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

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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.

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22
23

24
25 Word count: 3.337
26
27

28 29 30 Abstract

31
32 **Introduction:** Exercise – based cardiovascular rehabilitation is a beneficial tool for
33 the secondary prevention of cardiovascular diseases with, however, low participation
34 rates. Telerehabilitation, intergrading mobile technologies and wireless sensors, may
35 advance the cardiac patients' adherence. This study will investigate the efficacy and
36 safety of a telerehabilitation program based on objective exercise telemonitoring and
37 evaluation of physical activity.
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47 **Methods and Analysis:** A supervised, parallel-group, single-blind, randomized
48 controlled trial will be conducted. One hundred and twenty four coronary disease
49 patients will be randomized at a 1:1 ratio into two groups: intervention
50 telerehabilitation group (TELE-CR) (n=62) and control, center – based cardiovascular
51 rehabilitation group (CB-CR) (n=62). Participants will receive a 12 – week exercise
52 based rehabilitation program; remotely monitored for the telerehabilitation group and
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3 standard supervised for the center – based group. All participants will train at 70% of
4
5 their maximal heart rate, as obtained from cardiopulmonary exercise testing (CPET)
6
7 for 60", three times/ week. The primary outcomes will be the assessment of
8
9 cardiorespiratory fitness, expressed as peak oxygen uptake assessed by the CPET test
10
11 or the 6 minute walking test (6MWT). Secondary outcomes will be the physical
12
13 activity, the safety of the exercise intervention, (number of adverse events that may
14
15 occur during the exercise), quality of life, training adherence, and cost – effectiveness.
16
17 Assessments will be held at baseline, end of intervention (12 weeks) and follow up
18
19 (36 weeks).
20
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23

24
25 **Ethics and dissemination:** The study protocol has been reviewed and approved by
26
27 the Ethics Committee of the University of Thessaly and by the Ethics Committee of
28
29 the General University Hospital of Larissa. The results of this study will be
30
31 disseminated through manuscript publications and conference presentations.
32
33

34
35 **Keywords:** cardiovascular rehabilitation; telerehabilitation; wearable sensors;
36
37 physical fitness; physical activity
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41 **Trial registration:** Clinical Trial.gov, Identifier: NCT05019157. Registered 24
42
43 August 2021.

44
45 [https://clinicaltrials.gov/ct2/show/NCT05019157?cond=cardiac+telerehabilitation&cn](https://clinicaltrials.gov/ct2/show/NCT05019157?cond=cardiac+telerehabilitation&country=GR&draw=2&rank=1)
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47 [try=GR&draw=2&rank=1](https://clinicaltrials.gov/ct2/show/NCT05019157?cond=cardiac+telerehabilitation&country=GR&draw=2&rank=1)
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50 51 **Strengths and limitations of this study**

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- Telerehabilitation 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 factors⁷ 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-

1
2
3 hospitalizations rates,^{13 14} physical inactivity and all CVD risk factors including blood
4
5 pressure, blood lipid profile, glucose metabolism and weight status.^{15 16} Despite
6
7 global recommendations, patients' participation in CR programs is low, mainly due to
8
9 insufficient medical referral, travel distance, low self-efficacy, perceived body image
10
11 and lack of time.¹⁷⁻¹⁹ Moreover, during the COVID-19 pandemic, new barriers have
12
13 arisen, such as the suspension of centre-based CR and in-person sessions, travelling
14
15 and circulation restrictions.^{20 21} Thus the need to avoid the downgrading of CR is
16
17 imperative.²²

22
23 Rapid development in information and communication technologies (ICTs) may help
24
25 to overcome the barriers to CR.²³⁻²⁵ Telerehabilitation is proposed as a feasible,^{26 27}
26
27 safe and cost – effective intervention,^{28 29} leading to long-term improvement of CVD
28
29 risk factors, reduced healthcare costs and increased CR participation adherence.
30
31 ³⁰.Recent systematic reviews advocate to the use of telehealth interventions as an
32
33 adjunct to CR ³¹⁻³³ for the continuance of CR through pandemic circumstances. ^{20 21}

37
38 A recent review proclaims the integration of remote technologies and wearable
39
40 sensors in the telerehabilitation, mentioning though the need for further investigation.
41
42 ³⁴ Another systematic review indicates that, software-enabled systems reduce timing-
43
44 related barriers to patients' participation.³² The feasibility and safety of cardiac
45
46 telerehabilitation need further investigation since most relevant studies are not
47
48 addressing safety matters and a formal cost - effectiveness analysis.^{32 34}

51
52 Our study focuses on the objective recording and monitoring of the exercise
53
54 implementation and physical activity, through the use of wearable sensors (heart rate
55
56 monitors, accelerometers). Based on thorough literature review, it is the first study to
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60

1
2
3 integrate real time supervision (use of videoconference platforms) and a group based
4
5 design for home exercising (up to 5 participants).
6
7

8
9 The primary aims of this study are to compare the effect between telerehabilitation
10
11 and regular outpatient CR methods, related to cardiorespiratory fitness (CRF) and
12
13 functional capacity. Whilst possible effects in physical activity, training adherence,
14
15 anxiety and stress management, safety and cost – effectiveness are considered as
16
17 secondary aims.
18
19

20
21 The hypothesis of the study will be that the telerehabilitation intervention will have at
22
23 least the same efficiency with the regular, centre - based rehabilitation and that it will
24
25 be as safe as and even more cost-effective than the centre - based rehabilitation
26
27 intervention.
28
29

30 31 **METHODS**

32 33 **Study design**

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35 A supervised, parallel-group, single-blind, randomized controlled trial with 6 months
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37 follow-up will be employed. The study includes CAD patients, enrolled in a
38
39 telerehabilitation group (TELE-CR) and a control group undertaking regular
40
41 outpatient CR rehabilitation (CB-CR) for comparison reasons. Three assessments will
42
43 take place at baseline (A_0), end of intervention (A_{12}) and follow up 36 weeks (A_{36}). A
44
45 CONSORT (Consolidated Standard of Reporting Trials) flow diagram is shown in
46
47 Fig. 1.
48
49
50
51

52
53 The study protocol complies with the SPIRIT 2013 statement guidelines³⁵ and the
54
55 intervention procedures are described according to the CONSORT- E- HEALTH
56
57 checklist.³⁶ We used the SPIRIT checklist when writing our report.³⁵ The trial is
58
59 registered at ClinicalTrials.gov with registration number NCT05019157.
60

1				
2				
3	Spirometry, TTE	X		
4				
5				
6	Strength evaluation test	X		
7				
8				
9	Cardiac biomarkers			
10				
11				
12	(BNP, NT-proBNP,	X	X	
13				
14	Troponines, CPK)			
15				
16				
17				
18	CPET – 6MWT	X	X	X
19				
20				
21	HRQoL	X	X	X
22				
23				
24	HADS	X	X	X
25				
26				
27	IPAQ	X	X	X
28				
29				
30	FTND	X	X	X
31				
32				
33				
34	Cost analysis		X	
35				
36				
37	Training Adherence		X	
38				
39				

40 TTE: Transthoracic echocardiography, CPET: cardiopulmonary exercise testing,
 41
 42 6MWT: 6 Minute Walking Test, BMP: B-type natriuretic peptide, CPK: Creatine
 43 phosphokinase, HRQoL: Health related quality of life, HADS: Hospital Anxiety
 44 and Depression scale, IPAQ: International Physical Activity Questionnaire FTND:
 45 Fagestrom Test for Nicotine Dependence
 46
 47
 48
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 50

51 52 53 54 55 56 57 **Patient population and eligibility** 58 59 60

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
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<p>-Absence of angina or other symptoms (eg unusual shortness of breath, mild headache or dizziness)</p> <p>-Functional capacity > 7 METs, left ventricular ejection fraction (LVEF) \geq 50%</p> <p>-Absence of arrhythmia at rest</p> <p>-Absence of depression</p>	<p>- Presence of angina or other symptoms (eg unusual shortness of breath, mild headache or dizziness, dizziness occurring at high levels of exercise \geq 7 METs)</p> <p>-Mild to moderate silent ischemia (ST eruption <2 mm)</p> <p>-Functional capacity > 5 METs</p> <p>-LVEF = 40-49%</p>	<p>-Presence of arrhythmias</p> <p>- Presence of angina or other symptoms (eg unusual breathlessness, mild headache or dizziness, dizziness occurring at high levels of exercise <5 METs)</p> <p>-Silent ischemia (ST stroke \geq 2 mm)</p> <p>-Presence of abnormal hemodynamics during exercise (reduction of BP) or post-exercise hypotension</p> <p>-LVEF <40%</p>
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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	10'
*Moving hands slowly	
*Stretching exercises	

Table 5: TELE-CR exercise program

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

Aerobic Training	Strengthening Training	Balance Training
------------------	------------------------	------------------

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

<p>*Marching on the spot gently</p> <p>*Moving hands slowly</p> <p>*Stretching exercises</p>	<p>10'</p>
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2
3 Blood samplings will be taken, in all assessment endpoints, from all study participants
4
5 to assess any effects of the intervention on the cardiac biomarkers' blood
6
7 concentration (BNP, NT-proBNP, Troponines, CPK).
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9

10
11 All patients will be receiving educational and informational videoconference
12
13 sessions regarding issues of upright exercising, physical activity, diet/nutritional and
14
15 smoking cessation counseling (based on recent guidelines)¹⁰ and psychosocial
16
17 support (via psychotherapy) on stress and anxiety management. Consultation sessions
18
19 may include a family member or friend, especially for elderly patients.⁴¹
20
21 Communication strategies such as motivational interviewing, during telephone calls
22
23 or videoconferences, will be integrated, as they appear to be useful in helping promote
24
25 patients' adherence and avoid incidents of early drop outs. Motivational interviewing
26
27 will be based on the OARS (Open-ended questions, Affirmation, Reflective listening,
28
29 and Summarizing) principle that helps patients to present their perceptions, and
30
31 clinicians to summarize.
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37 Any adverse effects that may occur during the intervention period will be reported for
38
39 safety monitoring and future data interpretation analysis.⁴² Adverse effects are defined
40
41 as all-cause mortality, hospitalization for CVD or serious atrial or ventricular
42
43 arrhythmia, musculoskeletal problems (muscle, tendon or joint problems) or other
44
45 diseases preventing exercise participation. Constant supervision of the CB –CR
46
47 exercise program and the existence of a defibrillator will ensure the participants'
48
49 safety. Whilst for the TELE – CR group, real time exercise telemonitoring via
50
51 videoconference platforms and exercise training within the prescribed HR zone will
52
53 ensure safety. Table 6 summarizes the indications for dropping out training sessions.
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57

