flow diagram is shown in Fig. 1.

The study protocol complies with the SPIRIT 2013 statement guidelines[35] and the intervention procedures are described according to the CONSORT- E- HEALTH checklist.[36] We used the SPIRIT checklist when writing our report.[35] The trial is registered at ClinicalTrials.gov with registration number NCT05019157.

Table 1 presents a summary of the study schedule and assessments.

Table 1. Summary of study schedule

	Enrollment	Baseline (A_0)	End of Intervention (A_{12})	Follow Up (A_{36})
Eligibility screening	X			
Informed consent	X			
Randomization		X		
Allocation		X		
Interventions				
Center – based CR		←	→	
Telerehabilitation		←	→	
Assessments				
Demographic characteristics Spirometry, TTE		X x		
Strength evaluation test		X		
Cardiac biomarkers(BNP , NT proBNP, Troponines, CPK)		X	X	
CPET – 6MWT		X	X	X
HRQoL		X	X	X
HADS		X	X	X
IPAQ		X	X	X
FTND		X	X	X
Cost analysis			X	
Training Adherence			X	

TTE: Transthoracic echocardiography, CPET: cardiopulmonary exercise testing, 6MWT: 6 Minute Walking Test, BMP: B-type natriuretic peptide, CPK: Creatine phosphokinase, HRQoL: Health related quality of life, HADS: Hospital Anxiety and Depression scale, IPAQ: International Physical Activity Questionnaire FTND: Fagestrom Test for Nicotine Dependence

Patient population and eligibility

Patients will be recruited- prior to their hospital discharge- from the Cardiology Department of the General University Hospital of Larissa in Greece and will be screened for eligibility by the medical staff (cardiologists and medical physicians) of the corresponding hospital, according to the criteria shown in Table 2. Through risk stratification and pre – exercise assessment only low and moderate cardiac risk patients will be included in the study groups (Table 3). Risk stratification and pre-exercise procedures will be implemented by cardiologists and an exercise physiologist, trained in the CPET, from the corresponding hospital. Those who consent to participation will be screened for eligibility and will be provided with a trial information sheet (explanation of the study design and scopes, participants' responsibilities, confidentiality of the collected data) and a consent form to be signed. Basic sociodemographic data including sex, age, weight, height, cardiac diagnosis, pharmacologic treatment, educational level, place of residence and profession will also be collected.

Table 2. Inclusion and exclusion criteria	
Inclusion criteria	
i.	adults > 18 years old
ii.	diagnosed with coronary artery disease (CAD) (stable angina, myocardial infarction, patients after coronary revascularization or coronary artery bypass grafting) in the last 6 months, with left ventricular ejection fraction > 45%
iii.	current outpatients, stable for at least four weeks prior to the intervention enrollment
iv.	able to perform physical exercise,
v.	able to speak, read and write Greek
vi.	possession of a mobile phone/smartphone
vii.	internet access at home
Exclusion criteria	
i.	severe ventricular arrhythmia, with functional or prognostic significance or exercise – induced myocardial ischemia as assessed by CPET at baseline
ii.	heart failure
iii.	comorbidity precluding exercise training (e.g. orthopedic, neurological or cognitive conditions)
iv.	unstable angina
v.	uncontrolled atrial or ventricular arrhythmia
vi.	acute pulmonary embolism
vii.	acute myocarditis or pericardial effusion
viii.	uncontrolled diabetes mellitus (Type I, II)
ix.	severe obstructive respiratory disease (forced expiratory volume 1 (FEV1)<50%).

Table 3. Cardiac risk stratification

Low Risk	Moderate Risk	High Risk
-Absence of angina or other symptoms (eg unusual shortness of breath, mild headache or dizziness) -Functional capacity> 7 METs, left ventricular ejection fraction (LVEF) ≥ 50% -Absence of arrhythmia at rest -Absence of depression	- Presence of angina or other symptoms (eg unusual shortness of breath, mild headache or dizziness, dizziness occurring at high levels of exercise ≥ 7 METs) -Mild to moderate silent ischemia (ST eruption <2 mm) -Functional capacity> 5 METs -LVEF = 40-49%	-Presence of arrhythmias - Presence of angina or other symptoms (eg unusual breathlessness, mild headache or dizziness, dizziness occurring at high levels of exercise <5 METs) -Silent ischemia (ST stroke ≥ 2 mm) -Presence of abnormal hemodynamics during exercise (reduction of BP) or post-exercise hypotension -LEVF <40%

Randomization and blinding

A total of 124 eligible patients will be randomized, via a computerized randomization system, in a 1:1 ratio (adjusted for age and gender) into two groups: center-based CR (CB-CR) and telerehabilitation group (TELE-CR). The allocation will be hidden until the completion of the baseline assessment in sequentially numbered, sealed, opaque envelopes. Due to the nature of the intervention, both the participants and the hospital's staff supervising the exercise programs are unable to be blinded to the treatment allocation. The researchers, responsible for all study assessments, will be blinded to the intervention allocation. Primery investigators will be unaware of the randomization allocation until the completion of the intervention and the collection of all study data.

Patient and public involvement

There was no patient or public involvement in the design of this study (setting of the research question or the outcome measures). The patients will not be asked to take part either in the interpretation or the writing procedures of the results of this study.

Interventions

Individually determined CR programs will be implemented in both study groups based on the participants' referral diagnosis, physical fitness level and expected training goals. All participants will undertake a 12 – week, exercise - based CR program, including 3 training sessions of 60min/week. Exercise will be prescribed individually, according to the results of the baseline CPET and to the FITT [frequency, intensity, time (duration), and type of exercise] model.[37] Participants will exercise with an intensity of 70% of their maximal heart rate (HR_{max}), as assessed during baseline CPET and the 6MWT assessment and at a level of 12/20–14/20 of Borg scale.[10] Each exercise circuit will consist of 20 structured stations for aerobic, strength and balance training of 2min duration/station (Tables 4, 5). Aerobic progression will go through the duration, followed by an increase of 5–10% / week in the exercise intensity.[38 39] Progression in the resistance training involves, primarily, the achievement of the desired volume (number of training sets), followed by the gradual increase in intensity (amount of load lifted) and adaptations in density (rest periods).[38 40] Resistance training will follow a low pace, rest/recovery to work/contraction ratio: 2:1.[37] Participants in the CB-CR group will use free weights or machines for their resistance training, whilst participants in the TELE – CR group will exercise using their body weight or resistance bands. At the completion of the intervention, the effectiveness of the training program will be assessed and patients will be encouraged to maintain a physically active lifestyle.

However, no specific exercise prescription or face - to - face feedback will be provided until the follow - up assessment.

Table 4: CB-CR exercise program

Warm Up	
Cycling or mild treadmill walking	5 min
Stretching activities *Upper back *Chest *Lower back, waist mobility *Calf *Hamstring *Quadriceps	5 min
Main training part	
Aerobic Training	
Cycling or treadmill walking	Exercise with an intensity of 70% of the patients' maximal heart rate (HRmax) at a level of 12/20–14/20 of Borg scale
Strengthening Training	
*Biceps curls *Shoulder press *Triceps *Lateral fly *Front deltoid raise *Mini squats *Hamstring curls *Plantar flex *Side leg raise	12 repetitions 1 set/exercise, starting at 30 and 70% of one-repetition maximum (1RM) for the upper body and lower body respectively. Increase gradually to 70% of 1RM and 80% of 1RM for the upper and lower body, respectively
Balance Training	
*Standing on one foot *Walking heel to toe *Reaching -front -lateral -back	Starting with the patient's own body weight. Later add unstable surfaces
Duration 40 min 1RM: the maximum weight a patient can lift in one complete repetition for a given exercise in a controlled way through a full range of motion with good posture	
Cool Down	
*Cycling or mild treadmill walking *Moving hands slowly *Stretching exercises	10 min

Table 5: TELE-CR exercise program

Warm Up

Marching on the spot	5 min
Stretching activities *Upper back *Chest *Lower back, waist mobility *Calf *Hamstring *Quadriceps	5 min
Main training part	
Aerobic Training	
*Box stepping *Knee raises only -With hand to opposite knee -Hand to opposite ankle *Knee bends only -With swinging arms -With reaching arms *Side steps -Just tapping -With half arm lift -Reaching over *Marching -Heal lift only -With arms moving	10 repetitions 2 sets/ exercise
Strengthening Training	
*Biceps curls *Shoulder press *Triceps *Lateral fly *Front deltoid raise *Mini squats *Hamstring curls *Plantar flex *Side leg raise	12 repetitions 1 set/exercise, starting at 30 and 70% of one-repetition maximum (1RM) for the upper body and lower body respectively. Increase gradually to 70% of 1RM and 80% of 1RM for the upper and lower body, respectively
Balance Training	
*Standing on one foot *Walking heel to toe *Reaching -front -lateral -back	Starting with the patient's own body weight. Later add unstable surfaces
Duration 40 min 1RM: the maximum weight a patient can lift in one complete repetition for a given exercise in a controlled way through a full range of motion with good posture	
Cool Down	

*Marching on the spot gently *Moving hands slowly *Stretching exercises	10 min

Blood samplings will be taken, in all assessment endpoints, from all study participants to assess any effects of the intervention on the cardiac biomarkers' blood concentration (BNP, NT-proBNP, Troponines, CPK).

All patients will be receiving educational and informational videoconference sessions regarding issues of upright exercising, physical activity, diet/nutritional and smoking cessation counseling (based on recent guidelines)[10] and psychosocial support (via psychotherapy) on stress and anxiety management. Consultation sessions may include a family member or friend, especially for elderly patients.[41] Communication strategies such as motivational interviewing, during telephone calls or videoconferences, will be integrated, as they appear to be useful in helping promote patients' adherence and avoid incidents of early drop outs. Motivational interviewing will be based on the OARS (Open-ended questions, Affirmation, Reflective listening, and Summarizing) principle that helps patients to present their perceptions, and clinicians to summarize.

Any adverse effects that may occur during the intervention period will be reported for safety monitoring and future data interpretation analysis.[42] Adverse effects are defined as all-cause mortality, hospitalization for CVD or serious atrial or ventricular arrhythmia, musculoskeletal problems (muscle, tendon or joint problems) or other diseases preventing exercise participation. Constant supervision of the CB –CR exercise program and the existence of a defibrillator will ensure the participants' safety. Whilst for the TELE – CR group, real time exercise telemonitoring via videoconference

platforms and exercise training within the prescribed HR zone will ensure safety. Table 6 summarizes the indications for dropping out training sessions.

Table 6. Indications for dropping out training session

• Exercise induced angina
• Fatigue, shortness of breath, dizziness, sweating, cyanosis, headache
• Orthostatic hypotension, drop in SBP> 20 mmHg during exercise
• SBP≥ 220 mmHg, DBP ≥ 110 mmHg
• HR drop (> 10 bpm) during exercise
• Ventricular tachycardia (> 120 bpm)
• When participant reaches the intensity limit of the exercise

SPB: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate

Participants who might withdraw from the study will consent for follow-up assessment of at least the primary outcomes and will be willing to continue with assessments for other outcomes, if they wish to.

Auditing of the study is planned to be performed by periodic- in person- visits of the trial investigator at the hospital facilities or via telephone conducts with the leading physiotherapist of the corresponding hospital.

Any substantive protocol amendments will be reviewed by the institutional review boards/research ethics committees (IRBs/RECs) of the University of Thessaly and will be communicated to all relevant stakeholders (REC/IRBs, trial registries)

Centre – based Cardiac Rehabilitation group (CB- CR group)

Participants will attend a supervised, individually tailored, exercise - based CR program at the hospital's facilities. CB-CR participants will be instructed to wear an accelerometer during the entire study period. Due to the accelerometer's storage

capacity of 30 days, recorded data will be uploaded with a USB-connection and stored in the hospital server in an encrypted way on a monthly basis. Total training attendance rate will be documented by the hospital's staff

Telerehabilitation group (TELE - CR group)

Participants in the TELE-CR group will undertake three training sessions (or more if needed) in the hospital's outpatient clinic for familiarization with the use of the wearable sensors, the uploading of the training data to the web application (Polar Flow) and the exercising within their individually determined exercise intensity.