58 Table 6. Indications for dropping out training session
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60

-
- Exercise induced angina
 - Fatigue, shortness of breath, dizziness, sweating, cyanosis, headache
 - Orthostatic hypotension, drop in SBP > 20 mmHg during exercise
 - SBP \geq 220 mmHg, DBP \geq 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 intensity⁴³ 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

1
2
3 processed and evaluated by the trial investigator after the completion of the
4
5 intervention.
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9 Additionally, all patients will be lent a tri-axial accelerometer (Actigraph wGT3X,
10 Actigraph), that they will wear around their waist during the 12 week intervention
11 period. Patients should visit the hospital's outpatient clinic on a monthly basis to
12 upload the recorded data to a secure PC application in an encrypted manner. Training
13 adherence will be monitored by the specialized physiotherapist supervising the
14 telerehabilitation exercise sessions.
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26 **OUTCOME MEASURES**

27 **Primary outcome**

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29 The primary outcome will be the assessment of the cardiorespiratory fitness, at
30 baseline, the completion of the intervention (A₁₂) and follow up (A₃₆) in all study
31 groups (CB-CR, TELE-CR).
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43 **Secondary outcomes**

44
45 Secondary outcomes will be the physical activity level, safety, health related quality
46 of life (HRQoL), training adherence, depression and anxiety levels, nicotine
47 dependence and cost effectiveness. Physical activity, HRQoL, nicotine dependence
48 and psychosocial well-being will be measured and assessed at baseline, end of
49 intervention (A₁₂) and follow up (A₃₆). Training adherence and cost evaluation will be
50 assessed at the completion of the intervention (A₁₂).
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60 **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 (A₁₂). 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

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3 The cost-effectiveness analysis will be performed using the assessment of Quality-
4 adjusted life years (QALYs) at baseline (A_0) and end of intervention (A_{12}). Patients
5 will complete the EQ-5D questionnaire (EuroQol-5D) individually⁵¹ and their final
6 scores will be converted into QALYs. The cardiovascular readmission costs (as
7 derived from the invoices from the hospital's financial department), the cardiologist
8 follow-up visits and the diagnostic tests will constitute the healthcare costs. The CB-
9 CR costs will be calculated based on the price list of medical expenses provided by
10 hospital regarding professional wages (physiotherapist, cardiologist), exercise testing
11 assessment costs, and transportation costs to and from the patients' homes to the
12 hospital. In the TELE-CR group the costs will include the purchase of the necessary
13 equipment and consumables (internet connection subscription, telephone
14 communication cost).

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

$$\text{ICER} = (\text{cost}_{\text{intervention group}} - \text{cost}_{\text{control group}}) / (\text{effectiveness}_{\text{intervention group}} - \text{effectiveness}_{\text{control group}}).$$

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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

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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

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3 anxiety and depression subscales.⁵² HADS is a validated measure to assess anxiety
4 and depression symptoms, recommended for CAD patients.^{53 54} Nicotine dependence
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6 will be assessed through the Fagestrom Test for Nicotine Dependence.
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10 11 12 13 **Training adherence**

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15 Patients' training adherence is defined as a percentage of the total number of
16 completed training sessions (100%=36). Patients' adherence in both study groups will
17 be recorded by the supervising hospital outpatient clinic's staff and will be evaluated
18 at the end of intervention (A₁₂).
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23 24 25 **STATISTICAL ANALYSIS**

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27 Normality of data will be examined with Kolmogorov-Smirnov tests. Descriptive
28 statistics will be used to report demographics and baseline characteristics. Between-
29 group and within group differences in the outcome measures will be evaluated using
30 multivariate analysis of variance (MANOVA). The effectiveness of the control (CB-
31 CR) and intervention (TELE-CR) group will be examined with dependent t-test for
32 each group (pre- and post-scores). All participants will be included in an intention to
33 treat analysis, regardless of adherence, for at least the assessment of the primary
34 outcomes. Significance level will be set at P=0.05. Statistical Package for Social
35 Sciences (SPSS), version 25, will be used for all data analysis.
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50 51 **Sample size calculation**

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53 The calculation of the sample size was performed with G * Power 3.1.9.4 software.
54 For test F, h detection of moderate effect size (f = 0.3) after the interaction test (α
55 level = 0.05, 80%) a total of 111 participants were required to examine the recurrent
56 MANOVA. After adjusting for potential drop-outs (estimated attrition rate \leq 10%) a
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3 minimum sample of 124 participants is required. Therefore, at least 62 participants
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5 will be recruited in each group.
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8 **ETHICS AND DISSEMINATION**

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11 The study protocol is approved by the Ethics Committee of the University of Thessaly
12 (#1108/01-12-2021) and by the Ethics Committee of the General University Hospital
13 of Larissa. Written informed consent will be obtained from all study participants
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18 prior to their enrollment to the study intervention.
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21 The findings of this study will be disseminated at a local, national and international
22 level through publications in peer-reviewed journals, national and international
23 conference presentations, social, broadcast and print media. Additionally all study
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28 participants will receive the study findings through electronic and postal mail.
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30 **DISCUSSION**

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35 This trial is aiming to evaluate the efficacy, the efficiency and the safety of an
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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 PA⁵⁵⁻⁵⁷ or than the perceived rate of exertion on its own.⁵⁵

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3 Although a cost-effectiveness analysis is almost prerequisite for any novel
4 intervention, only a few telerehabilitation studies have performed one. Frederix et al.
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6 have showed the cost - effectiveness of an internet-based telerehabilitation program.²⁸
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8 Whilst Kidholm et al. outlined the non-cost effectiveness of a telerehabilitation
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10 program compared to center-based CR.⁵⁸ In our study, we intent to include a
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12 comprehensive cost- effectiveness analysis to evaluate any possible economic gains.
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17 Moreover, the geographical features of Greece, with many islands and remote areas,
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19 contribute to the care inequality being observed, combined with the high variability of
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21 access to primary care professionals.⁵⁹ CR is almost absent from the Greek public
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23 health system, partly owing to the lack of clinics and training in its delivery.
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25 Furthermore, while some studies have already investigated the implications of
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27 telerehabilitation in other diseases, such COPD, with favorable outcomes,⁶⁰ no similar
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29 study, to our knowledge, has not yet been carried out for CAD patients, leaving a
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31 great gap open. In accordance to these statements recent guidelines support the
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33 implementation of home-based CR, telehealth, and mHealth interventions, with the
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35 use of wearable activity trackers to increase cardiac patients' participation rates and
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37 long-term adherence to healthy behaviors.¹¹
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44 Therefore, there is an urgent need for innovative, safe, more cost-effective CR
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46 strategies. If an exercise based telerehabilitation program, using wearable sensors,
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48 meets these prerequisites, it can act as a supplementary and/or substitutional
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50 (according to the needs) to traditional center - based CR in CAD patients of low to
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52 moderate cardiac risk, thus allowing more patients to have access to CR with the least
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54 possible economic burden.
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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.

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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

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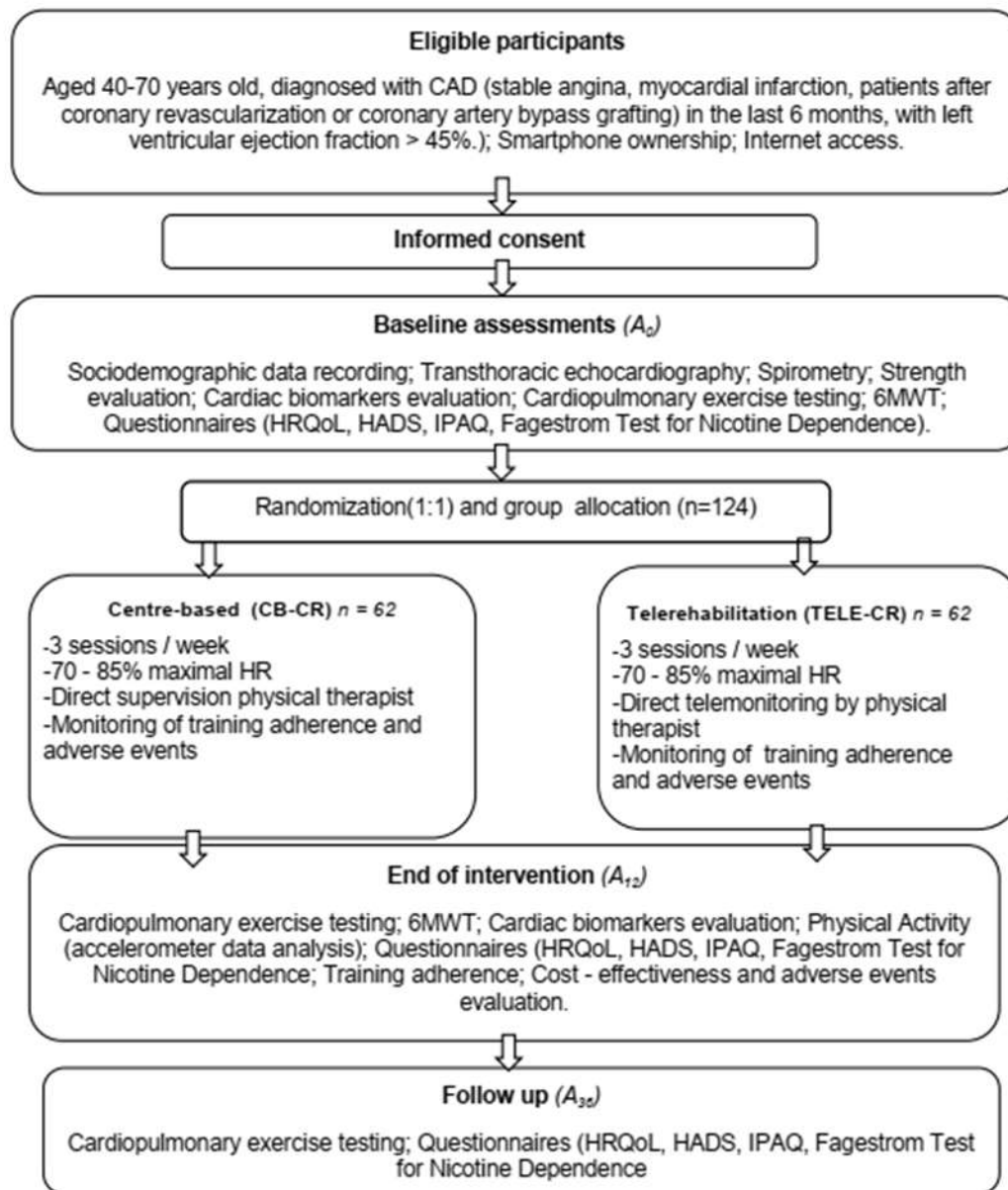
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Fig 1 Flowchart of the study design



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.

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			Page
		Reporting Item	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

1		name of intended registry	
2			
3			
4	Trial registration: data	#2b All items from the World Health Organization Trial	n/a
5			
6	set	Registration Data Set	
7			
8			
9	Protocol version	#3 Date and version identifier	n/a
10			
11			
12	Funding	#4 Sources and types of financial, material, and other support	35
13			
14			
15	Roles and	#5a Names, affiliations, and roles of protocol contributors	1, 25
16			
17	responsibilities:		
18			
19	contributorship		
20			
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22			
23	Roles and	#5b Name and contact information for the trial sponsor	25
24			
25	responsibilities:		
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27	sponsor contact		
28			
29	information		
30			
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32			
33	Roles and	#5c Role of study sponsor and funders, if any, in study design;	n/a
34			
35	responsibilities:	collection, management, analysis, and interpretation of	
36			
37	sponsor and funder	data; writing of the report; and the decision to submit the	
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45	Roles and	#5d Composition, roles, and responsibilities of the coordinating	n/a
46			
47	responsibilities:	centre, steering committee, endpoint adjudication	
48			
49	committees	committee, data management team, and other individuals	
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57	Introduction		
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1	Background and	#6a	Description of research question and justification for	4-6
2				
3	rationale		undertaking the trial, including summary of relevant studies	
4			(published and unpublished) examining benefits and harms	
5			for each intervention	
6				
7				
8				
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10				
11	Background and	#6b	Explanation for choice of comparators	6
12				
13	rationale: choice of			
14				
15	comparators			
16				
17				
18	Objectives	#7	Specific objectives or hypotheses	6
19				
20				
21				
22	Trial design	#8	Description of trial design including type of trial (eg, parallel	6
23			group, crossover, factorial, single group), allocation ratio,	
24			and framework (eg, superiority, equivalence, non-inferiority,	
25			exploratory)	
26				
27				
28				
29				
30				
31	Methods:			
32				
33	Participants,			
34				
35	interventions, and			
36				
37	outcomes			
38				
39				
40				
41	Study setting	#9	Description of study settings (eg, community clinic,	8
42			academic hospital) and list of countries where data will be	
43			collected. Reference to where list of study sites can be	
44			obtained	
45				
46				
47				
48				
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50				
51	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If	9,10
52			applicable, eligibility criteria for study centres and	
53			individuals who will perform the interventions (eg,	
54				
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1		surgeons, psychotherapists)	
2			
3			
4	Interventions:	#11a Interventions for each group with sufficient detail to allow	12-19
5			
6	description	replication, including how and when they will be	
7			
8		administered	
9			
10			
11	Interventions:	#11b Criteria for discontinuing or modifying allocated	17
12			
13	modifications	interventions for a given trial participant (eg, drug dose	
14			
15		change in response to harms, participant request, or	
16			
17		improving / worsening disease)	
18			
19			
20			
21	Interventions:	#11c Strategies to improve adherence to intervention protocols,	17,19
22			
23	adherence	and any procedures for monitoring adherence (eg, drug	
24			
25		tablet return; laboratory tests)	
26			
27			
28			
29	Interventions:	#11d Relevant concomitant care and interventions that are	n/a
30			
31	concomitant care	permitted or prohibited during the trial	
32			
33			
34	Outcomes	#12 Primary, secondary, and other outcomes, including the	19-22
35			
36		specific measurement variable (eg, systolic blood	
37			
38		pressure), analysis metric (eg, change from baseline, final	
39			
40		value, time to event), method of aggregation (eg, median,	
41			
42		proportion), and time point for each outcome. Explanation	
43			
44		of the clinical relevance of chosen efficacy and harm	
45			
46		outcomes is strongly recommended	
47			
48			
49			
50			
51	Participant timeline	#13 Time schedule of enrolment, interventions (including any	7-8
52			
53		run-ins and washouts), assessments, and visits for	
54			
55		participants. A schematic diagram is highly recommended	
56			
57		(see Figure)	
58			
59			
60			

1	Sample size	#14	Estimated number of participants needed to achieve study	22
2			objectives and how it was determined, including clinical and	
3			statistical assumptions supporting any sample size	
4			calculations	
5				
6				
7				
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9				
10				
11	Recruitment	#15	Strategies for achieving adequate participant enrolment to	9
12			reach target sample size	
13				
14				
15				
16	Methods: Assignment			
17	of interventions (for			
18	controlled trials)			
19				
20				
21				
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23				
24	Allocation: sequence	#16a	Method of generating the allocation sequence (eg,	11
25	generation		computer-generated random numbers), and list of any	
26			factors for stratification. To reduce predictability of a	
27			random sequence, details of any planned restriction (eg,	
28			blocking) should be provided in a separate document that is	
29			unavailable to those who enrol participants or assign	
30			interventions	
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41	Allocation	#16b	Mechanism of implementing the allocation sequence (eg,	11
42	concealment		central telephone; sequentially numbered, opaque, sealed	
43	mechanism		envelopes), describing any steps to conceal the sequence	
44			until interventions are assigned	
45				
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51	Allocation:	#16c	Who will generate the allocation sequence, who will enrol	9
52	implementation		participants, and who will assign participants to	
53			interventions	
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1	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg,	11
2			trial participants, care providers, outcome assessors, data	
3			analysts), and how	
4				
5				
6				
7				
8				
9	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is	n/a
10	emergency		permissible, and procedure for revealing a participant's	
11			allocated intervention during the trial	
12	unblinding			
13				
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15				
16	Methods: Data			
17	collection,			
18	management, and			
19	analysis			
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26	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline,	17,18,
27			and other trial data, including any related processes to	
28			promote data quality (eg, duplicate measurements, training	20-22
29			of assessors) and a description of study instruments (eg,	
30			questionnaires, laboratory tests) along with their reliability	
31			and validity, if known. Reference to where data collection	
32			forms can be found, if not in the protocol	
33				
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43	Data collection plan:	#18b	Plans to promote participant retention and complete follow-	17
44	retention		up, including list of any outcome data to be collected for	
45			participants who discontinue or deviate from intervention	
46			protocols	
47				
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53	Data management	#19	Plans for data entry, coding, security, and storage,	17-19
54			including any related processes to promote data quality	
55			(eg, double data entry; range checks for data values).	
56				
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1		Reference to where details of data management	
2			
3		procedures can be found, if not in the protocol	
4			
5			
6	Statistics: outcomes	#20a Statistical methods for analysing primary and secondary	22
7			
8		outcomes. Reference to where other details of the	
9			
10		statistical analysis plan can be found, if not in the protocol	
11			
12			
13	Statistics: additional	#20b Methods for any additional analyses (eg, subgroup and	n/a
14			
15	analyses	adjusted analyses)	
16			
17			
18			
19	Statistics: analysis	#20c Definition of analysis population relating to protocol non-	22
20			
21	population and	adherence (eg, as randomised analysis), and any statistical	
22			
23	missing data	methods to handle missing data (eg, multiple imputation)	
24			
25			
26	Methods: Monitoring		
27			
28			
29	Data monitoring:	#21a Composition of data monitoring committee (DMC);	n/a
30			
31	formal committee	summary of its role and reporting structure; statement of	
32			
33		whether it is independent from the sponsor and competing	
34			
35		interests; and reference to where further details about its	
36			
37		charter can be found, if not in the protocol. Alternatively, an	
38			
39		explanation of why a DMC is not needed	
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43			
44	Data monitoring:	#21b Description of any interim analyses and stopping	n/a
45			
46	interim analysis	guidelines, including who will have access to these interim	
47			
48		results and make the final decision to terminate the trial	
49			
50			
51	Harms	#22 Plans for collecting, assessing, reporting, and managing	16-17
52			
53		solicited and spontaneously reported adverse events and	
54			
55		other unintended effects of trial interventions or trial	
56			
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1		conduct	
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3			
4	Auditing	#23 Frequency and procedures for auditing trial conduct, if any,	17
5			
6		and whether the process will be independent from	
7			
8		investigators and the sponsor	
9			
10			
11	Ethics and		
12			
13	dissemination		
14			
15			
16	Research ethics	#24 Plans for seeking research ethics committee / institutional	23
17			
18	approval	review board (REC / IRB) approval	
19			
20			
21	Protocol	#25 Plans for communicating important protocol modifications	17
22			
23	amendments	(eg, changes to eligibility criteria, outcomes, analyses) to	
24		relevant parties (eg, investigators, REC / IRBs, trial	
25		participants, trial registries, journals, regulators)	
26			
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31	Consent or assent	#26a Who will obtain informed consent or assent from potential	9
32		trial participants or authorised surrogates, and how (see	
33		Item 32)	
34			
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39	Consent or assent:	#26b Additional consent provisions for collection and use of	9
40			
41	ancillary studies	participant data and biological specimens in ancillary	
42		studies, if applicable	
43			
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46			
47	Confidentiality	#27 How personal information about potential and enrolled	9,19
48			
49		participants will be collected, shared, and maintained in	
50		order to protect confidentiality before, during, and after the	
51		trial	
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57	Declaration of	#28 Financial and other competing interests for principal	25
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1	interests		investigators for the overall trial and each study site	
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3				
4	Data access	#29	Statement of who will have access to the final trial dataset,	19
5			and disclosure of contractual agreements that limit such	
6			access for investigators	
7				
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10				
11	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care, and for	n/a
12			compensation to those who suffer harm from trial	
13	trial care		participation	
14				
15				
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17				
18				
19	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial	23
20			results to participants, healthcare professionals, the public,	
21	trial results		and other relevant groups (eg, via publication, reporting in	
22			results databases, or other data sharing arrangements),	
23			including any publication restrictions	
24				
25				
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29				
30				
31	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	n/a
32			professional writers	
33	authorship			
34				
35				
36	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol,	25
37			participant-level dataset, and statistical code	
38	reproducible research			
39				
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41				
42	Appendices			
43				
44				
45	Informed consent	#32	Model consent form and other related documentation given	n/a
46			to participants and authorised surrogates	
47	materials			
48				
49				
50	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	n/a
51			biological specimens for genetic or molecular analysis in	
52			the current trial and for future use in ancillary studies, if	
53			applicable	
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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](#)