Following the training period, TELE-CR participants will be lent a Polar H10 chest strap that records HR data and a wrist sports watch (Polar M430, Kempele, Finland) and will proceed with the telerehabilitation program at their homes. Both wearable sensors are validated and reliable tools, allowing effective assessment of exercise intensity[43] and will be used only during the exercise training sessions. The wrist sports watch will display continuous HR reading from the Polar H10 chest strap, enabling patients to exercise within their prescribed HR zone and exercise data (duration, training mode, physical activity tracking). Participants in the TELE-CR group will be exercising in groups of up to maximum 5 participants in each session. Real time supervision of this group – based exercise session by a specialized physiotherapist will be implemented via videoconference web platforms or applications. At the end of every training session, patients will upload training data to the web platform (Polar Flow) via Bluetooth or USB connection. Each patient will have his/her username and login account and can check his/her training data graphically and correlate it to his/her personal goals. CR specialized staff from the corresponding hospital will have access to all patients' accounts so as to monitor successful data uploading, assess the collected

data and provide them with training feedback once a week via telephone video calls. Uploaded data will be further backed up to an external hard drive to be processed and evaluated by the trial investigator after the completion of the intervention.

Additionally, all patients will be lent a tri-axial accelerometer (Actigraph wGT3X, Actigraph), that they will wear around their waist during the 12 week intervention period. Patients should visit the hospital's outpatient clinic on a monthly basis to upload the recorded data to a secure PC application in an encrypted manner. Training adherence will be monitored by the specialized physiotherapist supervising the telerehabilitation exercise sessions.

OUTCOME MEASURES

Primary outcome

The primary outcome will be the assessment of the cardiorespiratory fitness, at baseline, the completion of the intervention (A_{12}) and follow up (A_{36}) in all study groups (CB-CR, TELE-CR).

Secondary outcomes

Secondary outcomes will be the physical activity level, safety, health related quality of life (HRQoL), training adherence, depression and anxiety levels, nicotine dependence and cost effectiveness. Physical activity, HRQoL, nicotine dependence and psychosocial well-being will be measured and assessed at baseline, end of intervention (A_{12}) and follow up (A_{36}). Training adherence and cost evaluation will be assessed at the completion of the intervention (A_{12}).

MEASUREMENTS

Cardiorespiratory fitness

CRF will be assessed in all study groups by peak oxygen uptake (peak VO2), determined by CPET and a 6MWT at the corresponding hospital at baseline, at the completion of the intervention (A12) and follow up (A36). CPET will be set according to recommendations of ESC and the American Heart Association. [44 45] The test will be performed on a cycle ergometer, using an individual ramp protocol aiming at total test duration of 8min–12min. Patients will be instructed to maintain a pedalling frequency of 60-70 rounds per minute. A twelve lead ECG and blood pressure will be recorded continuously during the test. Peak VO2 will be defined as the average value during the last 30sec of exercise. Patients will be encouraged to exercise until they reach respiratory exchange ratio (RER) ≥1.10. If a participant fails to achieve a RER≥1.10, he/she will be excluded from the study. A cardiologist will be present while testing to deal with any emergencies that may arise.

Physical Activity

Daily physical activity (PA) will be measured via a tri-axial accelerometer (ActiGraph wGT3X, ActiGraph) at baseline and at the completion of the intervention (A_{12}). The ActiGraph will be worn continuously and has been previously identified as a reliable PA tool [46 47] validated, in healthy and cardiac patients. [48 49]

The self-reported PA will be assessed at all three assessments endpoints, by the offline international physical activity questionnaire, adopted in the Greek language (IPAQ-Gr) that presents acceptable reliability and high repeatability values.[50]

Cost-effectiveness

The cost-effectiveness analysis will be performed using the assessment of Quality-adjusted life years (QALYs) at baseline (A_0) and end of intervention (A_{12}).Patients will complete the EQ-5D questionnaire (EuroQol-5D) individually[51]and their final scores will be converted into QALYs. The cardiovascular readmission costs (as derived from the invoices from the hospital's financial department), the cardiologist follow-up visits and the diagnostic tests will constitute the healthcare costs. The CB-CR costs will be calculated based on the price list of medical expenses provided by hospital regarding professional wages (physiotherapist, cardiologist), exercise testing assessment costs, and transportation costs to and from the patients' homes to the hospital. In the TELE-CR group the costs will include the purchase of the necessary equipment and consumables (internet connection subscription, telephone communication cost).

The cost / benefit analysis will result from the calculation of the incremental cost-effectiveness ratio (ICER):

$$ICER = (cost_{\text{intervention group}} - cost_{\text{control group}}) / (effectiveness_{\text{intervention group}} - effectiveness_{\text{control group}}).$$

Incremental cost refers to the difference/patient, in the total average cost between the intervention (TELE-CR) and the control group (CB-CR). Incremental effectiveness is defined as the difference in the mean change in QALYs between the study groups**.**

Anxiety and depression/Smoking cessation

Anxiety/depression rates and nicotine dependence will be assessed at all three assessment points. Anxiety levels will be evaluated through the Greek version of the Hospital Anxiety and Depression Scale (HADS) that comprises of 7 items, each for

anxiety and depression subscales.[52] HADS is a validated measure to assess anxiety and depression symptoms, recommended for CAD patients.[53 54] Nicotine dependence will be assessed through the Fagestrom Test for Nicotine Dependence.

Training adherence

Patients' training adherence is defined as a percentage of the total number of completed training sessions (100%=36). Patients' adherence in both study groups will be recorded by the supervising hospital outpatient clinic's staff and will be evaluated at the end of intervention (A_{12}). Based on the percentage of the sessions attended, participants will be categorized in adherent (> 80%), partly adherent (20 to 80%) and non-adherent (< 20%).

STATISTICAL ANALYSIS

Normality of data will be examined with Kolmogorov-Smirnov tests. Descriptive statistics will be used to report demographics and baseline characteristics. Between-group and within group differences in the outcome measures will be evaluated using multivariate analysis of variance (MANOVA). The effectiveness of the control (CB-CR) and intervention (TELE-CR) group will be examined with dependent t-test for each group (pre- and post-scores). All participants will be included in an intention to treat analysis, regardless of adherence, for at least the assessment of the primary outcomes. Significance level will be set at P=0.05. Statistical Package for Social Sciences (SPSS), version 25, will be used for all data analysis.

Sample size calculation

The calculation of the sample size was performed with G * Power 3.1.9.4 software. For test F, h detection of moderate effect size (f = 0.3) after the interaction test (α level =

0.05, 80%) a total of 111 participants were required to examine the recurrent MANOVA. After adjusting for potential drop-outs (estimated attrition rate ≤ 10%) a minimum sample of 124 participants is required. Therefore, at least 62 participants will be recruited in each group.

ETHICS AND DISSEMINATION

The study protocol is approved by the Ethics Committee of the University of Thessaly (#1108/01-12-2021) and by the Ethics Committee of the General University Hospital of Larissa. Written informed consent will be obtained from all study participants prior to their enrollment to the study intervention.

The findings of this study will be disseminated at a local, national and international level through publications in peer-reviewed journals, national and international conference presentations, social, broadcast and print media. Additionally all study participants will receive the study findings through electronic and postal mail.

DISCUSSION

This trial is aiming to evaluate the efficacy, the efficiency and the safety of an exercise-based telerehabilitation program using wearable sensors and web applications compared to a traditional supervised center - based CR.

The objective assessment of functional capacity through CPET and the objective monitoring and recording of exercising and physical activity via the use of wearable sensors are the main features of this study that increase its reliability. Objective measurement of PA and training intensity, using accelerometer and heart rate data is

suggested to be more reliable than using questionnaires than self-reported PA[55-57] or than the perceived rate of exertion on its own.[55]

Although a cost-effectiveness analysis is almost prerequisite for any novel intervention, only a few telerehabilitation studies have performed one. Frederix et al. have showed the cost - effectiveness of an internet-based telerehabilitation program.[28] Whilst Kidholm et al. outlined the non-cost effectiveness of a telerehabilitation program compared to center-based CR.[58] In our study, we intent to include a comprehensive cost- effectiveness analysis to evaluate any possible economic gains.

Moreover, the geographical features of Greece, with many islands and remote areas, contribute to the care inequality being observed, combined with the high variability of access to primary care professionals.[59] CR is almost absent from the Greek public health system, partly owing to the lack of clinics and training in its delivery. Furthermore, while some studies have already investigated the implications of telerehabilitation in other diseases, such COPD, with favorable outcomes,[60] no similar study, to our knowledge, has not yet been carried out for CAD patients, leaving a great gap open. In accordance to these statements recent guidelines support the implementation of home-based CR, telehealth, and mHealth interventions, with the use of wearable activity trackers to increase cardiac patients' participation rates and long-term adherence to healthy behaviors.[11] Furthermore, although CVD patients' digital literacy is presented as a barrier to CR participation[61] data from a recent study reveal encouraging results concerning the successive use of smartphones and wearable technology by an elderly cardiac population.[62] Additionally, adherence in telerehabilitation interventions appears to present higher rates[63-65].

Therefore, there is an urgent need for innovative, safe, more cost-effective CR strategies. If an exercise based telerehabilitation program, using wearable sensors, meets these prerequisites, it can act as a supplementary and/or substitutional (according to the needs) to traditional center - based CR in CAD patients of low to moderate cardiac risk, thus allowing more patients to have access to CR with the least possible economic burden.

FOOTNOTES

Contributorship statement

Varsamo Antoniou (VA), Garyfallia Pepera (GP) conceived the study design, and Andrew Xanthopoulos (AX), Gregory Giamouzis (GG), Konstantinos I. Gourgoulianis (KG), John Skoularigis (JS), Konstantinos Davos (KD), Eleni Kapreli (EK), Vasileios Stavrou (VS) contributed to the conception of the design. Varsamo Antoniou (VA), Garyfallia Pepera (GP) and Ladislav Batalik (LB) drafted the manuscript and all authors reviewed several drafts of the manuscript. All authors approved the final manuscript to be published.

Conflicts of interests

The authors declare that they have no conflicts of interests.

Funding statement

This work was supported by the Ministry of Health of the Czech Republic project for conceptual development in research organizations, ref. no. 65269705 (University Hospital Brno, Brno, Czech Republic).

Data sharing statement

The trial protocol, the full study report and the statistical code for generating the results will be made publicly available through publications in peer reviewed journals and trial registries

References

1. Bansilal S, Castellano JM, Fuster V. Global burden of CVD: focus on secondary prevention of cardiovascular disease. *International journal of cardiology* 2015;201 Suppl 1:S1-7. doi: 10.1016/s0167-5273(15)31026-3 [published Online First: 2016/01/10]

2. Kyu HH, Abate D, Abate KH, et al. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet* 2018;392(10159):1859-922. doi: 10.1016/S0140-6736(18)32335-3

3. Cook C, Cole G, Asaria P, et al. The annual global economic burden of heart failure. *International journal of cardiology* 2014;171(3):368-76. doi: 10.1016/j.ijcard.2013.12.028 [published Online First: 2014/01/09]

4. Savarese G, Lund LH. Global Public Health Burden of Heart Failure. *Card Fail Rev* 2017;3(1):7-11. doi: 10.15420/cfr.2016:25:2 [published Online First: 2017/08/09]

5. Abreu A, Pesah E, Supervia M, et al. Cardiac rehabilitation availability and delivery in Europe: How does it differ by region and compare with other high-income countries?: Endorsed by the European Association of Preventive Cardiology. *European journal of preventive cardiology* 2019;26(11):1131-46. doi: 10.1177/2047487319827453 [published Online First: 2019/02/21]

6. Vos T, Lim SS, Abbafati C, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet* 2020;396(10258):1204-22. doi: 10.1016/S0140-6736(20)30925-9

7. Kotseva K, De Backer G, De Bacquer D, et al. Lifestyle and impact on cardiovascular risk factor control in coronary patients across 27 countries: Results from the European Society of Cardiology ESC-EORP EUROASPIRE V registry. *European journal of preventive cardiology* 2019;26(8):824-35. doi: 10.1177/2047487318825350 [published Online First: 2019/02/12]

8. Touloumi G, Karakosta A, Kalpourtzi N, et al. High prevalence of cardiovascular risk factors in adults living in Greece: the EMENO National Health Examination Survey. *BMC Public Health* 2020;20(1):1665. doi: 10.1186/s12889-020-09757-4

9. Piepoli MF, Hoes AW, Brotons C, et al. Main messages for primary care from the 2016 European Guidelines on cardiovascular disease prevention in clinical practice. *The European journal of general practice* 2018;24(1):51-56. doi: 10.1080/13814788.2017.1398320 [published Online First: 2017/11/24]

10. 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. *European journal of preventive cardiology* 2021;28(5):460-95. doi: 10.1177/2047487320913379

11. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for

cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC). *European heart journal* 2021 doi: 10.1093/eurheartj/ehab484