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BMJ Open

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

Journal:	<i>BMJ Open</i>
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Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS, REHABILITATION MEDICINE, Cardiology < INTERNAL MEDICINE

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TITLE PAGE

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

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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

1
2
3 Committee of the General University Hospital of Larissa (3780/31-12-2021). The
4
5 results of this study will be disseminated through manuscript publications and
6
7 conference presentations.
8
9

10
11 **Keywords:** cardiac rehabilitation; telerehabilitation; wearable sensors;
12
13 cardiorespiratory fitness; functional capacity
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19 **Trial registration:** Clinical Trial.gov, Identifier: NCT05019157. Registered 24
20
21 August 2021.
22

23
24 [https://clinicaltrials.gov/ct2/show/NCT05019157?cond=cardiac+telerehabilitation&cn](https://clinicaltrials.gov/ct2/show/NCT05019157?cond=cardiac+telerehabilitation&country=GR&draw=2&rank=1)
25
26 [try=GR&draw=2&rank=1](https://clinicaltrials.gov/ct2/show/NCT05019157?cond=cardiac+telerehabilitation&country=GR&draw=2&rank=1)
27
28

29 **Strengths and limitations of this study**

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32
33 • Telerehabilitation as an alternative tool to contemporary centre/community
34 based cardiac rehabilitation.
35
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37 • Intergrading real-time supervision and group-based exercise sessions in
38 cardiac telerehabilitation.
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44 • Objective monitoring and evaluation of physical activity and exercise intensity
45 in cardiac rehabilitation interventions.
46
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48 • Inability, by study design, to blind participants to treatment allocation
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51 • Possible selection bias, since only low and moderate cardiac risk patients will
52 be recruited.
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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 Greece⁶ with cardiac risk factors⁷ 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

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3 Rapid development in information and communication technologies (ICTs) may help
4 to overcome the barriers to CR.²³⁻²⁵ Telerehabilitation is proposed as a feasible,^{26 27}
5 safe and cost – effective intervention,^{28 29} leading to long-term improvement of CVD
6 risk factors, reduced healthcare costs and increased CR participation adherence.
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Recent systematic reviews advocate to the use of telehealth interventions as an adjunct to CR³¹⁻³³ 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

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3 be as safe as and even more cost-effective than the centre - based rehabilitation
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5 intervention.
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8 **METHODS**

9 **Study design**

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15 A supervised, parallel-group, single-blind, randomized controlled trial with 6 months
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17 follow-up will be employed. The study includes CAD patients, enrolled in a
18
19 telerehabilitation group (TELE-CR) and a control group undertaking regular outpatient
20
21 CR rehabilitation (CB-CR) for comparison reasons. Three assessments will take place
22
23 at baseline (A_0), end of intervention (A_{12}) and follow up 36 weeks (A_{36}). A CONSORT
24
25 (Consolidated Standard of Reporting Trials) flow diagram is shown in Fig. 1.
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30 The study protocol complies with the SPIRIT 2013 statement guidelines³⁵ and the
31
32 intervention procedures are described according to the CONSORT- E- HEALTH
33
34 checklist.³⁶ We used the SPIRIT checklist when writing our report.³⁵ The trial is
35
36 registered at ClinicalTrials.gov with registration number NCT05019157.
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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		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). 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
<ul style="list-style-type: none"> -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 	<ul style="list-style-type: none"> - 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% 	<ul style="list-style-type: none"> -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 -LVEF <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. Primary 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	
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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 -Heel 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
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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

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

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3 capacity of 30 days, recorded data will be uploaded with a USB-connection and stored
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5 in the hospital server in an encrypted way on a monthly basis. Total training attendance
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7 rate will be documented by the hospital's staff
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10 **Telerehabilitation group (TELE - CR group)**

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14 Participants in the TELE-CR group will undertake three training sessions (or more if
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16 needed) in the hospital's outpatient clinic for familiarization with the use of the
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18 wearable sensors, the uploading of the training data to the web application (Polar Flow)
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20 and the exercising within their individually determined exercise intensity.
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24 Following the training period, TELE-CR participants will be lent a Polar H10 chest
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26 strap that records HR data and a wrist sports watch (Polar M430, Kempele, Finland)
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28 and will proceed with the telerehabilitation program at their homes. Both wearable
29
30 sensors are validated and reliable tools, allowing effective assessment of exercise
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32 intensity⁴³ and will be used only during the exercise training sessions. The wrist sports
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34 watch will display continuous HR reading from the Polar H10 chest strap, enabling
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36 patients to exercise within their prescribed HR zone and exercise data (duration,
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38 training mode, physical activity tracking). Participants in the TELE-CR group will be
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40 exercising in groups of up to maximum 5 participants in each session. Real time
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42 supervision of this group – based exercise session by a specialized physiotherapist will
43
44 be implemented via videoconference web platforms or applications. At the end of every
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46 training session, patients will upload training data to the web platform (Polar Flow) via
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48 Bluetooth or USB connection. Each patient will have his/her username and login
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50 account and can check his/her training data graphically and correlate it to his/her
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52 personal goals. CR specialized staff from the corresponding hospital will have access
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54 to all patients' accounts so as to monitor successful data uploading, assess the collected
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3 data and provide them with training feedback once a week via telephone video calls.
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5 Uploaded data will be further backed up to an external hard drive to be processed and
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7 evaluated by the trial investigator after the completion of the intervention.
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11 Additionally, all patients will be lent a tri-axial accelerometer (Actigraph wGT3X,
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13 Actigraph), that they will wear around their waist during the 12 week intervention
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15 period. Patients should visit the hospital's outpatient clinic on a monthly basis to upload
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17 the recorded data to a secure PC application in an encrypted manner. Training
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19 adherence will be monitored by the specialized physiotherapist supervising the
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21 telerehabilitation exercise sessions.
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24 25 **OUTCOME MEASURES**

26 27 **Primary outcome**

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29 The primary outcome will be the assessment of the cardiorespiratory fitness, at baseline,
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31 the completion of the intervention (A_{12}) and follow up (A_{36}) in all study groups (CB-
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33 CR, TELE-CR).
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39 40 **Secondary outcomes**

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42 Secondary outcomes will be the physical activity level, safety, health related quality of
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44 life (HRQoL), training adherence, depression and anxiety levels, nicotine dependence
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46 and cost effectiveness. Physical activity, HRQoL, nicotine dependence and
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48 psychosocial well-being will be measured and assessed at baseline, end of intervention
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50 (A_{12}) and follow up (A_{36}). Training adherence and cost evaluation will be assessed at
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52 the completion of the intervention (A_{12}).
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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 (A₁₂). 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) individually⁵¹ 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):

$$\text{ICER} = (\text{cost}_{\text{intervention group}} - \text{cost}_{\text{control group}}) / (\text{effectiveness}_{\text{intervention group}} - \text{effectiveness}_{\text{control group}}).$$

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

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2
3 anxiety and depression subscales.⁵² HADS is a validated measure to assess anxiety and
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5 depression symptoms, recommended for CAD patients.^{53 54} Nicotine dependence will
6
7 be assessed through the Fagestrom Test for Nicotine Dependence.
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10 **Training adherence**

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14 Patients' training adherence is defined as a percentage of the total number of completed
15
16 training sessions (100%=36). Patients' adherence in both study groups will be recorded
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18 by the supervising hospital outpatient clinic's staff and will be evaluated at the end of
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20 intervention (A₁₂). Based on the percentage of the sessions attended, participants will
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22 be categorized in adherent (> 80%), partly adherent (20 to 80%) and non-adherent (<
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24 20%).
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28 **STATISTICAL ANALYSIS**

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32 Normality of data will be examined with Kolmogorov-Smirnov tests. Descriptive
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34 statistics will be used to report demographics and baseline characteristics. Between-
35
36 group and within group differences in the outcome measures will be evaluated using
37
38 multivariate analysis of variance (MANOVA). The effectiveness of the control (CB-
39
40 CR) and intervention (TELE-CR) group will be examined with dependent t-test for each
41
42 group (pre- and post-scores). All participants will be included in an intention to treat
43
44 analysis, regardless of adherence, for at least the assessment of the primary outcomes.
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46 Significance level will be set at P=0.05. Statistical Package for Social Sciences (SPSS),
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48 version 25, will be used for all data analysis.
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52 **Sample size calculation**

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56 The calculation of the sample size was performed with G * Power 3.1.9.4 software. For
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58 test F, h detection of moderate effect size (f = 0.3) after the interaction test (α level =
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3 0.05, 80%) a total of 111 participants were required to examine the recurrent
4 MANOVA. After adjusting for potential drop-outs (estimated attrition rate $\leq 10\%$) a
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6 minimum sample of 124 participants is required. Therefore, at least 62 participants will
7
8 be recruited in each group.
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11 12 13 **ETHICS AND DISSEMINATION** 14

15
16 The study protocol is approved by the Ethics Committee of the University of Thessaly
17 (#1108/01-12-2021) and by the Ethics Committee of the General University Hospital
18 of Larissa. Written informed consent will be obtained from all study participants prior
19 to their enrollment to the study intervention.
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25 The findings of this study will be disseminated at a local, national and international
26 level through publications in peer-reviewed journals, national and international
27 conference presentations, social, broadcast and print media. Additionally all study
28 participants will receive the study findings through electronic and postal mail.
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40 **DISCUSSION** 41

42 This trial is aiming to evaluate the efficacy, the efficiency and the safety of an exercise-
43 based telerehabilitation program using wearable sensors and web applications
44 compared to a traditional supervised center - based CR.
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50 The objective assessment of functional capacity through CPET and the objective
51 monitoring and recording of exercising and physical activity via the use of wearable
52 sensors are the main features of this study that increase its reliability. Objective
53 measurement of PA and training intensity, using accelerometer and heart rate data is
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3 suggested to be more reliable than using questionnaires than self-reported PA⁵⁵⁻⁵⁷ or
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5 than the perceived rate of exertion on its own.⁵⁵
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9 Although a cost-effectiveness analysis is almost prerequisite for any novel intervention,
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11 only a few telerehabilitation studies have performed one. Frederix et al. have showed
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13 the cost - effectiveness of an internet-based telerehabilitation program.²⁸ Whilst
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15 Kidholm et al. outlined the non-cost effectiveness of a telerehabilitation program
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17 compared to center-based CR.⁵⁸ In our study, we intent to include a comprehensive
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19 cost- effectiveness analysis to evaluate any possible economic gains.
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24 Moreover, the geographical features of Greece, with many islands and remote areas,
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26 contribute to the care inequality being observed, combined with the high variability of
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28 access to primary care professionals.⁵⁹ CR is almost absent from the Greek public health
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30 system, partly owing to the lack of clinics and training in its delivery. Furthermore,
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32 while some studies have already investigated the implications of telerehabilitation in
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34 other diseases, such COPD, with favorable outcomes,⁶⁰ no similar study, to our
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36 knowledge, has not yet been carried out for CAD patients, leaving a great gap open. In
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38 accordance to these statements recent guidelines support the implementation of home-
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40 based CR, telehealth, and mHealth interventions, with the use of wearable activity
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42 trackers to increase cardiac patients' participation rates and long-term adherence to
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44 healthy behaviors.¹¹ Furthermore, although CVD patients' digital literacy is presented
45
46 as a barrier to CR participation⁶¹ data from a recent study reveal encouraging results
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48 concerning the successive use of smartphones and wearable technology by an elderly
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50 cardiac population.⁶² Additionally, adherence in telerehabilitation interventions appears
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52 to present higher rates⁶³⁻⁶⁵.
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3 Therefore, there is an urgent need for innovative, safe, more cost-effective CR
4 strategies. If an exercise based telerehabilitation program, using wearable sensors,
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6 meets these prerequisites, it can act as a supplementary and/or substitutional (according
7
8 to the needs) to traditional center - based CR in CAD patients of low to moderate cardiac
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10 risk, thus allowing more patients to have access to CR with the least possible economic
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12 burden.
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17 **FOOTNOTES**

18 **Contributorship statement**

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21
22
23
24 Varsamo Antoniou (VA), Garyfallia Pepera (GP) conceived the study design, and
25
26 Andrew Xanthopoulos (AX), Gregory Giamouzis (GG), Konstantinos I. Gourgoulianis
27
28 (KG), John Skoularigis (JS), Konstantinos Davos (KD), Eleni Kapreli (EK), Vasileios
29
30 Stavrou (VS) contributed to the conception of the design. Varsamo Antoniou (VA),
31
32 Garyfallia Pepera (GP) and Ladislav Batalik (LB) drafted the manuscript and all authors
33
34 reviewed several drafts of the manuscript. All authors approved the final manuscript to
35
36 be published.
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41 **Conflicts of interests**

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43
44 The authors declare that they have no conflicts of interests.
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46

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48
49
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51
52 conceptual development in research organizations, ref. no. 65269705 (University
53
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57 **Data sharing statement**

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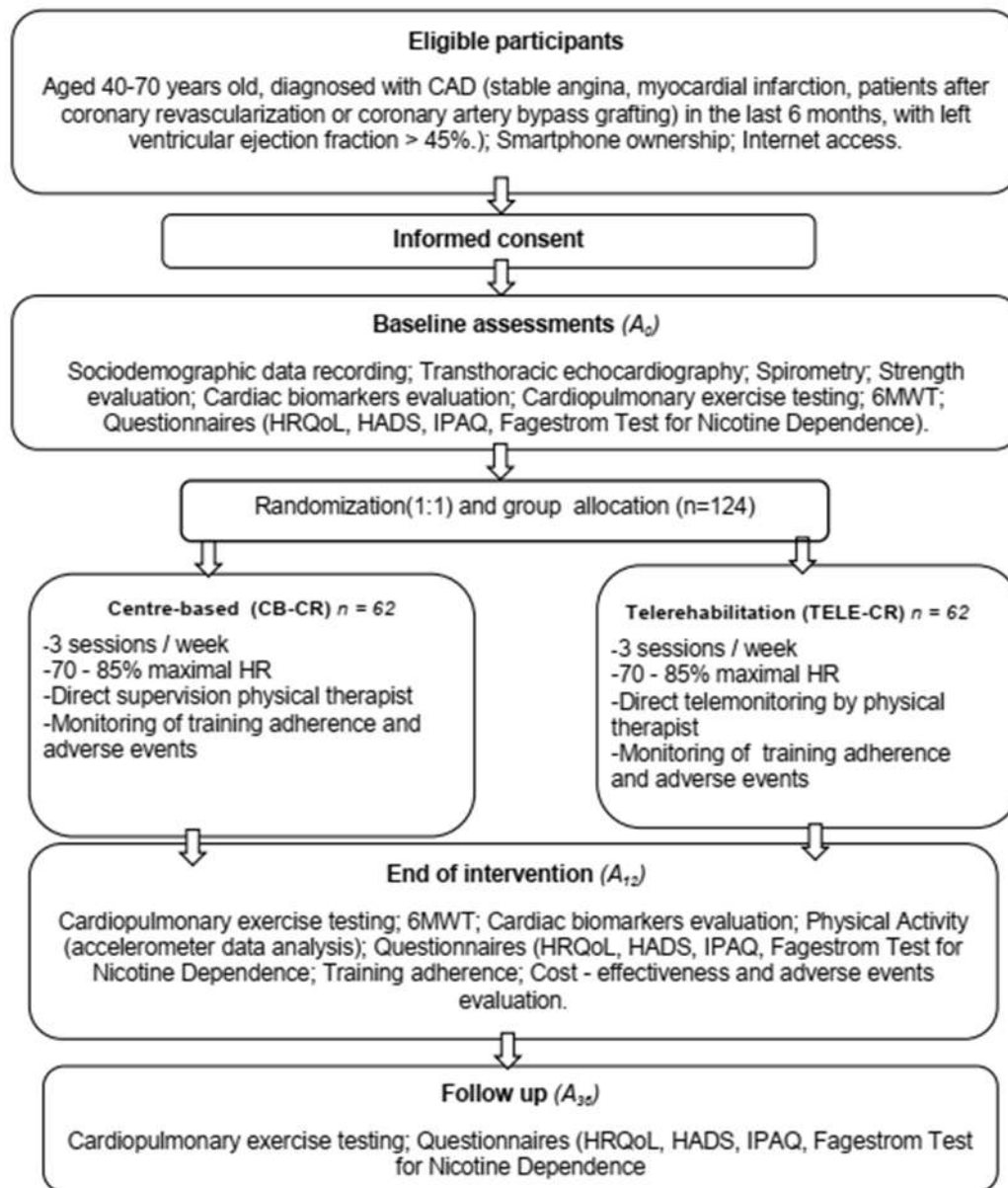
For peer review only

Figure 1. Flowchart of the study design

For peer review only

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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.

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			Page
		Reporting Item	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

1		name of intended registry	
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9	Protocol version	#3 Date and version identifier	n/a
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12	Funding	#4 Sources and types of financial, material, and other support	35
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15	Roles and	#5a Names, affiliations, and roles of protocol contributors	1, 25
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23	Roles and	#5b Name and contact information for the trial sponsor	25
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25	responsibilities:		
26			
27	sponsor contact		
28			
29	information		
30			
31			
32			
33	Roles and	#5c Role of study sponsor and funders, if any, in study design;	n/a
34			
35	responsibilities:	collection, management, analysis, and interpretation of	
36			
37	sponsor and funder	data; writing of the report; and the decision to submit the	
38			
39		report for publication, including whether they will have	
40			
41		ultimate authority over any of these activities	
42			
43			
44			
45	Roles and	#5d Composition, roles, and responsibilities of the coordinating	n/a
46			
47	responsibilities:	centre, steering committee, endpoint adjudication	
48			
49	committees	committee, data management team, and other individuals	
50			
51		or groups overseeing the trial, if applicable (see Item 21a	
52			
53		for data monitoring committee)	
54			
55			
56			
57	Introduction		
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1	Background and	#6a	Description of research question and justification for	4-6
2				
3	rationale		undertaking the trial, including summary of relevant studies	
4			(published and unpublished) examining benefits and harms	
5			for each intervention	
6				
7				
8				
9				
10				
11	Background and	#6b	Explanation for choice of comparators	6
12				
13	rationale: choice of			
14				
15	comparators			
16				
17				
18	Objectives	#7	Specific objectives or hypotheses	6
19				
20				
21				
22	Trial design	#8	Description of trial design including type of trial (eg, parallel	6
23			group, crossover, factorial, single group), allocation ratio,	
24			and framework (eg, superiority, equivalence, non-inferiority,	
25			exploratory)	
26				
27				
28				
29				
30				
31	Methods:			
32				
33	Participants,			
34				
35	interventions, and			
36				
37	outcomes			
38				
39				
40				
41	Study setting	#9	Description of study settings (eg, community clinic,	8
42			academic hospital) and list of countries where data will be	
43			collected. Reference to where list of study sites can be	
44			obtained	
45				
46				
47				
48				
49				
50				
51	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If	9,10
52			applicable, eligibility criteria for study centres and	
53			individuals who will perform the interventions (eg,	
54				
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1		surgeons, psychotherapists)	
2			
3			
4	Interventions:	#11a Interventions for each group with sufficient detail to allow	12-19
5			
6	description	replication, including how and when they will be	
7			
8		administered	
9			
10			
11	Interventions:	#11b Criteria for discontinuing or modifying allocated	17
12			
13	modifications	interventions for a given trial participant (eg, drug dose	
14			
15		change in response to harms, participant request, or	
16			
17		improving / worsening disease)	
18			
19			
20			
21	Interventions:	#11c Strategies to improve adherence to intervention protocols,	17,19
22			
23	adherence	and any procedures for monitoring adherence (eg, drug	
24			
25		tablet return; laboratory tests)	
26			
27			
28			
29	Interventions:	#11d Relevant concomitant care and interventions that are	n/a
30			
31	concomitant care	permitted or prohibited during the trial	
32			
33			
34	Outcomes	#12 Primary, secondary, and other outcomes, including the	19-22
35			
36		specific measurement variable (eg, systolic blood	
37			
38		pressure), analysis metric (eg, change from baseline, final	
39			
40		value, time to event), method of aggregation (eg, median,	
41			
42		proportion), and time point for each outcome. Explanation	
43			
44		of the clinical relevance of chosen efficacy and harm	
45			
46		outcomes is strongly recommended	
47			
48			
49			
50			
51	Participant timeline	#13 Time schedule of enrolment, interventions (including any	7-8
52			
53		run-ins and washouts), assessments, and visits for	
54			
55		participants. A schematic diagram is highly recommended	
56			
57		(see Figure)	
58			
59			
60			