12. Sandercock GR, Cardoso F, Almodhy M, et al. Cardiorespiratory fitness changes in patients receiving comprehensive outpatient cardiac rehabilitation in the UK: a multicentre study. *Heart* 2013;99(11):785-90. doi: 10.1136/heartjnl-2012-303055 [published Online First: 2012/11/28]
13. Anderson L, Oldridge N, Thompson DR, et al. Exercise-Based Cardiac Rehabilitation for Coronary Heart Disease: Cochrane Systematic Review and Meta-Analysis. *Journal of the American College of Cardiology* 2016;67(1):1-12. doi: 10.1016/j.jacc.2015.10.044 [published Online First: 2016/01/15]
14. Salzwedel A, Jensen K, Rauch B, et al. Effectiveness of comprehensive cardiac rehabilitation in coronary artery disease patients treated according to contemporary evidence based medicine: Update of the Cardiac Rehabilitation Outcome Study (CROS-II). *European journal of preventive cardiology* 2020;27(16):1756-74. doi: 10.1177/2047487320905719 [published Online First: 2020/02/23]
15. de Vries H, Kemps HM, van Engen-Verheul MM, et al. Cardiac rehabilitation and survival in a large representative community cohort of Dutch patients. *European heart journal* 2015;36(24):1519-28. doi: 10.1093/eurheartj/ehv111 [published Online First: 2015/04/19]
16. Long L, Mordi IR, Bridges C, et al. Exercise-based cardiac rehabilitation for adults with heart failure. *The Cochrane database of systematic reviews*

2019;1(1):Cd003331. doi: 10.1002/14651858.CD003331.pub5 [published Online First: 2019/01/30]

17. Neubeck L, Freedman SB, Clark AM, et al. Participating in cardiac rehabilitation: a systematic review and meta-synthesis of qualitative data. *European journal of preventive cardiology* 2012;19(3):494-503. doi: 10.1177/1741826711409326 [published Online First: 2012/07/11]

18. Dunlay SM, Witt BJ, Allison TG, et al. Barriers to participation in cardiac rehabilitation. *American heart journal* 2009;158(5):852-9. doi: 10.1016/j.ahj.2009.08.010 [published Online First: 2009/10/27]

19. Ruano-Ravina A, Pena-Gil C, Abu-Assi E, et al. Participation and adherence to cardiac rehabilitation programs. A systematic review. *International journal of cardiology* 2016;223:436-43. doi: 10.1016/j.ijcard.2016.08.120 [published Online First: 2016/08/25]

20. Sari DM, Wijaya LCG. Cardiac rehabilitation via telerehabilitation in COVID-19 pandemic situation. *The Egyptian Heart Journal* 2021;73(1):31. doi: 10.1186/s43044-021-00156-7

21. Besnier F, Gayda M, Nigam A, et al. Cardiac Rehabilitation During Quarantine in COVID-19 Pandemic: Challenges for Center-Based Programs. *Arch Phys Med Rehabil* 2020;101(10):1835-38. doi: 10.1016/j.apmr.2020.06.004 [published Online First: 2020/06/27]

22. Ambrosetti M, Abreu A, Cornelissen V, et al. Delphi consensus recommendations on how to provide cardiovascular rehabilitation in the COVID-19 era. *European journal of preventive cardiology* 2021;28(5):541-57. doi: 10.1093/eurjpc/zwaa080

23. Batalik L, Dosbaba F, Hartman M, et al. Long-term exercise effects after cardiac telerehabilitation in patients with coronary artery disease: 1-year follow-up results of the randomized study. *European journal of physical and rehabilitation medicine* 2021 doi: 10.23736/s1973-9087.21.06653-3 [published Online First: 2021/02/24]

24. Batalik L, Pepera G, Papathanasiou J, et al. Is the Training Intensity in Phase Two Cardiovascular Rehabilitation Different in Telehealth versus Outpatient Rehabilitation? *Journal of Clinical Medicine* 2021;10(18) doi: 10.3390/jcm10184069

25. Batalik L, Konecny V, Dosbaba F, et al. Cardiac rehabilitation based on the walking test and telerehabilitation improved cardiorespiratory fitness in people diagnosed with coronary heart disease during the covid-19 pandemic. *International Journal of Environmental Research and Public Health* 2021;18(5):1-11. doi: 10.3390/ijerph18052241

26. Kraal JJ, Peek N, Van den Akker-Van Marle ME, et al. Effects of home-based training with telemonitoring guidance in low to moderate risk patients entering cardiac rehabilitation: short-term results of the FIT@Home study. *European journal of preventive cardiology* 2014;21(2 Suppl):26-31. doi: 10.1177/2047487314552606 [published Online First: 2014/10/31]

27. Piotrowicz E, Piotrowicz R, Opolski G, et al. Hybrid comprehensive telerehabilitation in heart failure patients (TELEREH-HF): A randomized, multicenter, prospective, open-label, parallel group controlled trial—Study design and description of the intervention. *American heart journal* 2019;217:148-58. doi: 10.1016/j.ahj.2019.08.015

28. Frederix I, Solmi F, Piepoli MF, et al. Cardiac telerehabilitation: A novel cost-efficient care delivery strategy that can induce long-term health benefits. *European journal of preventive cardiology* 2017;24(16):1708-17. doi: 10.1177/2047487317732274 [published Online First: 2017/09/20]

29. Maddison R, Rawstorn JC, Stewart RAH, et al. Effects and costs of real-time cardiac telerehabilitation: randomised controlled non-inferiority trial. *Heart* 2019;105(2):122. doi: 10.1136/heartjnl-2018-313189

30. Brouwers RWM, van Exel HJ, van Hal JMC, et al. Cardiac telerehabilitation as an alternative to centre-based cardiac rehabilitation. *Netherlands heart journal : monthly journal of the Netherlands Society of Cardiology and the Netherlands Heart Foundation* 2020;28(9):443-51. doi: 10.1007/s12471-020-01432-y [published Online First: 2020/06/05]

31. Cavalheiro AH, Silva Cardoso J, Rocha A, et al. Effectiveness of Tele-rehabilitation Programs in Heart Failure: A Systematic Review and Meta-analysis. *Health Serv Insights* 2021;14:11786329211021668-68. doi: 10.1177/11786329211021668

32. Jin K, Khonsari S, Gallagher R, et al. Telehealth interventions for the secondary prevention of coronary heart disease: A systematic review and meta-analysis. *European journal of cardiovascular nursing : journal of the Working Group on Cardiovascular Nursing of the European Society of Cardiology* 2019;18(4):260-71. doi: 10.1177/1474515119826510 [published Online First: 2019/01/23]

33. Subedi N, Rawstorn JC, Gao L, et al. Implementation of Telerehabilitation Interventions for the Self-Management of Cardiovascular Disease: Systematic

Review. *JMIR mHealth and uHealth* 2020;8(11):e17957. doi: 10.2196/17957 [published Online First: 2020/11/28]

34. Batalik L, Filakova K, Batalikova K, et al. Remotely monitored telerehabilitation for cardiac patients: A review of the current situation. *World J Clin Cases* 2020;8(10):1818-31. doi: 10.12998/wjcc.v8.i10.1818

35. Chan A-W, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Annals of internal medicine* 2013;158(3):200-07. doi: 10.7326/0003-4819-158-3-201302050-00583

36. Eysenbach G. CONSORT-EHEALTH: Improving and Standardizing Evaluation Reports of Web-based and Mobile Health Interventions. *Journal of medical Internet research* 2011;13(4):e126. doi: 10.2196/jmir.1923

37. 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. *European journal of preventive cardiology* 2020:2047487320913379. doi: 10.1177/2047487320913379 [published Online First: 2020/04/01]

38. Hansen D, Abreu A, Ambrosetti M, et al. Exercise intensity assessment and prescription in cardiovascular rehabilitation and beyond: why and how: a position statement from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology. *European journal of preventive cardiology* 2021 doi: 10.1093/eurjpc/zwab007

39. Hansen D, Mathijs W, Michiels Y, et al. Phase III multidisciplinary exercise-based rehabilitation is associated with fewer hospitalizations due to adverse

cardiovascular events in coronary artery disease patients. *European journal of preventive cardiology* 2020 doi: 10.1093/eurjpc/zwaa038

40. La Scala Teixeira CV, Evangelista AL, Pereira PEA, et al. Complexity: A Novel Load Progression Strategy in Strength Training. *Front Physiol* 2019;10:839. doi: 10.3389/fphys.2019.00839 [published Online First: 2019/07/30]
41. Lee WW, Choi KC, Yum RW, et al. Effectiveness of motivational interviewing on lifestyle modification and health outcomes of clients at risk or diagnosed with cardiovascular diseases: A systematic review. *Int J Nurs Stud* 2016;53:331-41. doi: 10.1016/j.ijnurstu.2015.09.010 [published Online First: 2015/10/24]
42. Pepera GB, Paul D;Sandercock, Gavin R H. A pilot study to investigate the safety of exercise training and testing in cardiac rehabilitation patients. *The British Journal of Cardiology* 2013;20:78. doi: http://dx.doi.org/10.5837/bjc.2013.012
43. Bethell HJ. Exercise-based cardiac rehabilitation. *Medicine (Baltimore)* 2006;34(5):195-96. doi: 10.1383/medc.2006.34.5.195
44. Guazzi M, Arena R, Halle M, et al. 2016 focused update: clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *European heart journal* 2018;39(14):1144-61. doi: 10.1093/eurheartj/ehw180 [published Online First: 2016/05/04]
45. Fletcher GF, Ades PA, Kligfield P, et al. Exercise standards for testing and training: A scientific statement from the American heart association. *Circulation* 2013;128(8):873-934. doi: 10.1161/CIR.0b013e31829b5b44
46. Santos-Lozano A, Santín-Medeiros F, Cardon G, et al. Actigraph GT3X: Validation and Determination of Physical Activity Intensity Cut Points. *Int J Sports Med* 2013;34(11):975-82. [published Online First: 22.05.2013]

47. Mâsse LC, Fuemmeler BF, Anderson CB, et al. Accelerometer data reduction: a comparison of four reduction algorithms on select outcome variables. *Medicine and science in sports and exercise* 2005;37(11 Suppl):S544-54. doi: 10.1249/01.mss.0000185674.09066.8a [published Online First: 2005/11/19]

48. Van Remoortel H, Raste Y, Louvaris Z, et al. Validity of six activity monitors in chronic obstructive pulmonary disease: a comparison with indirect calorimetry. *PloS one* 2012;7(6):e39198. doi: 10.1371/journal.pone.0039198 [published Online First: 2012/06/30]

49. Healy GN, Matthews CE, Dunstan DW, et al. Sedentary time and cardio-metabolic biomarkers in US adults: NHANES 2003-06. *European heart journal* 2011;32(5):590-7. doi: 10.1093/eurheartj/ehq451 [published Online First: 2011/01/13]

50. Papathanasiou G, Georgoudis G, Papandreou M, et al. Reliability Measures of the Short International Physical Activity Questionnaire (IPAQ) in Greek Young Adults. *Hellenic journal of cardiology : HJC = Hellēnikē kardiologikē epitheōrēsē* 2009;50:283-94.