1	Sample size	#14	Estimated number of participants needed to achieve study	22
2				
3			objectives and how it was determined, including clinical and	
4			statistical assumptions supporting any sample size	
5			calculations	
6				
7				
8				
9				
10				
11	Recruitment	#15	Strategies for achieving adequate participant enrolment to	9
12			reach target sample size	
13				
14				
15				
16	Methods: Assignment			
17	of interventions (for			
18	controlled trials)			
19				
20				
21				
22				
23				
24	Allocation: sequence	#16a	Method of generating the allocation sequence (eg,	11
25	generation		computer-generated random numbers), and list of any	
26			factors for stratification. To reduce predictability of a	
27			random sequence, details of any planned restriction (eg,	
28			blocking) should be provided in a separate document that is	
29			unavailable to those who enrol participants or assign	
30			interventions	
31				
32				
33				
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41	Allocation	#16b	Mechanism of implementing the allocation sequence (eg,	11
42	concealment		central telephone; sequentially numbered, opaque, sealed	
43	mechanism		envelopes), describing any steps to conceal the sequence	
44			until interventions are assigned	
45				
46				
47				
48				
49				
50				
51	Allocation:	#16c	Who will generate the allocation sequence, who will enrol	9
52	implementation		participants, and who will assign participants to	
53			interventions	
54				
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1	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg,	11
2			trial participants, care providers, outcome assessors, data	
3			analysts), and how	
4				
5				
6				
7				
8	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is	n/a
9	emergency		permissible, and procedure for revealing a participant's	
10			allocated intervention during the trial	
11	unblinding			
12				
13				
14				
15				
16	Methods: Data			
17	collection,			
18	management, and			
19	analysis			
20				
21				
22				
23				
24				
25				
26	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline,	17,18,
27			and other trial data, including any related processes to	
28			promote data quality (eg, duplicate measurements, training	20-22
29			of assessors) and a description of study instruments (eg,	
30			questionnaires, laboratory tests) along with their reliability	
31			and validity, if known. Reference to where data collection	
32			forms can be found, if not in the protocol	
33				
34				
35				
36				
37				
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39				
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41				
42				
43	Data collection plan:	#18b	Plans to promote participant retention and complete follow-	17
44	retention		up, including list of any outcome data to be collected for	
45			participants who discontinue or deviate from intervention	
46			protocols	
47				
48				
49				
50				
51				
52				
53	Data management	#19	Plans for data entry, coding, security, and storage,	17-19
54			including any related processes to promote data quality	
55			(eg, double data entry; range checks for data values).	
56				
57				
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1		Reference to where details of data management	
2			
3		procedures can be found, if not in the protocol	
4			
5			
6	Statistics: outcomes	#20a Statistical methods for analysing primary and secondary	22
7			
8		outcomes. Reference to where other details of the	
9			
10		statistical analysis plan can be found, if not in the protocol	
11			
12			
13	Statistics: additional	#20b Methods for any additional analyses (eg, subgroup and	n/a
14			
15	analyses	adjusted analyses)	
16			
17			
18			
19	Statistics: analysis	#20c Definition of analysis population relating to protocol non-	22
20			
21	population and	adherence (eg, as randomised analysis), and any statistical	
22			
23	missing data	methods to handle missing data (eg, multiple imputation)	
24			
25			
26	Methods: Monitoring		
27			
28			
29	Data monitoring:	#21a Composition of data monitoring committee (DMC);	n/a
30			
31	formal committee	summary of its role and reporting structure; statement of	
32			
33		whether it is independent from the sponsor and competing	
34			
35		interests; and reference to where further details about its	
36			
37		charter can be found, if not in the protocol. Alternatively, an	
38			
39		explanation of why a DMC is not needed	
40			
41			
42			
43			
44	Data monitoring:	#21b Description of any interim analyses and stopping	n/a
45			
46	interim analysis	guidelines, including who will have access to these interim	
47			
48		results and make the final decision to terminate the trial	
49			
50			
51	Harms	#22 Plans for collecting, assessing, reporting, and managing	16-17
52			
53		solicited and spontaneously reported adverse events and	
54			
55		other unintended effects of trial interventions or trial	
56			
57			
58			
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1		conduct	
2			
3			
4	Auditing	#23 Frequency and procedures for auditing trial conduct, if any,	17
5		and whether the process will be independent from	
6			
7			
8		investigators and the sponsor	
9			
10			
11	Ethics and		
12			
13	dissemination		
14			
15			
16	Research ethics	#24 Plans for seeking research ethics committee / institutional	23
17			
18	approval	review board (REC / IRB) approval	
19			
20			
21	Protocol	#25 Plans for communicating important protocol modifications	17
22			
23	amendments	(eg, changes to eligibility criteria, outcomes, analyses) to	
24		relevant parties (eg, investigators, REC / IRBs, trial	
25		participants, trial registries, journals, regulators)	
26			
27			
28			
29			
30			
31	Consent or assent	#26a Who will obtain informed consent or assent from potential	9
32		trial participants or authorised surrogates, and how (see	
33		Item 32)	
34			
35			
36			
37			
38			
39	Consent or assent:	#26b Additional consent provisions for collection and use of	9
40			
41	ancillary studies	participant data and biological specimens in ancillary	
42		studies, if applicable	
43			
44			
45			
46			
47	Confidentiality	#27 How personal information about potential and enrolled	9,19
48			
49		participants will be collected, shared, and maintained in	
50		order to protect confidentiality before, during, and after the	
51			
52		trial	
53			
54			
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57	Declaration of	#28 Financial and other competing interests for principal	25
58			
59			
60			

1	interests		investigators for the overall trial and each study site	
2				
3				
4	Data access	#29	Statement of who will have access to the final trial dataset,	19
5			and disclosure of contractual agreements that limit such	
6			access for investigators	
7				
8				
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10				
11	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care, and for	n/a
12			compensation to those who suffer harm from trial	
13	trial care		participation	
14				
15				
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18				
19	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial	23
20			results to participants, healthcare professionals, the public,	
21	trial results		and other relevant groups (eg, via publication, reporting in	
22			results databases, or other data sharing arrangements),	
23			including any publication restrictions	
24				
25				
26				
27				
28				
29				
30				
31	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	n/a
32			professional writers	
33	authorship			
34				
35				
36	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol,	25
37			participant-level dataset, and statistical code	
38	reproducible research			
39				
40				
41				
42	Appendices			
43				
44				
45	Informed consent	#32	Model consent form and other related documentation given	n/a
46			to participants and authorised surrogates	
47	materials			
48				
49				
50	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	n/a
51			biological specimens for genetic or molecular analysis in	
52			the current trial and for future use in ancillary studies, if	
53			applicable	
54				
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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](#)

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TITLE PAGE

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

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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

- Telerehabilitation 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 Greece⁶ with cardiac risk factors⁷ 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

1
2
3 Rapid development in information and communication technologies (ICTs) may help
4 to overcome the barriers to CR.²³⁻²⁵ Telerehabilitation is proposed as a feasible,^{26 27}
5 safe and cost – effective intervention,^{28 29} leading to long-term improvement of CVD
6 risk factors, reduced healthcare costs and increased CR participation adherence.
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Recent systematic reviews advocate to the use of telehealth interventions as an adjunct to CR³¹⁻³³ 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

1
2
3 be as safe as and even more cost-effective than the centre - based rehabilitation
4
5 intervention.
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7

8 **METHODS**

9 **Study design**

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15 A supervised, parallel-group, single-blind, randomized controlled trial with 6 months
16
17 follow-up will be employed. The study includes CAD patients, enrolled in a
18
19 telerehabilitation group (TELE-CR) and a control group undertaking regular outpatient
20
21 CR rehabilitation (CB-CR) for comparison reasons. Three assessments will take place
22
23 at baseline (A_0), end of intervention (A_{12}) and follow up 36 weeks (A_{36}). A CONSORT
24
25 (Consolidated Standard of Reporting Trials) flow diagram is shown in Fig. 1.
26
27

28
29 The study protocol complies with the SPIRIT 2013 statement guidelines³⁵ and the
30
31 intervention procedures are described according to the CONSORT- E- HEALTH
32
33 checklist.³⁶ We used the SPIRIT checklist when writing our report.³⁵ The trial is
34
35 registered at ClinicalTrials.gov with registration number NCT05019157.
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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		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). 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
<ul style="list-style-type: none"> -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 	<ul style="list-style-type: none"> - 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% 	<ul style="list-style-type: none"> -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 -LVEF <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. Primary 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	
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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 -Heel 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
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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

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

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2
3 capacity of 30 days, recorded data will be uploaded with a USB-connection and stored
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5 in the hospital server in an encrypted way on a monthly basis. Total training attendance
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7 rate will be documented by the hospital's staff
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10 **Telerehabilitation group (TELE - CR group)**

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14 Participants in the TELE-CR group will undertake three training sessions (or more if
15
16 needed) in the hospital's outpatient clinic for familiarization with the use of the
17
18 wearable sensors, the uploading of the training data to the web application (Polar Flow)
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20 and the exercising within their individually determined exercise intensity.
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24 Following the training period, TELE-CR participants will be lent a Polar H10 chest
25
26 strap that records HR data and a wrist sports watch (Polar M430, Kempele, Finland)
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28 and will proceed with the telerehabilitation program at their homes. Both wearable
29
30 sensors are validated and reliable tools, allowing effective assessment of exercise
31
32 intensity⁴³ and will be used only during the exercise training sessions. The wrist sports
33
34 watch will display continuous HR reading from the Polar H10 chest strap, enabling
35
36 patients to exercise within their prescribed HR zone and exercise data (duration,
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38 training mode, physical activity tracking). Participants in the TELE-CR group will be
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40 exercising in groups of up to maximum 5 participants in each session. Real time
41
42 supervision of this group – based exercise session by a specialized physiotherapist will
43
44 be implemented via videoconference web platforms or applications. At the end of every
45
46 training session, patients will upload training data to the web platform (Polar Flow) via
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48 Bluetooth or USB connection. Each patient will have his/her username and login
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50 account and can check his/her training data graphically and correlate it to his/her
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52 personal goals. CR specialized staff from the corresponding hospital will have access
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54 to all patients' accounts so as to monitor successful data uploading, assess the collected
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3 data and provide them with training feedback once a week via telephone video calls.
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5 Uploaded data will be further backed up to an external hard drive to be processed and
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7 evaluated by the trial investigator after the completion of the intervention.
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11 Additionally, all patients will be lent a tri-axial accelerometer (Actigraph wGT3X,
12
13 Actigraph), that they will wear around their waist during the 12 week intervention
14
15 period. Patients should visit the hospital's outpatient clinic on a monthly basis to upload
16
17 the recorded data to a secure PC application in an encrypted manner. Training
18
19 adherence will be monitored by the specialized physiotherapist supervising the
20
21 telerehabilitation exercise sessions.
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23