51. Kontodimopoulos N, Pappa E, Niakas D, et al. Validity of the EuroQoL (EQ-5D) instrument in a Greek general population. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2008;11(7):1162-9. doi: 10.1111/j.1524-4733.2008.00356.x [published Online First: 2008/05/21]

52. Rishi P, Rishi E, Maitray A, et al. Hospital anxiety and depression scale assessment of 100 patients before and after using low vision care: A prospective study in a tertiary eye-care setting. *Indian journal of ophthalmology* 2017;65(11):1203-08. doi: 10.4103/ijo.IJO_436_17

53. Bjelland I, Dahl AA, Haug TT, et al. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *Journal of psychosomatic research* 2002;52(2):69-77. doi: 10.1016/s0022-3999(01)00296-3 [published Online First: 2002/02/08]

54. Michopoulos I, Kalkavoura C, Michalopoulou P, et al. [Hospital anxiety and depression scale (HADS): Validation in a Greek general hospital sample]. *Psychiatrike = Psychiatriki* 2007;18(3):217-24. [published Online First: 2007/07/01]

55. Butte NF, Ekelund U, Westerterp KR. Assessing physical activity using wearable monitors: measures of physical activity. *Medicine and science in sports and exercise* 2012;44(1 Suppl 1):S5-12. doi: 10.1249/MSS.0b013e3182399c0e [published Online First: 2011/12/23]

56. Warren JM, Ekelund U, Besson H, et al. Assessment of physical activity - a review of methodologies with reference to epidemiological research: a report of the exercise physiology section of the European Association of Cardiovascular Prevention and Rehabilitation. *Eur J Cardiovasc Prev Rehabil* 2010;17(2):127-39. doi: 10.1097/HJR.0b013e32832ed875 [published Online First: 2010/03/11]

57. Westerterp KR. Reliable assessment of physical activity in disease: an update on activity monitors. *Curr Opin Clin Nutr Metab Care* 2014;17(5):401-6. doi: 10.1097/mco.0000000000000080 [published Online First: 2014/08/12]

58. Kidholm K, Rasmussen MK, Andreasen JJ, et al. Cost-Utility Analysis of a Cardiac Telerehabilitation Program: The Teledialog Project. *Telemedicine journal and e-health : the official journal of the American Telemedicine Association* 2016;22(7):553-63. doi: 10.1089/tmj.2015.0194 [published Online First: 2015/12/30]

59. Network HFP. Heart failure policy and practice in Europe: Greece, 2020.

60. Vasilopoulou M, Papaioannou AI, Kaltsakas G, et al. Home-based maintenance tele-rehabilitation reduces the risk for acute exacerbations of COPD, hospitalisations and emergency department visits. *European Respiratory Journal* 2017;49(5):1602129. doi: 10.1183/13993003.02129-2016

61. Falter M, Scherrenberg M, Dendale P. Digital health in cardiac rehabilitation and secondary prevention: A search for the ideal tool. *Sensors (Switzerland)* 2021;21(1):1-11. doi: 10.3390/s21010012

62. Snoek JA, Prescott EI, van der Velde AE, et al. Effectiveness of Home-Based Mobile Guided Cardiac Rehabilitation as Alternative Strategy for Nonparticipation in Clinic-Based Cardiac Rehabilitation Among Elderly Patients in Europe: A Randomized Clinical Trial. *JAMA cardiology* 2021;6(4):463-68. doi: 10.1001/jamacardio.2020.5218 %J JAMA Cardiology

63. Batalik L, Dosbaba F, Hartman M, et al. Benefits and effectiveness of using a wrist heart rate monitor as a telerehabilitation device in cardiac patients: A randomized controlled trial. *Medicine (Baltimore)* 2020;99(11):e19556-e56. doi: 10.1097/MD.0000000000019556

64. Kraal JJ, Van den Akker-Van Marle ME, Abu-Hanna A, et al. Clinical and cost-effectiveness of home-based cardiac rehabilitation compared to conventional, centre-based cardiac rehabilitation: Results of the FIT@Home study. *European journal of preventive cardiology* 2017;24(12):1260-73. doi: 10.1177/2047487317710803

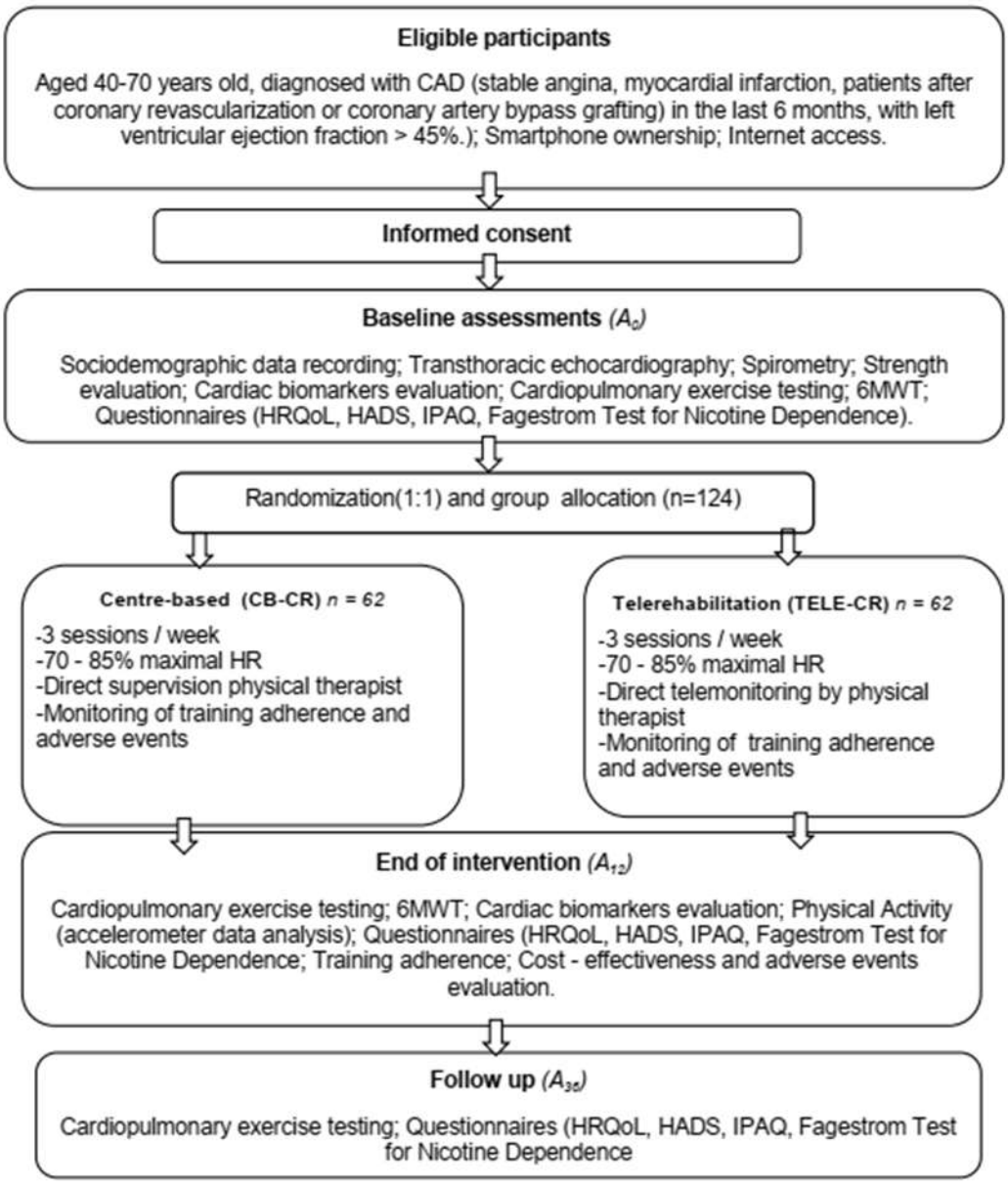
65. Hwang R, Bruning J, Morris NR, et al. Home-based telerehabilitation is not inferior to a centre-based program in patients with chronic heart failure: a randomised

trial. *Journal of physiotherapy* 2017;63(2):101-07. doi: 10.1016/j.jphys.2017.02.017 [published Online First: 2017/03/25]

Figure 1. Flowchart of the study design

.

Fig 1 Flowchart of the study design



HR: heart rate, HRQoL: Health related quality of life, HADS: Hospital Anxiety and Depression scale, IPAQ: International Physical Activity Questionnaire, CAD: Coronary Artery Disease

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered,	3,6

		name of intended registry	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	n/a
Funding	#4	Sources and types of financial, material, and other support	35
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 25
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	25
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a

Introduction

Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg,	9,10

		surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12-19
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	17
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	17,19
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	19-22
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7-8

Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	22
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	17,18, 20-22
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	17
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values).	17-19

		Reference to where details of data management procedures can be found, if not in the protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	22
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	22
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial	16-17

		conduct	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	23
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	17
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	9
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9,19
Declaration of	#28	Financial and other competing interests for principal	25

interests		investigators for the overall trial and each study site	
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	23
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	25
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

Notes:

- 18a: 15,16,18-20 The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons Attribution License CC-BY-NC. This checklist was completed on 05. December 2021 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Efficacy, Efficiency and Safety of a Cardiac Telerehabilitation Program Using Wearable Sensors in Coronary Heart Disease Patients: The TELEWEAR-CR study protocol.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-059945.R2
Article Type:	Protocol
Date Submitted by the Author:	07-Apr-2022
Complete List of Authors:	Antoniou, Varsamo; University of Thessaly School of Health Sciences, Clinical Exercise Physiology and Rehabilitation Research Laboratory, Physiotherapy Department Xanthopoulos, Andrew; University of Thessaly Faculty of Medicine, Cardiology Giamouzis, Gregory; University of Thessaly Faculty of Medicine, Cardiology Davos, Constantinos ; Biomedical Research Foundation of the Academy of Athens, Cardiovascular Research Batalik, Ladislav; University Hospital Brno, Rehabilitation; Department of Rehabilitation, University Hospital Brno, Czech Republic Stavrou, Vasileios; University of Thessaly Faculty of Medicine, Laboratory of Cardio-Pulmonary Testing, Department of Respiratory Medicine Gourgoulianis, Konstantinos; University of Thessaly Faculty of Medicine, Laboratory of Cardio-Pulmonary Testing, Department of Respiratory Medicine Kapreli, Eleni; University of Thessaly School of Health Sciences, Clinical Exercise Physiology and Rehabilitation Research Laboratory, Physiotherapy Department Skoularigis, John; University of Thessaly Faculty of Medicine, Cardiology Pepera, Garyfallia; University of Thessaly School of Health Sciences, Clinical Exercise Physiology and Rehabilitation Research Laboratory, Physiotherapy Department
Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Cardiovascular medicine, Sports and exercise medicine
Keywords:	Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS, REHABILITATION MEDICINE, Cardiology < INTERNAL MEDICINE

TITLE PAGE

Efficacy, Efficiency and Safety of a Cardiac Telerehabilitation Program Using Wearable Sensors in Coronary Heart Disease Patients: The TELEWEAR-CR study protocol

Authors

Varsamo Antoniou, PT, BSc, MSc, PhD$_{(c)}$[a]

Andrew Xanthopoulos, MD, PhD[b]

Gregory Giamouzis, MD, PhD[b]

Konstantinos Davos, MD, PhD, FESC[c]

Ladislav Batalik, PT, MSc, PhD[d,e]

Vasileios Stavrou, BSc, MSc, PhD[f]

Konstantinos I. Gourgoulianis MD, PhD[f]

Eleni Kapreli, PT, BSc, MSc, PhD[a]

John Skoularigis, MD, PhD[b]

Garyfallia Pepera, PT, BSc, MSc, PhD[a]

[a] Clinical Exercise Physiology and Rehabilitation Research Laboratory, Physiotherapy Department, School of Health Sciences, University of Thessaly, Lamia, Greece

[b] Department of Cardiology, Faculty of Medicine School of Health Sciences, University of Thessaly Larissa Greece.

[c] Cardiovascular Research Laboratory, Biomedical Research Foundation, Academy of Athens, 4 Soranou Ephessiou Street, 115 27, Athens, Greece

[d] Department of Rehabilitation, University Hospital Brno, Jihlavska 20, Brno, 62500, Czech Republic

[e] Department of Public Health, Masaryk University Brno, Zerotinovo nam. 617/9, Brno, 601 77, Czech Republic

[f] Laboratory of Cardio-Pulmonary Testing, Department of Respiratory Medicine, Faculty of Medicine, University of Thessaly, Larissa, Greece

Corresponding author:

Garyfallia Pepera
Assistant Professor in Cardiac Rehabilitation, Clinical Exercise Physiology & Rehabilitation Research Laboratory, Physiotherapy Department, Faculty of Health Sciences, University of Thessaly, Lamia, Greece.
3rd km of Old National Road, GR-35100 Lamia, Greece
Tel: +302231060207
e-mail: gpepera@uth.gr

Antoniou A. e-mail: varsamoantoniou@uth.gr

Xanthopoulos A. e-mail: andrewvxanth@gmail.com

Giamouzis G. e-mail: grgiamouzis@med.uth.gr

Davos C. e-mail: cdavos@bioacademy.gr

Batalik L. e-mail: Batalik.Ladislav@fnbrno.cz

Stavrou V. e-mail: vasileiosstavrou@hotmail.com

Gourgoulianis K. e-mail: kgourg@med.uth.gr

Kapreli E. e-mail: ekapreli@uth.gr

Skoularigis J. e-mail: iskoular@med.uth.gr

Pepera G. e-mail: gpepera@uth.gr

Word count: 3.435

Abstract

Introduction: Exercise – based cardiac rehabilitation (CR) is a beneficial tool for the secondary prevention of cardiovascular diseases with, however, low participation rates. Telerehabilitation, intergrading mobile technologies and wireless sensors, may advance the cardiac patients' adherence. This study will investigate the efficacy, efficiency, safety and cost-effectiveness of a telerehabilitation program based on objective exercise telemonitoring and evaluation of cardiorespiratory fitness.