24 25 **OUTCOME MEASURES**

26 27 **Primary outcome**

28
29 The primary outcome will be the assessment of the cardiorespiratory fitness, at baseline,
30
31 the completion of the intervention (A_{12}) and follow up (A_{36}) in all study groups (CB-
32
33 CR, TELE-CR).
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39 40 **Secondary outcomes**

41
42 Secondary outcomes will be the physical activity level, safety, health related quality of
43
44 life (HRQoL), training adherence, depression and anxiety levels, nicotine dependence
45
46 and cost effectiveness. Physical activity, HRQoL, nicotine dependence and
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48 psychosocial well-being will be measured and assessed at baseline, end of intervention
49
50 (A_{12}) and follow up (A_{36}). Training adherence and cost evaluation will be assessed at
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52 the completion of the intervention (A_{12}).
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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 (A₁₂). 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) individually⁵¹ 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):

$$\text{ICER} = (\text{cost}_{\text{intervention group}} - \text{cost}_{\text{control group}}) / (\text{effectiveness}_{\text{intervention group}} - \text{effectiveness}_{\text{control group}}).$$

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

1
2
3 anxiety and depression subscales.⁵² HADS is a validated measure to assess anxiety and
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5 depression symptoms, recommended for CAD patients.^{53 54} Nicotine dependence will
6
7 be assessed through the Fagestrom Test for Nicotine Dependence.
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10 **Training adherence**

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14 Patients' training adherence is defined as a percentage of the total number of completed
15
16 training sessions (100%=36). Patients' adherence in both study groups will be recorded
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18 by the supervising hospital outpatient clinic's staff and will be evaluated at the end of
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20 intervention (A₁₂). Based on the percentage of the sessions attended, participants will
21
22 be categorized in adherent (> 80%), partly adherent (20 to 80%) and non-adherent (<
23
24 20%).
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26
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28 **STATISTICAL ANALYSIS**

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32 Normality of data will be examined with Kolmogorov-Smirnov tests. Descriptive
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34 statistics will be used to report demographics and baseline characteristics. Between-
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36 group and within group differences in the outcome measures will be evaluated using
37
38 multivariate analysis of variance (MANOVA). The effectiveness of the control (CB-
39
40 CR) and intervention (TELE-CR) group will be examined with dependent t-test for each
41
42 group (pre- and post-scores). All participants will be included in an intention to treat
43
44 analysis, regardless of adherence, for at least the assessment of the primary outcomes.
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46 Significance level will be set at P=0.05. Statistical Package for Social Sciences (SPSS),
47
48 version 25, will be used for all data analysis.
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52 **Sample size calculation**

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56 The calculation of the sample size was performed with G * Power 3.1.9.4 software. For
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58 test F, h detection of moderate effect size (f = 0.3) after the interaction test (α level =
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3 0.05, 80%) a total of 111 participants were required to examine the recurrent
4 MANOVA. After adjusting for potential drop-outs (estimated attrition rate $\leq 10\%$) a
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6 minimum sample of 124 participants is required. Therefore, at least 62 participants will
7
8 be recruited in each group.
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11 12 13 **ETHICS AND DISSEMINATION** 14

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16 The study protocol is approved by the Ethics Committee of the University of Thessaly
17 (#1108/01-12-2021) and by the Ethics Committee of the General University Hospital
18 of Larissa. Written informed consent will be obtained from all study participants prior
19 to their enrollment to the study intervention.
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25 The findings of this study will be disseminated at a local, national and international
26 level through publications in peer-reviewed journals, national and international
27 conference presentations, social, broadcast and print media. Additionally all study
28 participants will receive the study findings through electronic and postal mail.
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40 **DISCUSSION** 41

42 This trial is aiming to evaluate the efficacy, the efficiency and the safety of an exercise-
43 based telerehabilitation program using wearable sensors and web applications
44 compared to a traditional supervised center - based CR.
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50 The objective assessment of functional capacity through CPET and the objective
51 monitoring and recording of exercising and physical activity via the use of wearable
52 sensors are the main features of this study that increase its reliability. Objective
53 measurement of PA and training intensity, using accelerometer and heart rate data is
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3 suggested to be more reliable than using questionnaires than self-reported PA⁵⁵⁻⁵⁷ or
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5 than the perceived rate of exertion on its own.⁵⁵
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9 Although a cost-effectiveness analysis is almost prerequisite for any novel intervention,
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11 only a few telerehabilitation studies have performed one. Frederix et al. have showed
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13 the cost - effectiveness of an internet-based telerehabilitation program.²⁸ Whilst
14
15 Kidholm et al. outlined the non-cost effectiveness of a telerehabilitation program
16
17 compared to center-based CR.⁵⁸ In our study, we intent to include a comprehensive
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19 cost- effectiveness analysis to evaluate any possible economic gains.
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23
24 Moreover, the geographical features of Greece, with many islands and remote areas,
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26 contribute to the care inequality being observed, combined with the high variability of
27
28 access to primary care professionals.⁵⁹ CR is almost absent from the Greek public health
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30 system, partly owing to the lack of clinics and training in its delivery. Furthermore,
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32 while some studies have already investigated the implications of telerehabilitation in
33
34 other diseases, such COPD, with favorable outcomes,⁶⁰ no similar study, to our
35
36 knowledge, has not yet been carried out for CAD patients, leaving a great gap open. In
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38 accordance to these statements recent guidelines support the implementation of home-
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40 based CR, telehealth, and mHealth interventions, with the use of wearable activity
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42 trackers to increase cardiac patients' participation rates and long-term adherence to
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44 healthy behaviors.¹¹ Furthermore, although CVD patients' digital literacy is presented
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46 as a barrier to CR participation⁶¹ data from a recent study reveal encouraging results
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48 concerning the successive use of smartphones and wearable technology by an elderly
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50 cardiac population.⁶² Additionally, adherence in telerehabilitation interventions appears
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52 to present higher rates⁶³⁻⁶⁵.
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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.

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Data sharing statement

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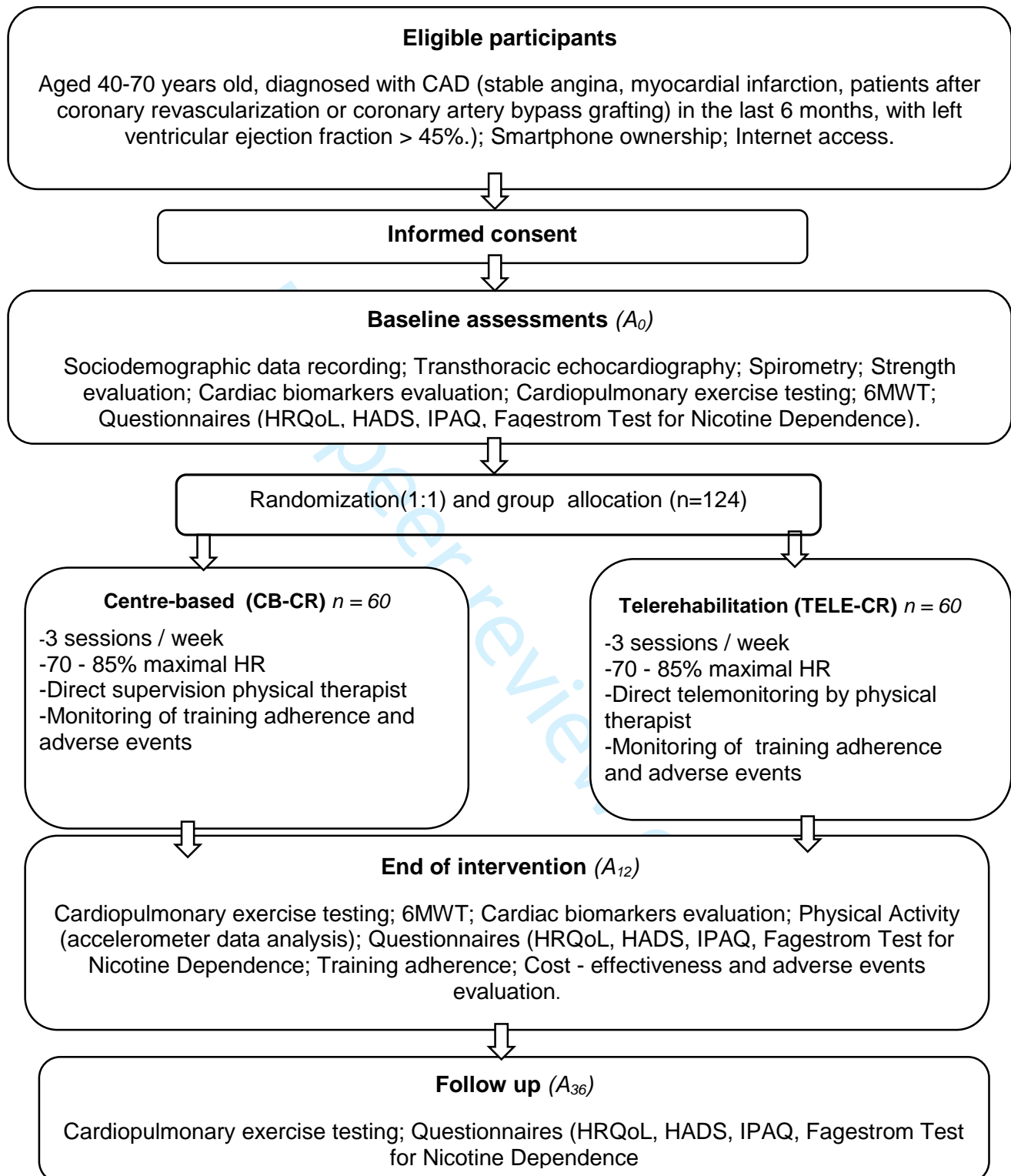
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For peer review only

Figure 1. Flowchart of the study design

For peer review only

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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 SPIRIT reporting 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

			Page
		Reporting Item	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

1		name of intended registry	
2			
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4	Trial registration: data	#2b All items from the World Health Organization Trial	n/a
5			
6	set	Registration Data Set	
7			
8			
9	Protocol version	#3 Date and version identifier	n/a
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12	Funding	#4 Sources and types of financial, material, and other support	35
13			
14			
15	Roles and	#5a Names, affiliations, and roles of protocol contributors	1, 25
16			
17	responsibilities:		
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19	contributorship		
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23	Roles and	#5b Name and contact information for the trial sponsor	25
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25	responsibilities:		
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27	sponsor contact		
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29	information		
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32			
33	Roles and	#5c Role of study sponsor and funders, if any, in study design;	n/a
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35	responsibilities:	collection, management, analysis, and interpretation of	
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37	sponsor and funder	data; writing of the report; and the decision to submit the	
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45	Roles and	#5d Composition, roles, and responsibilities of the coordinating	n/a
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47	responsibilities:	centre, steering committee, endpoint adjudication	
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49	committees	committee, data management team, and other individuals	
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57	Introduction		
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1	Background and	#6a	Description of research question and justification for	4-6
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3	rationale		undertaking the trial, including summary of relevant studies	
4			(published and unpublished) examining benefits and harms	
5			for each intervention	
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11	Background and	#6b	Explanation for choice of comparators	6
12				
13	rationale: choice of			
14				
15	comparators			
16				
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18	Objectives	#7	Specific objectives or hypotheses	6
19				
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21				
22	Trial design	#8	Description of trial design including type of trial (eg, parallel	6
23			group, crossover, factorial, single group), allocation ratio,	
24			and framework (eg, superiority, equivalence, non-inferiority,	
25			exploratory)	
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31	Methods:			
32				
33	Participants,			
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35	interventions, and			
36				
37	outcomes			
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40				
41	Study setting	#9	Description of study settings (eg, community clinic,	8
42			academic hospital) and list of countries where data will be	
43			collected. Reference to where list of study sites can be	
44			obtained	
45				
46				
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51	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If	9,10
52			applicable, eligibility criteria for study centres and	
53			individuals who will perform the interventions (eg,	
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1		surgeons, psychotherapists)	
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3			
4	Interventions:	#11a Interventions for each group with sufficient detail to allow	12-19
5			
6	description	replication, including how and when they will be	
7			
8		administered	
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11	Interventions:	#11b Criteria for discontinuing or modifying allocated	17
12			
13	modifications	interventions for a given trial participant (eg, drug dose	
14			
15		change in response to harms, participant request, or	
16			
17		improving / worsening disease)	
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21	Interventions:	#11c Strategies to improve adherence to intervention protocols,	17,19
22			
23	adherence	and any procedures for monitoring adherence (eg, drug	
24			
25		tablet return; laboratory tests)	
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29	Interventions:	#11d Relevant concomitant care and interventions that are	n/a
30			
31	concomitant care	permitted or prohibited during the trial	
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34	Outcomes	#12 Primary, secondary, and other outcomes, including the	19-22
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36		specific measurement variable (eg, systolic blood	
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38		pressure), analysis metric (eg, change from baseline, final	
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40		value, time to event), method of aggregation (eg, median,	
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42		proportion), and time point for each outcome. Explanation	
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44		of the clinical relevance of chosen efficacy and harm	
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46		outcomes is strongly recommended	
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51	Participant timeline	#13 Time schedule of enrolment, interventions (including any	7-8
52			
53		run-ins and washouts), assessments, and visits for	
54			
55		participants. A schematic diagram is highly recommended	
56			
57		(see Figure)	
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1	Sample size	#14	Estimated number of participants needed to achieve study	22
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3			objectives and how it was determined, including clinical and	
4			statistical assumptions supporting any sample size	
5			calculations	
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11	Recruitment	#15	Strategies for achieving adequate participant enrolment to	9
12			reach target sample size	
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16	Methods: Assignment			
17	of interventions (for			
18	controlled trials)			
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24	Allocation: sequence	#16a	Method of generating the allocation sequence (eg,	11
25	generation		computer-generated random numbers), and list of any	
26			factors for stratification. To reduce predictability of a	
27			random sequence, details of any planned restriction (eg,	
28			blocking) should be provided in a separate document that is	
29			unavailable to those who enrol participants or assign	
30			interventions	
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41	Allocation	#16b	Mechanism of implementing the allocation sequence (eg,	11
42	concealment		central telephone; sequentially numbered, opaque, sealed	
43	mechanism		envelopes), describing any steps to conceal the sequence	
44			until interventions are assigned	
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51	Allocation:	#16c	Who will generate the allocation sequence, who will enrol	9
52	implementation		participants, and who will assign participants to	
53			interventions	
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1	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg,	11
2			trial participants, care providers, outcome assessors, data	
3			analysts), and how	
4				
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8	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is	n/a
9	emergency		permissible, and procedure for revealing a participant's	
10			allocated intervention during the trial	
11	unblinding			
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16	Methods: Data			
17	collection,			
18	management, and			
19	analysis			
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26	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline,	17,18,
27			and other trial data, including any related processes to	
28			promote data quality (eg, duplicate measurements, training	20-22
29			of assessors) and a description of study instruments (eg,	
30			questionnaires, laboratory tests) along with their reliability	
31			and validity, if known. Reference to where data collection	
32			forms can be found, if not in the protocol	
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43	Data collection plan:	#18b	Plans to promote participant retention and complete follow-	17
44	retention		up, including list of any outcome data to be collected for	
45			participants who discontinue or deviate from intervention	
46			protocols	
47				
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51				
52				
53	Data management	#19	Plans for data entry, coding, security, and storage,	17-19
54			including any related processes to promote data quality	
55			(eg, double data entry; range checks for data values).	
56				
57				
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1		Reference to where details of data management	
2			
3		procedures can be found, if not in the protocol	
4			
5			
6	Statistics: outcomes	#20a Statistical methods for analysing primary and secondary	22
7			
8		outcomes. Reference to where other details of the	
9			
10		statistical analysis plan can be found, if not in the protocol	
11			
12			
13	Statistics: additional	#20b Methods for any additional analyses (eg, subgroup and	n/a
14			
15	analyses	adjusted analyses)	
16			
17			
18			
19	Statistics: analysis	#20c Definition of analysis population relating to protocol non-	22
20			
21	population and	adherence (eg, as randomised analysis), and any statistical	
22			
23	missing data	methods to handle missing data (eg, multiple imputation)	
24			
25			
26	Methods: Monitoring		
27			
28			
29	Data monitoring:	#21a Composition of data monitoring committee (DMC);	n/a
30			
31	formal committee	summary of its role and reporting structure; statement of	
32			
33		whether it is independent from the sponsor and competing	
34			
35		interests; and reference to where further details about its	
36			
37		charter can be found, if not in the protocol. Alternatively, an	
38			
39		explanation of why a DMC is not needed	
40			
41			
42			
43			
44	Data monitoring:	#21b Description of any interim analyses and stopping	n/a
45			
46	interim analysis	guidelines, including who will have access to these interim	
47			
48		results and make the final decision to terminate the trial	
49			
50			
51	Harms	#22 Plans for collecting, assessing, reporting, and managing	16-17
52			
53		solicited and spontaneously reported adverse events and	
54			
55		other unintended effects of trial interventions or trial	
56			
57			
58			
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1		conduct	
2			
3			
4	Auditing	#23 Frequency and procedures for auditing trial conduct, if any,	17
5		and whether the process will be independent from	
6			
7			
8		investigators and the sponsor	
9			
10			
11	Ethics and		
12			
13	dissemination		
14			
15			
16	Research ethics	#24 Plans for seeking research ethics committee / institutional	23
17			
18	approval	review board (REC / IRB) approval	
19			
20			
21	Protocol	#25 Plans for communicating important protocol modifications	17
22			
23	amendments	(eg, changes to eligibility criteria, outcomes, analyses) to	
24		relevant parties (eg, investigators, REC / IRBs, trial	
25		participants, trial registries, journals, regulators)	
26			
27			
28			
29			
30			
31	Consent or assent	#26a Who will obtain informed consent or assent from potential	9
32		trial participants or authorised surrogates, and how (see	
33		Item 32)	
34			
35			
36			
37			
38			
39	Consent or assent:	#26b Additional consent provisions for collection and use of	9
40			
41	ancillary studies	participant data and biological specimens in ancillary	
42		studies, if applicable	
43			
44			
45			
46			
47	Confidentiality	#27 How personal information about potential and enrolled	9,19
48			
49		participants will be collected, shared, and maintained in	
50		order to protect confidentiality before, during, and after the	
51			
52		trial	
53			
54			
55			
56			
57	Declaration of	#28 Financial and other competing interests for principal	25
58			
59			
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1	interests		investigators for the overall trial and each study site	
2				
3				
4	Data access	#29	Statement of who will have access to the final trial dataset,	19
5			and disclosure of contractual agreements that limit such	
6			access for investigators	
7				
8				
9				
10				
11	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care, and for	n/a
12	trial care		compensation to those who suffer harm from trial	
13			participation	
14				
15				
16				
17				
18				
19	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial	23
20	trial results		results to participants, healthcare professionals, the public,	
21			and other relevant groups (eg, via publication, reporting in	
22			results databases, or other data sharing arrangements),	
23			including any publication restrictions	
24				
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31	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	n/a
32	authorship		professional writers	
33				
34				
35				
36	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol,	25
37	reproducible research		participant-level dataset, and statistical code	
38				
39				
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41				
42	Appendices			
43				
44				
45	Informed consent	#32	Model consent form and other related documentation given	n/a
46	materials		to participants and authorised surrogates	
47				
48				
49				
50	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	n/a
51			biological specimens for genetic or molecular analysis in	
52			the current trial and for future use in ancillary studies, if	
53			applicable	
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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](#)

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