Methods and Analysis: A supervised, parallel-group, single-blind, randomized controlled trial will be conducted. A total of 124 coronary disease patients will be randomized at a 1:1 ratio into two groups: intervention telerehabilitation group (TELE-CR) (n=62) and control, center – based cardiovascular rehabilitation group (CB-CR) (n=62). Participants will receive a 12 – week exercise based rehabilitation program; remotely monitored for the TELE-CR group and standard supervised for the CB-CR group. All participants will perform aerobic training at 70% of their maximal heart rate, as obtained from cardiopulmonary exercise testing (CPET) for 20 minutes plus 20 minutes for strengthening and balance training, three times/ week. The primary outcomes will be the assessment of cardiorespiratory fitness, expressed as peak oxygen uptake assessed by the CPET test and the 6 minute walking test (6MWT). Secondary outcomes will be the physical activity, the safety of the exercise intervention, (number of adverse events that may occur during the exercise), the quality of life, the training adherence, the anxiety and depression levels, the nicotine dependence and cost – effectiveness. Assessments will be held at baseline, end of intervention (12 weeks) and follow up (36 weeks).

Ethics and dissemination: The study protocol has been reviewed and approved by the Ethics Committee of the University of Thessaly (1108/1-12-2021) and by the Ethics Committee of the General University Hospital of Larissa (3780/31-12-2021). The results of this study will be disseminated through manuscript publications and conference presentations.

Keywords: cardiac rehabilitation; telerehabilitation; wearable sensors; cardiorespiratory fitness; functional capacity

Trial registration: Clinical Trial.gov, Identifier: NCT05019157. Registered 24 August 2021. https://clinicaltrials.gov/ct2/show/NCT05019157?cond=cardiac+telerehabilitation&country=GR&draw=2&rank=1

Strengths and limitations of this study

- Telelerehabilitation as an alternative tool to contemporary centre/community based cardiac rehabilitation.
- Intergrading real-time supervision and group-based exercise sessions in cardiac telerehabilitation.

.

- Objective monitoring and evaluation of physical activity and exercise intensity in cardiac rehabilitation interventions.
- Inability, by study design, to blind participants to treatment allocation
- Possible selection bias, since only low and moderate cardiac risk patients will be recruited.

INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of morbidity and premature mortality globally.[1-5] Coronary artery diseases (CAD) account for the largest proportion of CVD mortality.[6] A systematic review by the Global Public Health Burden (GBD) reveals an increase of 11.8% in the mortality rates due to ischemic CVDs in Greece [6] with cardiac risk factors[7] being very common among Greek patients and without signs of future decline.[8] The increased rates of CVDs put additional pressure on the health care systems, especially under the ongoing austerity climate across Europe.

Cardiac rehabilitation (CR) can play a key role as a multidisciplinary secondary intervention aiming to the reduction of CVDs' risk factors, the adoption of healthy lifestyle behaviors and the minimization of disability among CVD patients.[9] Recent guidelines on CVD prevention recommend a multifaceted approach addressing exercise training, dietary counseling, smoking cessation, risk factor modification and psychosocial support.[10-12] A number of meta-analysis confirm the effectiveness of exercise training in reducing cardiovascular mortality, morbidity, re-hospitalizations rates,[13 14] physical inactivity and all CVD risk factors including blood pressure, blood lipid profile, glucose metabolism and weight status.[15 16] Despite global recommendations, patients' participation in CR programs is low, mainly due to insufficient medical referral, travel distance, low self-efficacy, perceived body image and lack of time.[17-19] Moreover, during the COVID-19 pandemic, new barriers have arisen, such as the suspension of centre-based CR and in-person sessions, travelling and circulation restrictions.[20 21] Thus the need to avoid the downgrading of CR is imperative.[22]

Rapid development in information and communication technologies (ICTs) may help to overcome the barriers to CR. [23-25] Telerehabilitation is proposed as a feasible, [26 27] safe and cost – effective intervention, [28 29] leading to long-term improvement of CVD risk factors, reduced healthcare costs and increased CR participation adherence. [30].Recent systematic reviews advocate to the use of telehealth interventions as an adjunct to CR [31-33] for the continuance of CR through pandemic circumstances. [20 21]

A recent review proclaims the integration of remote technologies and wearable sensors in the telerehabilitation, mentioning though the need for further investigation. [34] Another systematic review indicates that, software-enabled systems reduce timing-related barriers to patients' participation.[32] The feasibility and safety of cardiac telerehabilitation need further investigation since most relevant studies are not addressing safety matters and a formal cost - effectiveness analysis.[32 34]

Our study focuses on the objective recording and monitoring of the exercise implementation and physical activity, through the use of wearable sensors (heart rate monitors, accelerometers). Based on thorough literature review, it is the first study to integrate real time supervision (use of videoconference platforms) and a group based design for home exercising (up to 5 participants).

The primary aims of this study are to compare the effect between telerehabilitation and regular outpatient CR methods, related to cardiorespiratory fitness (CRF) and functional capacity. Whilst possible effects in physical activity, training adherence, health related quality of life (HRQoL), anxiety and depression levels , safety, nicotine dependence and cost – effectiveness are considered as secondary aims.

The hypothesis of the study will be that the telerehabilitation intervention will have at least the same efficiency with the regular, centre - based rehabilitation and that it will

be as safe as and even more cost-effective than the centre - based rehabilitation intervention.

METHODS

Study design

A supervised, parallel-group, single-blind, randomized controlled trial with 6 months follow-up will be employed. The study includes CAD patients, enrolled in a telerehabilitation group (TELE-CR) and a control group undertaking regular outpatient CR rehabilitation (CB-CR) for comparison reasons. Three assessments will take place at baseline (A_0), end of intervention (A_{12}) and follow up 36 weeks (A_{36}). A CONSORT (Consolidated Standard of Reporting Trials) flow diagram is shown in Fig. 1.

The study protocol complies with the SPIRIT 2013 statement guidelines[35] and the intervention procedures are described according to the CONSORT- E- HEALTH checklist.[36] We used the SPIRIT checklist when writing our report.[35] The trial is registered at ClinicalTrials.gov with registration number NCT05019157.

Table 1 presents a summary of the study schedule and assessments.

Table 1. Summary of study schedule

	Enrollment	Baseline (A_0)	End of Intervention (A_{12})	Follow Up (A_{36})
Eligibility screening	X			
Informed consent	X			
Randomization		X		
Allocation		X		
Interventions				
Center – based CR		←	→	
Telerehabilitation		←	→	
Assessments				
Demographic characteristics Spirometry, TTE		X x		
Strength evaluation test		X		
Cardiac biomarkers(BNP , NT proBNP, Troponines, CPK)		X	X	
CPET – 6MWT		X	X	X
HRQoL		X	X	X
HADS		X	X	X
IPAQ		X	X	X
FTND		X	X	X
Cost analysis			X	
Training Adherence			X	

TTE: Transthoracic echocardiography, CPET: cardiopulmonary exercise testing, 6MWT: 6 Minute Walking Test, BMP: B-type natriuretic peptide, CPK: Creatine phosphokinase, HRQoL: Health related quality of life, HADS: Hospital Anxiety and Depression scale, IPAQ: International Physical Activity Questionnaire FTND: Fagestrom Test for Nicotine Dependence

Patient population and eligibility

Patients will be recruited- prior to their hospital discharge- from the Cardiology Department of the General University Hospital of Larissa in Greece and will be screened for eligibility by the medical staff (cardiologists and medical physicians) of the corresponding hospital, according to the criteria shown in Table 2. Through risk stratification and pre – exercise assessment only low and moderate cardiac risk patients will be included in the study groups (Table 3). Risk stratification and pre-exercise procedures will be implemented by cardiologists and an exercise physiologist, trained in the CPET, from the corresponding hospital. Those who consent to participation will be screened for eligibility and will be provided with a trial information sheet (explanation of the study design and scopes, participants' responsibilities, confidentiality of the collected data) and a consent form to be signed. Basic sociodemographic data including sex, age, weight, height, cardiac diagnosis, pharmacologic treatment, educational level, place of residence and profession will also be collected.

Table 2. Inclusion and exclusion criteria	
Inclusion criteria	
i.	adults > 18 years old
ii.	diagnosed with coronary artery disease (CAD) (stable angina, myocardial infarction, patients after coronary revascularization or coronary artery bypass grafting) in the last 6 months, with left ventricular ejection fraction > 45%
iii.	current outpatients, stable for at least four weeks prior to the intervention enrollment
iv.	able to perform physical exercise,
v.	able to speak, read and write Greek
vi.	possession of a mobile phone/smartphone
vii.	internet access at home
Exclusion criteria	
i.	severe ventricular arrhythmia, with functional or prognostic significance or exercise – induced myocardial ischemia as assessed by CPET at baseline
ii.	heart failure
iii.	comorbidity precluding exercise training (e.g. orthopedic, neurological or cognitive conditions)
iv.	unstable angina
v.	uncontrolled atrial or ventricular arrhythmia
vi.	acute pulmonary embolism
vii.	acute myocarditis or pericardial effusion
viii.	uncontrolled diabetes mellitus (Type I, II)
ix.	severe obstructive respiratory disease (forced expiratory volume 1 (FEV1)<50%).

Table 3. Cardiac risk stratification

Low Risk	Moderate Risk	High Risk
-Absence of angina or other symptoms (eg unusual shortness of breath, mild headache or dizziness) -Functional capacity> 7 METs, left ventricular ejection fraction (LVEF) ≥ 50% -Absence of arrhythmia at rest -Absence of depression	- Presence of angina or other symptoms (eg unusual shortness of breath, mild headache or dizziness, dizziness occurring at high levels of exercise ≥ 7 METs) -Mild to moderate silent ischemia (ST eruption <2 mm) -Functional capacity> 5 METs -LVEF = 40-49%	-Presence of arrhythmias - Presence of angina or other symptoms (eg unusual breathlessness, mild headache or dizziness, dizziness occurring at high levels of exercise <5 METs) -Silent ischemia (ST stroke ≥ 2 mm) -Presence of abnormal hemodynamics during exercise (reduction of BP) or post-exercise hypotension -LEVF <40%

Randomization and blinding

A total of 124 eligible patients will be randomized, via a computerized randomization system, in a 1:1 ratio (adjusted for age and gender) into two groups: center-based CR (CB-CR) and telerehabilitation group (TELE-CR). The allocation will be hidden until the completion of the baseline assessment in sequentially numbered, sealed, opaque envelopes. Due to the nature of the intervention, both the participants and the hospital's staff supervising the exercise programs are unable to be blinded to the treatment allocation. The researchers, responsible for all study assessments, will be blinded to the intervention allocation. Primery investigators will be unaware of the randomization allocation until the completion of the intervention and the collection of all study data.

Patient and public involvement

There was no patient or public involvement in the design of this study (setting of the research question or the outcome measures). The patients will not be asked to take part either in the interpretation or the writing procedures of the results of this study.

Interventions

Individually determined CR programs will be implemented in both study groups based on the participants' referral diagnosis, physical fitness level and expected training goals. All participants will undertake a 12 – week, exercise - based CR program, including 3 training sessions of 60min/week. Exercise will be prescribed individually, according to the results of the baseline CPET and to the FITT [frequency, intensity, time (duration), and type of exercise] model.[37] Participants will exercise with an intensity of 70% of their maximal heart rate (HR_{max}), as assessed during baseline CPET.[10] Each exercise circuit will consist of 20 structured stations for aerobic, strength and balance training of 2min duration/station (Tables 4, 5). Aerobic progression will go through the duration, followed by an increase of 5–10% / week in the exercise intensity.[38 39] Progression in the resistance training involves, primarily, the achievement of the desired volume (number of training sets), followed by the gradual increase in intensity (amount of load lifted) and adaptations in density (rest periods).[38 40] Resistance training will follow a low pace, rest/recovery to work/contraction ratio: 2:1.[37] Participants in the CB-CR group will use free weights or machines for their resistance training, whilst participants in the TELE – CR group will exercise using their body weight or resistance bands. At the completion of the intervention, the effectiveness of the training program will be assessed and patients will be encouraged to maintain a physically active lifestyle.

However, no specific exercise prescription or face - to - face feedback will be provided until the follow - up assessment.

Table 4: CB-CR exercise program

Warm Up	
Cycling or mild treadmill walking	5 min
Stretching activities *Upper back *Chest *Lower back, waist mobility *Calf *Hamstring *Quadriceps	5 min
Main training part	
Aerobic Training	
Cycling or treadmill walking	Exercise with an intensity of 70% of the patients' maximal heart rate (HRmax) at a level of 12/20–14/20 of Borg scale
Strengthening Training	
*Biceps curls *Shoulder press *Triceps *Lateral fly *Front deltoid raise *Mini squats *Hamstring curls *Plantar flex *Side leg raise	12 repetitions 1 set/exercise, starting at 30 and 70% of one-repetition maximum (1RM) for the upper body and lower body respectively. Increase gradually to 70% of 1RM and 80% of 1RM for the upper and lower body, respectively
Balance Training	
*Standing on one foot *Walking heel to toe *Reaching -front -lateral -back	Starting with the patient's own body weight. Later add unstable surfaces
Duration 40 min 1RM: the maximum weight a patient can lift in one complete repetition for a given exercise in a controlled way through a full range of motion with good posture	
Cool Down	
*Cycling or mild treadmill walking *Moving hands slowly *Stretching exercises	10 min

Table 5: TELE-CR exercise program

Warm Up

Marching on the spot	5 min
Stretching activities *Upper back *Chest *Lower back, waist mobility *Calf *Hamstring *Quadriceps	5 min
Main training part	
Aerobic Training	
*Box stepping *Knee raises only -With hand to opposite knee -Hand to opposite ankle *Knee bends only -With swinging arms -With reaching arms *Side steps -Just tapping -With half arm lift -Reaching over *Marching -Heal lift only -With arms moving	10 repetitions 2 sets/ exercise
Strengthening Training	
*Biceps curls *Shoulder press *Triceps *Lateral fly *Front deltoid raise *Mini squats *Hamstring curls *Plantar flex *Side leg raise	12 repetitions 1 set/exercise, starting at 30 and 70% of one-repetition maximum (1RM) for the upper body and lower body respectively. Increase gradually to 70% of 1RM and 80% of 1RM for the upper and lower body, respectively
Balance Training	
*Standing on one foot *Walking heel to toe *Reaching -front -lateral -back	Starting with the patient's own body weight. Later add unstable surfaces
Duration 40 min 1RM: the maximum weight a patient can lift in one complete repetition for a given exercise in a controlled way through a full range of motion with good posture	
Cool Down	

*Marching on the spot gently *Moving hands slowly *Stretching exercises	10 min

Blood samplings will be taken, in all assessment endpoints, from all study participants to assess any effects of the intervention on the cardiac biomarkers' blood concentration (BNP, NT-proBNP, Troponines, CPK).

All patients will be receiving educational and informational videoconference sessions regarding issues of upright exercising, physical activity, diet/nutritional and smoking cessation counseling (based on recent guidelines)[10] and psychosocial support (via psychotherapy) on stress and anxiety management. Consultation sessions may include a family member or friend, especially for elderly patients.[41] Communication strategies such as motivational interviewing, during telephone calls or videoconferences, will be integrated, as they appear to be useful in helping promote patients' adherence and avoid incidents of early drop outs. Motivational interviewing will be based on the OARS (Open-ended questions, Affirmation, Reflective listening, and Summarizing) principle that helps patients to present their perceptions, and clinicians to summarize.

Any adverse effects that may occur during the intervention period will be reported for safety monitoring and future data interpretation analysis.[42] Adverse effects are defined as all-cause mortality, hospitalization for CVD or serious atrial or ventricular arrhythmia, musculoskeletal problems (muscle, tendon or joint problems) or other diseases preventing exercise participation. Constant supervision of the CB –CR exercise program and the existence of a defibrillator will ensure the participants' safety. Whilst for the TELE – CR group, real time exercise telemonitoring via videoconference

platforms and exercise training within the prescribed HR zone will ensure safety. Table 6 summarizes the indications for dropping out training sessions.

Table 6. Indications for dropping out training session

• Exercise induced angina
• Fatigue, shortness of breath, dizziness, sweating, cyanosis, headache
• Orthostatic hypotension, drop in SBP> 20 mmHg during exercise
• SBP≥ 220 mmHg, DBP ≥ 110 mmHg
• HR drop (> 10 bpm) during exercise
• Ventricular tachycardia (> 120 bpm)
• When participant reaches the intensity limit of the exercise

SPB: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate

Participants who might withdraw from the study will consent for follow-up assessment of at least the primary outcomes and will be willing to continue with assessments for other outcomes, if they wish to.

Auditing of the study is planned to be performed by periodic- in person- visits of the trial investigator at the hospital facilities or via telephone conducts with the leading physiotherapist of the corresponding hospital.

Any substantive protocol amendments will be reviewed by the institutional review boards/research ethics committees (IRBs/RECs) of the University of Thessaly and will be communicated to all relevant stakeholders (REC/IRBs, trial registries)

Centre – based Cardiac Rehabilitation group (CB- CR group)

Participants will attend a supervised, individually tailored, exercise - based CR program at the hospital's facilities. CB-CR participants will be instructed to wear an accelerometer during the entire study period. Due to the accelerometer's storage

capacity of 30 days, recorded data will be uploaded with a USB-connection and stored in the hospital server in an encrypted way on a monthly basis. Total training attendance rate will be documented by the hospital's staff

Telerehabilitation group (TELE - CR group)

Participants in the TELE-CR group will undertake three training sessions (or more if needed) in the hospital's outpatient clinic for familiarization with the use of the wearable sensors, the uploading of the training data to the web application (Polar Flow) and the exercising within their individually determined exercise intensity.

Following the training period, TELE-CR participants will be lent a Polar H10 chest strap that records HR data and a wrist sports watch (Polar M430, Kempele, Finland) and will proceed with the telerehabilitation program at their homes. Both wearable sensors are validated and reliable tools, allowing effective assessment of exercise intensity[43] and will be used only during the exercise training sessions. The wrist sports watch will display continuous HR reading from the Polar H10 chest strap, enabling patients to exercise within their prescribed HR zone and exercise data (duration, training mode, physical activity tracking). Participants in the TELE-CR group will be exercising in groups of up to maximum 5 participants in each session. Real time supervision of this group – based exercise session by a specialized physiotherapist will be implemented via videoconference web platforms or applications. At the end of every training session, patients will upload training data to the web platform (Polar Flow) via Bluetooth or USB connection. Each patient will have his/her username and login account and can check his/her training data graphically and correlate it to his/her personal goals. CR specialized staff from the corresponding hospital will have access to all patients' accounts so as to monitor successful data uploading, assess the collected

data and provide them with training feedback once a week via telephone video calls. Uploaded data will be further backed up to an external hard drive to be processed and evaluated by the trial investigator after the completion of the intervention.

Additionally, all patients will be lent a tri-axial accelerometer (Actigraph wGT3X, Actigraph), that they will wear around their waist during the 12 week intervention period. Patients should visit the hospital's outpatient clinic on a monthly basis to upload the recorded data to a secure PC application in an encrypted manner. Training adherence will be monitored by the specialized physiotherapist supervising the telerehabilitation exercise sessions.

OUTCOME MEASURES

Primary outcome

The primary outcome will be the assessment of the cardiorespiratory fitness, at baseline, the completion of the intervention (A_{12}) and follow up (A_{36}) in all study groups (CB-CR, TELE-CR).

Secondary outcomes

Secondary outcomes will be the physical activity level, safety, health related quality of life (HRQoL), training adherence, depression and anxiety levels, nicotine dependence and cost effectiveness. Physical activity, HRQoL, nicotine dependence and psychosocial well-being will be measured and assessed at baseline, end of intervention (A_{12}) and follow up (A_{36}). Training adherence and cost evaluation will be assessed at the completion of the intervention (A_{12}).

MEASUREMENTS

Cardiorespiratory fitness

CRF will be assessed in all study groups by peak oxygen uptake (peak VO2), determined by CPET and a 6MWT at the corresponding hospital at baseline, at the completion of the intervention (A12) and follow up (A36). CPET will be set according to recommendations of ESC and the American Heart Association. [44 45] The test will be performed on a cycle ergometer, using an individual ramp protocol aiming at total test duration of 8min–12min. Patients will be instructed to maintain a pedalling frequency of 60-70 rounds per minute. A twelve lead ECG and blood pressure will be recorded continuously during the test. Peak VO2 will be defined as the average value during the last 30sec of exercise. Patients will be encouraged to exercise until they reach respiratory exchange ratio (RER) ≥1.10. If a participant fails to achieve a RER≥1.10, he/she will be excluded from the study. A cardiologist will be present while testing to deal with any emergencies that may arise.

Physical Activity

Daily physical activity (PA) will be measured via a tri-axial accelerometer (ActiGraph wGT3X, ActiGraph) at baseline and at the completion of the intervention (A_{12}). The ActiGraph will be worn continuously and has been previously identified as a reliable PA tool [46 47] validated, in healthy and cardiac patients. [48 49]

The self-reported PA will be assessed at all three assessments endpoints, by the offline international physical activity questionnaire, adopted in the Greek language (IPAQ-Gr) that presents acceptable reliability and high repeatability values.[50]

Cost-effectiveness

The cost-effectiveness analysis will be performed using the assessment of Quality-adjusted life years (QALYs) at baseline (A_0) and end of intervention (A_{12}).Patients will complete the EQ-5D questionnaire (EuroQol-5D) individually[51]and their final scores will be converted into QALYs. The cardiovascular readmission costs (as derived from the invoices from the hospital's financial department), the cardiologist follow-up visits and the diagnostic tests will constitute the healthcare costs. The CB-CR costs will be calculated based on the price list of medical expenses provided by hospital regarding professional wages (physiotherapist, cardiologist), exercise testing assessment costs, and transportation costs to and from the patients' homes to the hospital. In the TELE-CR group the costs will include the purchase of the necessary equipment and consumables (internet connection subscription, telephone communication cost).

The cost / benefit analysis will result from the calculation of the incremental cost-effectiveness ratio (ICER):

$$ICER = (cost_{\text{intervention group}} - cost_{\text{control group}}) / (effectiveness_{\text{intervention group}} - effectiveness_{\text{control group}}).$$

Incremental cost refers to the difference/patient, in the total average cost between the intervention (TELE-CR) and the control group (CB-CR). Incremental effectiveness is defined as the difference in the mean change in QALYs between the study groups**.**

Anxiety and depression/Smoking cessation

Anxiety/depression rates and nicotine dependence will be assessed at all three assessment points. Anxiety levels will be evaluated through the Greek version of the Hospital Anxiety and Depression Scale (HADS) that comprises of 7 items, each for

anxiety and depression subscales.[52] HADS is a validated measure to assess anxiety and depression symptoms, recommended for CAD patients.[53 54] Nicotine dependence will be assessed through the Fagestrom Test for Nicotine Dependence.

Training adherence

Patients' training adherence is defined as a percentage of the total number of completed training sessions (100%=36). Patients' adherence in both study groups will be recorded by the supervising hospital outpatient clinic's staff and will be evaluated at the end of intervention (A_{12}). Based on the percentage of the sessions attended, participants will be categorized in adherent (> 80%), partly adherent (20 to 80%) and non-adherent (< 20%).

STATISTICAL ANALYSIS

Normality of data will be examined with Kolmogorov-Smirnov tests. Descriptive statistics will be used to report demographics and baseline characteristics. Between-group and within group differences in the outcome measures will be evaluated using multivariate analysis of variance (MANOVA). The effectiveness of the control (CB-CR) and intervention (TELE-CR) group will be examined with dependent t-test for each group (pre- and post-scores). All participants will be included in an intention to treat analysis, regardless of adherence, for at least the assessment of the primary outcomes. Significance level will be set at P=0.05. Statistical Package for Social Sciences (SPSS), version 25, will be used for all data analysis.

Sample size calculation

The calculation of the sample size was performed with G * Power 3.1.9.4 software. For test F, h detection of moderate effect size (f = 0.3) after the interaction test (α level =

0.05, 80%) a total of 111 participants were required to examine the recurrent MANOVA. After adjusting for potential drop-outs (estimated attrition rate ≤ 10%) a minimum sample of 124 participants is required. Therefore, at least 62 participants will be recruited in each group.

ETHICS AND DISSEMINATION

The study protocol is approved by the Ethics Committee of the University of Thessaly (#1108/01-12-2021) and by the Ethics Committee of the General University Hospital of Larissa. Written informed consent will be obtained from all study participants prior to their enrollment to the study intervention.

The findings of this study will be disseminated at a local, national and international level through publications in peer-reviewed journals, national and international conference presentations, social, broadcast and print media. Additionally all study participants will receive the study findings through electronic and postal mail.

DISCUSSION

This trial is aiming to evaluate the efficacy, the efficiency and the safety of an exercise-based telerehabilitation program using wearable sensors and web applications compared to a traditional supervised center - based CR.

The objective assessment of functional capacity through CPET and the objective monitoring and recording of exercising and physical activity via the use of wearable sensors are the main features of this study that increase its reliability. Objective measurement of PA and training intensity, using accelerometer and heart rate data is

suggested to be more reliable than using questionnaires than self-reported PA[55-57] or than the perceived rate of exertion on its own.[55]

Although a cost-effectiveness analysis is almost prerequisite for any novel intervention, only a few telerehabilitation studies have performed one. Frederix et al. have showed the cost - effectiveness of an internet-based telerehabilitation program.[28] Whilst Kidholm et al. outlined the non-cost effectiveness of a telerehabilitation program compared to center-based CR.[58] In our study, we intent to include a comprehensive cost- effectiveness analysis to evaluate any possible economic gains.

Moreover, the geographical features of Greece, with many islands and remote areas, contribute to the care inequality being observed, combined with the high variability of access to primary care professionals.[59] CR is almost absent from the Greek public health system, partly owing to the lack of clinics and training in its delivery. Furthermore, while some studies have already investigated the implications of telerehabilitation in other diseases, such COPD, with favorable outcomes,[60] no similar study, to our knowledge, has not yet been carried out for CAD patients, leaving a great gap open. In accordance to these statements recent guidelines support the implementation of home-based CR, telehealth, and mHealth interventions, with the use of wearable activity trackers to increase cardiac patients' participation rates and long-term adherence to healthy behaviors.[11] Furthermore, although CVD patients' digital literacy is presented as a barrier to CR participation[61] data from a recent study reveal encouraging results concerning the successive use of smartphones and wearable technology by an elderly cardiac population.[62] Additionally, adherence in telerehabilitation interventions appears to present higher rates[63-65].

Therefore, there is an urgent need for innovative, safe, more cost-effective CR strategies. If an exercise based telerehabilitation program, using wearable sensors, meets these prerequisites, it can act as a supplementary and/or substitutional (according to the needs) to traditional center - based CR in CAD patients of low to moderate cardiac risk, thus allowing more patients to have access to CR with the least possible economic burden.

FOOTNOTES

Contributorship statement

Varsamo Antoniou (VA), Garyfallia Pepera (GP) conceived the study design, and Andrew Xanthopoulos (AX), Gregory Giamouzis (GG), Konstantinos I. Gourgoulianis (KG), John Skoularigis (JS), Konstantinos Davos (KD), Eleni Kapreli (EK), Vasileios Stavrou (VS) contributed to the conception of the design. Varsamo Antoniou (VA), Garyfallia Pepera (GP) and Ladislav Batalik (LB) drafted the manuscript and all authors reviewed several drafts of the manuscript. All authors approved the final manuscript to be published.

Conflicts of interests

The authors declare that they have no conflicts of interests.

Funding statement

This work was supported by the Ministry of Health of the Czech Republic project for conceptual development in research organizations, ref. no. 65269705 (University Hospital Brno, Brno, Czech Republic).

Data sharing statement

The trial protocol, the full study report and the statistical code for generating the results will be made publicly available through publications in peer reviewed journals and trial registries

References

1. Bansilal S, Castellano JM, Fuster V. Global burden of CVD: focus on secondary prevention of cardiovascular disease. *International journal of cardiology* 2015;201 Suppl 1:S1-7. doi: 10.1016/s0167-5273(15)31026-3 [published Online First: 2016/01/10]

2. Kyu HH, Abate D, Abate KH, et al. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet* 2018;392(10159):1859-922. doi: 10.1016/S0140-6736(18)32335-3

3. Cook C, Cole G, Asaria P, et al. The annual global economic burden of heart failure. *International journal of cardiology* 2014;171(3):368-76. doi: 10.1016/j.ijcard.2013.12.028 [published Online First: 2014/01/09]

4. Savarese G, Lund LH. Global Public Health Burden of Heart Failure. *Card Fail Rev* 2017;3(1):7-11. doi: 10.15420/cfr.2016:25:2 [published Online First: 2017/08/09]

5. Abreu A, Pesah E, Supervia M, et al. Cardiac rehabilitation availability and delivery in Europe: How does it differ by region and compare with other high-income countries?: Endorsed by the European Association of Preventive Cardiology. *European journal of preventive cardiology* 2019;26(11):1131-46. doi: 10.1177/2047487319827453 [published Online First: 2019/02/21]

6. Vos T, Lim SS, Abbafati C, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet* 2020;396(10258):1204-22. doi: 10.1016/S0140-6736(20)30925-9

7. Kotseva K, De Backer G, De Bacquer D, et al. Lifestyle and impact on cardiovascular risk factor control in coronary patients across 27 countries: Results from the European Society of Cardiology ESC-EORP EUROASPIRE V registry. *European journal of preventive cardiology* 2019;26(8):824-35. doi: 10.1177/2047487318825350 [published Online First: 2019/02/12]

8. Touloumi G, Karakosta A, Kalpourtzi N, et al. High prevalence of cardiovascular risk factors in adults living in Greece: the EMENO National Health Examination Survey. *BMC Public Health* 2020;20(1):1665. doi: 10.1186/s12889-020-09757-4

9. Piepoli MF, Hoes AW, Brotons C, et al. Main messages for primary care from the 2016 European Guidelines on cardiovascular disease prevention in clinical practice. *The European journal of general practice* 2018;24(1):51-56. doi: 10.1080/13814788.2017.1398320 [published Online First: 2017/11/24]

10. 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. *European journal of preventive cardiology* 2021;28(5):460-95. doi: 10.1177/2047487320913379

11. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for

cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC). *European heart journal* 2021 doi: 10.1093/eurheartj/ehab484

12. Sandercock GR, Cardoso F, Almodhy M, et al. Cardiorespiratory fitness changes in patients receiving comprehensive outpatient cardiac rehabilitation in the UK: a multicentre study. *Heart* 2013;99(11):785-90. doi: 10.1136/heartjnl-2012-303055 [published Online First: 2012/11/28]
13. Anderson L, Oldridge N, Thompson DR, et al. Exercise-Based Cardiac Rehabilitation for Coronary Heart Disease: Cochrane Systematic Review and Meta-Analysis. *Journal of the American College of Cardiology* 2016;67(1):1-12. doi: 10.1016/j.jacc.2015.10.044 [published Online First: 2016/01/15]
14. Salzwedel A, Jensen K, Rauch B, et al. Effectiveness of comprehensive cardiac rehabilitation in coronary artery disease patients treated according to contemporary evidence based medicine: Update of the Cardiac Rehabilitation Outcome Study (CROS-II). *European journal of preventive cardiology* 2020;27(16):1756-74. doi: 10.1177/2047487320905719 [published Online First: 2020/02/23]
15. de Vries H, Kemps HM, van Engen-Verheul MM, et al. Cardiac rehabilitation and survival in a large representative community cohort of Dutch patients. *European heart journal* 2015;36(24):1519-28. doi: 10.1093/eurheartj/ehv111 [published Online First: 2015/04/19]
16. Long L, Mordi IR, Bridges C, et al. Exercise-based cardiac rehabilitation for adults with heart failure. *The Cochrane database of systematic reviews*

2019;1(1):Cd003331. doi: 10.1002/14651858.CD003331.pub5 [published Online First: 2019/01/30]

17. Neubeck L, Freedman SB, Clark AM, et al. Participating in cardiac rehabilitation: a systematic review and meta-synthesis of qualitative data. *European journal of preventive cardiology* 2012;19(3):494-503. doi: 10.1177/1741826711409326 [published Online First: 2012/07/11]

18. Dunlay SM, Witt BJ, Allison TG, et al. Barriers to participation in cardiac rehabilitation. *American heart journal* 2009;158(5):852-9. doi: 10.1016/j.ahj.2009.08.010 [published Online First: 2009/10/27]

19. Ruano-Ravina A, Pena-Gil C, Abu-Assi E, et al. Participation and adherence to cardiac rehabilitation programs. A systematic review. *International journal of cardiology* 2016;223:436-43. doi: 10.1016/j.ijcard.2016.08.120 [published Online First: 2016/08/25]

20. Sari DM, Wijaya LCG. Cardiac rehabilitation via telerehabilitation in COVID-19 pandemic situation. *The Egyptian Heart Journal* 2021;73(1):31. doi: 10.1186/s43044-021-00156-7

21. Besnier F, Gayda M, Nigam A, et al. Cardiac Rehabilitation During Quarantine in COVID-19 Pandemic: Challenges for Center-Based Programs. *Arch Phys Med Rehabil* 2020;101(10):1835-38. doi: 10.1016/j.apmr.2020.06.004 [published Online First: 2020/06/27]

22. Ambrosetti M, Abreu A, Cornelissen V, et al. Delphi consensus recommendations on how to provide cardiovascular rehabilitation in the COVID-19 era. *European journal of preventive cardiology* 2021;28(5):541-57. doi: 10.1093/eurjpc/zwaa080

23. Batalik L, Dosbaba F, Hartman M, et al. Long-term exercise effects after cardiac telerehabilitation in patients with coronary artery disease: 1-year follow-up results of the randomized study. *European journal of physical and rehabilitation medicine* 2021 doi: 10.23736/s1973-9087.21.06653-3 [published Online First: 2021/02/24]

24. Batalik L, Pepera G, Papathanasiou J, et al. Is the Training Intensity in Phase Two Cardiovascular Rehabilitation Different in Telehealth versus Outpatient Rehabilitation? *Journal of Clinical Medicine* 2021;10(18) doi: 10.3390/jcm10184069

25. Batalik L, Konecny V, Dosbaba F, et al. Cardiac rehabilitation based on the walking test and telerehabilitation improved cardiorespiratory fitness in people diagnosed with coronary heart disease during the covid-19 pandemic. *International Journal of Environmental Research and Public Health* 2021;18(5):1-11. doi: 10.3390/ijerph18052241

26. Kraal JJ, Peek N, Van den Akker-Van Marle ME, et al. Effects of home-based training with telemonitoring guidance in low to moderate risk patients entering cardiac rehabilitation: short-term results of the FIT@Home study. *European journal of preventive cardiology* 2014;21(2 Suppl):26-31. doi: 10.1177/2047487314552606 [published Online First: 2014/10/31]

27. Piotrowicz E, Piotrowicz R, Opolski G, et al. Hybrid comprehensive telerehabilitation in heart failure patients (TELEREH-HF): A randomized, multicenter, prospective, open-label, parallel group controlled trial—Study design and description of the intervention. *American heart journal* 2019;217:148-58. doi: 10.1016/j.ahj.2019.08.015

28. Frederix I, Solmi F, Piepoli MF, et al. Cardiac telerehabilitation: A novel cost-efficient care delivery strategy that can induce long-term health benefits. *European journal of preventive cardiology* 2017;24(16):1708-17. doi: 10.1177/2047487317732274 [published Online First: 2017/09/20]

29. Maddison R, Rawstorn JC, Stewart RAH, et al. Effects and costs of real-time cardiac telerehabilitation: randomised controlled non-inferiority trial. *Heart* 2019;105(2):122. doi: 10.1136/heartjnl-2018-313189

30. Brouwers RWM, van Exel HJ, van Hal JMC, et al. Cardiac telerehabilitation as an alternative to centre-based cardiac rehabilitation. *Netherlands heart journal : monthly journal of the Netherlands Society of Cardiology and the Netherlands Heart Foundation* 2020;28(9):443-51. doi: 10.1007/s12471-020-01432-y [published Online First: 2020/06/05]

31. Cavalheiro AH, Silva Cardoso J, Rocha A, et al. Effectiveness of Tele-rehabilitation Programs in Heart Failure: A Systematic Review and Meta-analysis. *Health Serv Insights* 2021;14:11786329211021668-68. doi: 10.1177/11786329211021668

32. Jin K, Khonsari S, Gallagher R, et al. Telehealth interventions for the secondary prevention of coronary heart disease: A systematic review and meta-analysis. *European journal of cardiovascular nursing : journal of the Working Group on Cardiovascular Nursing of the European Society of Cardiology* 2019;18(4):260-71. doi: 10.1177/1474515119826510 [published Online First: 2019/01/23]

33. Subedi N, Rawstorn JC, Gao L, et al. Implementation of Telerehabilitation Interventions for the Self-Management of Cardiovascular Disease: Systematic

Review. *JMIR mHealth and uHealth* 2020;8(11):e17957. doi: 10.2196/17957 [published Online First: 2020/11/28]

34. Batalik L, Filakova K, Batalikova K, et al. Remotely monitored telerehabilitation for cardiac patients: A review of the current situation. *World J Clin Cases* 2020;8(10):1818-31. doi: 10.12998/wjcc.v8.i10.1818

35. Chan A-W, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Annals of internal medicine* 2013;158(3):200-07. doi: 10.7326/0003-4819-158-3-201302050-00583

36. Eysenbach G. CONSORT-EHEALTH: Improving and Standardizing Evaluation Reports of Web-based and Mobile Health Interventions. *Journal of medical Internet research* 2011;13(4):e126. doi: 10.2196/jmir.1923

37. 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. *European journal of preventive cardiology* 2020:2047487320913379. doi: 10.1177/2047487320913379 [published Online First: 2020/04/01]

38. Hansen D, Abreu A, Ambrosetti M, et al. Exercise intensity assessment and prescription in cardiovascular rehabilitation and beyond: why and how: a position statement from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology. *European journal of preventive cardiology* 2021 doi: 10.1093/eurjpc/zwab007

39. Hansen D, Mathijs W, Michiels Y, et al. Phase III multidisciplinary exercise-based rehabilitation is associated with fewer hospitalizations due to adverse

cardiovascular events in coronary artery disease patients. *European journal of preventive cardiology* 2020 doi: 10.1093/eurjpc/zwaa038

40. La Scala Teixeira CV, Evangelista AL, Pereira PEA, et al. Complexity: A Novel Load Progression Strategy in Strength Training. *Front Physiol* 2019;10:839. doi: 10.3389/fphys.2019.00839 [published Online First: 2019/07/30]
41. Lee WW, Choi KC, Yum RW, et al. Effectiveness of motivational interviewing on lifestyle modification and health outcomes of clients at risk or diagnosed with cardiovascular diseases: A systematic review. *Int J Nurs Stud* 2016;53:331-41. doi: 10.1016/j.ijnurstu.2015.09.010 [published Online First: 2015/10/24]
42. Pepera GB, Paul D;Sandercock, Gavin R H. A pilot study to investigate the safety of exercise training and testing in cardiac rehabilitation patients. *The British Journal of Cardiology* 2013;20:78. doi: http://dx.doi.org/10.5837/bjc.2013.012
43. Bethell HJ. Exercise-based cardiac rehabilitation. *Medicine (Baltimore)* 2006;34(5):195-96. doi: 10.1383/medc.2006.34.5.195
44. Guazzi M, Arena R, Halle M, et al. 2016 focused update: clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *European heart journal* 2018;39(14):1144-61. doi: 10.1093/eurheartj/ehw180 [published Online First: 2016/05/04]
45. Fletcher GF, Ades PA, Kligfield P, et al. Exercise standards for testing and training: A scientific statement from the American heart association. *Circulation* 2013;128(8):873-934. doi: 10.1161/CIR.0b013e31829b5b44
46. Santos-Lozano A, Santín-Medeiros F, Cardon G, et al. Actigraph GT3X: Validation and Determination of Physical Activity Intensity Cut Points. *Int J Sports Med* 2013;34(11):975-82. [published Online First: 22.05.2013]

47. Mâsse LC, Fuemmeler BF, Anderson CB, et al. Accelerometer data reduction: a comparison of four reduction algorithms on select outcome variables. *Medicine and science in sports and exercise* 2005;37(11 Suppl):S544-54. doi: 10.1249/01.mss.0000185674.09066.8a [published Online First: 2005/11/19]

48. Van Remoortel H, Raste Y, Louvaris Z, et al. Validity of six activity monitors in chronic obstructive pulmonary disease: a comparison with indirect calorimetry. *PloS one* 2012;7(6):e39198. doi: 10.1371/journal.pone.0039198 [published Online First: 2012/06/30]

49. Healy GN, Matthews CE, Dunstan DW, et al. Sedentary time and cardio-metabolic biomarkers in US adults: NHANES 2003-06. *European heart journal* 2011;32(5):590-7. doi: 10.1093/eurheartj/ehq451 [published Online First: 2011/01/13]

50. Papathanasiou G, Georgoudis G, Papandreou M, et al. Reliability Measures of the Short International Physical Activity Questionnaire (IPAQ) in Greek Young Adults. *Hellenic journal of cardiology : HJC = Hellēnikē kardiologikē epitheōrēsē* 2009;50:283-94.

51. Kontodimopoulos N, Pappa E, Niakas D, et al. Validity of the EuroQoL (EQ-5D) instrument in a Greek general population. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2008;11(7):1162-9. doi: 10.1111/j.1524-4733.2008.00356.x [published Online First: 2008/05/21]

52. Rishi P, Rishi E, Maitray A, et al. Hospital anxiety and depression scale assessment of 100 patients before and after using low vision care: A prospective study in a tertiary eye-care setting. *Indian journal of ophthalmology* 2017;65(11):1203-08. doi: 10.4103/ijo.IJO_436_17

53. Bjelland I, Dahl AA, Haug TT, et al. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *Journal of psychosomatic research* 2002;52(2):69-77. doi: 10.1016/s0022-3999(01)00296-3 [published Online First: 2002/02/08]

54. Michopoulos I, Kalkavoura C, Michalopoulou P, et al. [Hospital anxiety and depression scale (HADS): Validation in a Greek general hospital sample]. *Psychiatrike = Psychiatriki* 2007;18(3):217-24. [published Online First: 2007/07/01]

55. Butte NF, Ekelund U, Westerterp KR. Assessing physical activity using wearable monitors: measures of physical activity. *Medicine and science in sports and exercise* 2012;44(1 Suppl 1):S5-12. doi: 10.1249/MSS.0b013e3182399c0e [published Online First: 2011/12/23]

56. Warren JM, Ekelund U, Besson H, et al. Assessment of physical activity - a review of methodologies with reference to epidemiological research: a report of the exercise physiology section of the European Association of Cardiovascular Prevention and Rehabilitation. *Eur J Cardiovasc Prev Rehabil* 2010;17(2):127-39. doi: 10.1097/HJR.0b013e32832ed875 [published Online First: 2010/03/11]

57. Westerterp KR. Reliable assessment of physical activity in disease: an update on activity monitors. *Curr Opin Clin Nutr Metab Care* 2014;17(5):401-6. doi: 10.1097/mco.0000000000000080 [published Online First: 2014/08/12]

58. Kidholm K, Rasmussen MK, Andreasen JJ, et al. Cost-Utility Analysis of a Cardiac Telerehabilitation Program: The Teledialog Project. *Telemedicine journal and e-health : the official journal of the American Telemedicine Association* 2016;22(7):553-63. doi: 10.1089/tmj.2015.0194 [published Online First: 2015/12/30]

59. Network HFP. Heart failure policy and practice in Europe: Greece, 2020.

60. Vasilopoulou M, Papaioannou AI, Kaltsakas G, et al. Home-based maintenance tele-rehabilitation reduces the risk for acute exacerbations of COPD, hospitalisations and emergency department visits. *European Respiratory Journal* 2017;49(5):1602129. doi: 10.1183/13993003.02129-2016

61. Falter M, Scherrenberg M, Dendale P. Digital health in cardiac rehabilitation and secondary prevention: A search for the ideal tool. *Sensors (Switzerland)* 2021;21(1):1-11. doi: 10.3390/s21010012

62. Snoek JA, Prescott EI, van der Velde AE, et al. Effectiveness of Home-Based Mobile Guided Cardiac Rehabilitation as Alternative Strategy for Nonparticipation in Clinic-Based Cardiac Rehabilitation Among Elderly Patients in Europe: A Randomized Clinical Trial. *JAMA cardiology* 2021;6(4):463-68. doi: 10.1001/jamacardio.2020.5218 %J JAMA Cardiology

63. Batalik L, Dosbaba F, Hartman M, et al. Benefits and effectiveness of using a wrist heart rate monitor as a telerehabilitation device in cardiac patients: A randomized controlled trial. *Medicine (Baltimore)* 2020;99(11):e19556-e56. doi: 10.1097/MD.0000000000019556

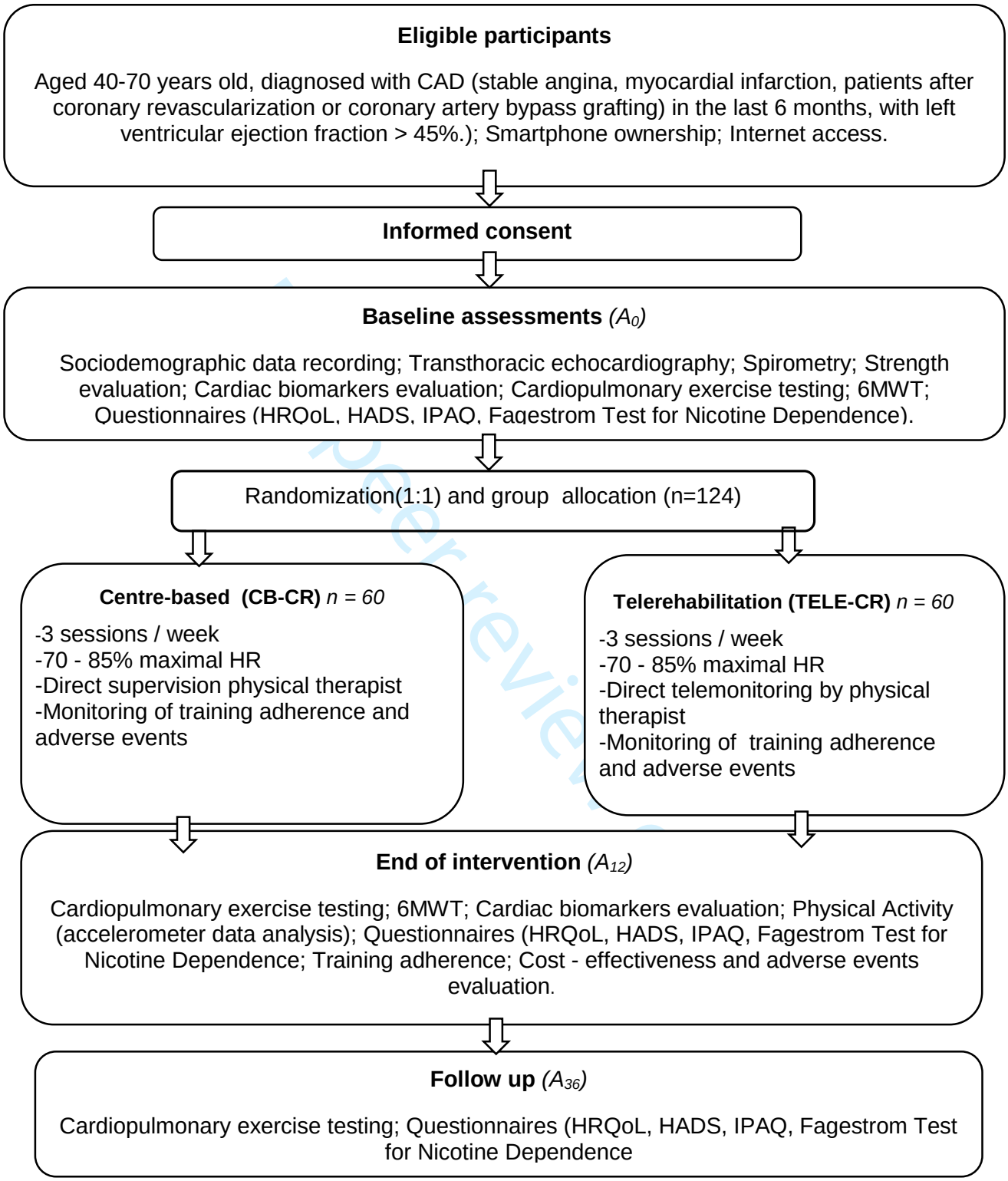
64. Kraal JJ, Van den Akker-Van Marle ME, Abu-Hanna A, et al. Clinical and cost-effectiveness of home-based cardiac rehabilitation compared to conventional, centre-based cardiac rehabilitation: Results of the FIT@Home study. *European journal of preventive cardiology* 2017;24(12):1260-73. doi: 10.1177/2047487317710803

65. Hwang R, Bruning J, Morris NR, et al. Home-based telerehabilitation is not inferior to a centre-based program in patients with chronic heart failure: a randomised

trial. *Journal of physiotherapy* 2017;63(2):101-07. doi: 10.1016/j.jphys.2017.02.017 [published Online First: 2017/03/25]

Figure 1. Flowchart of the study design

.



HR: heart rate, HRQoL: Health related quality of life, HADS: Hospital Anxiety and Depression scale, IPAQ: International Physical Activity Questionnaire, CAD: Coronary Artery Disease

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered,	3,6

		name of intended registry	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	n/a
Funding	#4	Sources and types of financial, material, and other support	35
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 25
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	25
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a

Introduction

Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg,	9,10

		surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12-19
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	17
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	17,19
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	19-22
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7-8

Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	22
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	17,18, 20-22
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	17
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values).	17-19

		Reference to where details of data management procedures can be found, if not in the protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	22
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	22
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial	16-17

		conduct	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	23
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	17
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	9
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9,19
Declaration of	#28	Financial and other competing interests for principal	25

interests		investigators for the overall trial and each study site	
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	23
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	25
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

Notes:

- 18a: 15,16,18-20 The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons Attribution License CC-BY-NC. This checklist was completed on 05. December 2021 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai