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Hybrid cardiac rehabilitation trial (HYCARET): protocol of a randomised, multicentre, non-inferiority trial in South America

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ABSTRACT

Introduction Cardiac rehabilitation (CR) programmes are well established, and their effectiveness and cost-effectiveness are proven. In spite of this, CR remains underused, especially in lower-resource settings such as Latin America. There is an urgent need to create more accessible CR delivery models to reach all patients in need. This trial aims to evaluate if the prevention of recurrent cardiovascular events is not inferior in a hybrid CR programme compared with a standard programme.

Method and analysis A non-inferiority, pragmatic, multicentre, parallel (1:1), prospective, randomised and open with blinded endpoint assessment clinical trial will be conducted. 308 patients with coronary artery disease will be recruited consecutively. Participants will be randomised to hybrid or standard rehabilitation programme. The hybrid CR programme includes 10 supervised exercise sessions and individualised lifestyle counselling by a physiotherapist, with a transition after 4–6 weeks to unsupervised delivery via text messages and phone calls. The standard CR consists of 18–22 supervised exercise sessions, as well as group education sessions about lifestyle. Intervention in both groups is between 8 and 12 weeks. The primary outcome is a composite of cardiovascular mortality and hospitalisations due to cardiovascular causes. Secondary outcomes are health-related quality of life, exercise capacity, muscle strength, heart-healthy behaviour, return-to-work, cardiovascular risk factor, adherence, and exercise-related adverse events. The outcomes will be measured at the end of intervention, at 6 months and at 12 months follow-up from recruitment. The primary outcome will be tracked through the end of the trial. Per-protocol and intention-to-treat analysis will be undertaken.Cox regression model will be used to compare primary outcome among study groups.

Ethics and dissemination Ethics committees at the sponsor institution and each centre where participants will be recruited approved the study protocol and the Informed Consent. Research findings will be published in peer-reviewed journals; additionally, results will be disseminated among region stakeholders.

Trial registration number NCT03881150; Pre-results.

Date and version 01 October 2019.

Strengths and limitations of this study

- This trial evaluates a hybrid cardiac rehabilitation programme, exploiting mobile technology to contain costs, suitable to be implemented in South America where there is grossly insufficient capacity to meet need yet no such trials.
- This non-inferiority and multicentre clinical trial has a pragmatic approach, ensuring external validity in the real-world where hybrid cardiac rehabilitation can be delivered.
- Randomisation with concealed allocation, blind assessment of outcome measures and protocol registration will minimise potential bias.
- The trial is powered for outcomes relevant for policy and clinical decision-making, namely cardiovascular mortality and hospitalisations, as well as to patients, namely quality of life.
- A limitation will be the impossibility of personnel and participant blinding.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the world, of which ischaemic heart disease produces the highest mortality and disability-adjusted life years.[1] In Latin America and the Caribbean, ischaemic heart disease is the predominant form of CVD, with an adjusted mortality of 66.4 per 100 000 persons.[2] In Chile, ischaemic heart disease is the leading cause of premature death (years of life lost in 2017). Also, it is the second leading cause of death and disability combined (disability-adjusted life years in 2017).[3] Disconcertingly, these indicators are both increasing (15% and 16% increases from 2007 to 2017, respectively).

Once CVD has been established, the fundamental objective is to prevent mortality, recurrent cardiovascular events and improve quality of life (QoL) through secondary prevention.[4] While secondary prevention

strategies are widely known, they are not widely implemented, particularly outside of North America and Europe.[5] This holds true in the South American region and in Chile in particular, where only 50% of patients suffering a myocardial infarction achieve four of eight secondary prevention recommendations.[6]

To achieve the secondary prevention goals, cardiac rehabilitation (CR) is recommended by the international guidelines.[7] It is an established, efficient, comprehensive model of care resulting in better outcomes. CR programmes include medical evaluation, education and prescription of exercise among their key components.[8] The latest Cochrane systematic review[9] testing the effects of CR, which included 63 clinical trials composed of 14 486 randomised patients, demonstrates that it reduces cardiovascular mortality (risk ratio (RR)=0.74; 95% CI 0.64 to 0.86) and recurrent hospitalisation (RR=0.82; 95% CI 0.70 to 0.96); CR also improves QoL,[10] all in a cost-effective manner.[11–13] CR benefits were independent of patients' specific diagnosis, type of CR (exercise only vs comprehensive rehabilitation) dose of exercise, length of follow-up, trial publication date, setting (centre vs home-based), study location (continent), sample size and risk of bias.[9]

Despite this knowledge, there are barriers to delivery of CR programmes. Indeed, CR is underused when compared with other recommended secondary prevention interventions, such as medication.[14] The barriers are multifactorial, relating to patients (eg, distance, work conflicts, lack of transportation), providers (eg, failure to refer patients) and the healthcare system itself (eg, lack of CR programmes, insufficient resources, lack of insurance coverage).[8] Worldwide, only 55% of countries have any CR programme. In South America specifically, there is only 1 CR 'spot' for every 55 ischaemic heart disease patient that needs it each year, and in Chile specifically, there are only 10 programmes with capacity to serve 2000 of the ~45 000 patients who develop ischaemic heart disease each year.[15] Clearly, there is grossly insufficient capacity, and thus, we need novel models of delivery to bridge this gap.

Several approaches to lowering the cost and increasing capacity/accessibility of CR have been described, such as delivery in unsupervised settings (to overcome distance, work and transportation barriers; lower space costs), using information and communication technology (which could increase capacity by reducing need for human resources), task shifting to lower-cost healthcare personnel and offering a lower dose (ie, fewer sessions). Other strategies include using lower-cost exercise equipment, and not universally monitoring patients with telemetry during exercise sessions.[16 17]

A systematic review characterised these models, and evaluated their effectiveness against traditional supervised programmes.[18] From eight broad categories of alternative models identified, two were shown to be effective. First, the multifactorial individualised telehealth model resulted in similar reductions in cardiovascular risk factors compared with traditional programmes; however, there is a lack of information about non-proximate outcomes such as rehospitalisations and subsequent cardiac events. Second, the community or home-based CR models were shown to result in equivalent effects as traditional programmes in terms of mortality and cardiovascular event rates.[19] Indeed, two other meta-analyses have supported the benefits of CR delivered with various forms of information and communications technology[20 21]: one trial demonstrated efficacy and cost-savings in comparison to traditional supervised programmes,[22] and a trial of a home telehealth-based CR programme with a cost–benefit analysis demonstrated significant advantages compared with standard hospital-based CR.[23] Specifically using mobile technology, some clinical trials have reported positive effects on adherence to lifestyle behavioural changes,[24] as well as CR utilisation,[25] but these studies did not consider non-proximate outcomes and have been conducted only in high-resource settings.

The International Council of Cardiovascular Prevention and Rehabilitation (ICCPR) developed a consensus statement, endorsed by 10 cardiac societies, on how to deliver each core component in an affordable, yet evidence-based manner in lower-resource (eg, grossly insufficient capacity, lack of reimbursement other than patients) settings.[17 26] They offer direction for delivery in unsupervised models, including mobile technology, but this has never been tested. Using their guidance and the evidence from trials of CR in alternative settings reviewed above, we developed a hybrid CR model where patients are transitioned from a supervised setting to mobile phone-based delivery, which is likely more accessible, cheaper, efficient and feasible for settings such as in Latin-American countries.

The primary aim of this trial is to evaluate if reduction in cardiovascular mortality and rehospitalisation (combined endpoint) is not inferior in hybrid CR in comparison to standard supervised CR. Secondarily, the aim is to evaluate if hybrid CR is not inferior to traditional supervised CR for health-related QoL, exercise capacity, muscle strength, heart-healthy behaviour, return-to-work, cardiovascular risk factor control (dyslipidaemia, hyperglycaemia, hypertension, obesity), adherence and exercise-related adverse events.

METHODS AND ANALYSIS

Design

As it is established that the standard model of CR is effective in reducing cardiovascular mortality and hospitalisations, comparing new alternative models against usual care is not ethically possible. Therefore, alternatively, we planned to conduct a non-inferiority clinical trial as the most suitable means to test the impact of the model. The Hybrid Cardiac Rehabilitation Trial (HYCARET) is a non-inferiority, pragmatic, multicentre, two parallel arm (1:1), prospective, randomised, open clinical trial, with blinded endpoint assessment. The objective is to

demonstrate that a hybrid mobile phone-based CR model is not inferior to the standard model. This trial is pragmatic because it examines the outcomes of the experimental intervention compared with a standard intervention under circumstances which closely approximate the real world.

Patients will be recruited in six health centres. Personnel undertaking outcome assessment will be blinded to group allocation. Figure 1 shows trial activities and the expected timeline of the study. The Standard Protocol Items: Recommendations for Interventional Trials reporting guidelines were used to write this protocol.[27]

Study population

The target population is coronary artery disease patients. The accessible population will consist of patients that attend one the six health centres involved in the study: four centres in Santiago, the capital of Chile (Complejo Hospitalario San José, Hospital San Juan de Dios, Hospital Clínico de la Universidad de Chile, Hospital Clínico San Borja Arriarán), one centre located in the north (Hospital Regional de Antofagasta), and a final one located in the south of Chile (Hospital Dr. Hernán Henriquez Aravena). The sample will consist of patients in the above centres that meet all the eligibility criteria presented in table 1.

Sample size

The sample size calculation was performed employing the Sealed Envelope platform,[28] and based on the hospitalisation and cardiovascular mortality outcomes that were reported in the systematic review by Anderson *et al*,[9] which totaled 18% in the first year of follow-up in those randomised to CR. The non-inferiority margin was established as 62% of the difference between the standard or current therapy (ie, standard CR) and the placebo (or usual care) obtained from meta-analysis, in this case again by Anderson *et al* (8%).

For the primary outcome analysis, if there is a true difference in favour of the hybrid CR of 7%, 268 patients are required (134 per group) to be 80% sure that the upper limit of a one-sided 97.5% CI will exclude a difference in favour of the standard CR group of more than 5% (figure 2). Considering anticipated loss of follow-up (15%), 308 patients will be recruited (154 per group).

Recruitment and randomisation

The patients are invited to participate in this clinical trial at the time of hospital discharge, during the first outpatient visit after discharge or emergency department visit, or when an angiogram or a stress test has been performed. All information about the study will be provided by a nurse or physiotherapist dedicated to recruit exclusively. When the patients consent to participate in the study, an initial evaluation will be performed to collect baseline sociodemographic and clinical characteristics.

Recruitment was initiated in April 2019, and it is anticipated to continue through to July 2020. With follow-up included, the end of study is anticipated in September 2021.

Assignment to the experimental or control group will be by permuted blocked randomisation. Concealment of assignment will be preserved through features in the Research Electronic Data Capture software, REDCap.

Experimental and comparison groups

The CR intervention in both groups is up to 12 weeks (between 8 and 12); with frequency of sessions per week (2 or 3) as is standard practice at participating sites, in accordance with the pragmatic nature of the trial.

The participants in the experimental group will be randomised to a hybrid CR programme adapted from the 'Cardiac Rehabilitation Delivery Model for Low-Resource Settings' proposed by the ICCPR Consensus Statement.[17 26] This programme will be delivered by an exercise specialist (physiotherapist), with the principal purpose of the exercise sessions being to develop patient self-management of physical activity, including educating them how to monitor exercise intensity at home and in daily life using heart rate and the Borg scale of perceived exertion,[29] in addition to delivering individual counselling. A nutritionist and psychologist will be actively involved in the design of counselling materials and as intervention/trial consultants. A referral and consultant physician also will serve on the team.

Participants will be transitioned to unsupervised programming after 6 weeks. Content of the voice calls and text messages will be extracted and adapted from a bank of 137 suggestions.[30] The messages were developed in accordance with the adult recommendations for physical activity by WHO and Mediterranean diet. Their content addresses: benefits of physical activity and heart-healthy nutritional habits, recommended behaviours and activities to achieve these benefits and medication adherence.

The participants in the control group receive the standard supervised CR that is delivered in participating centres. These programmes are delivered by physicians, nurses, nutritionists and physiotherapists in accordance with current guidelines.[31 32] The CR in the control arm includes group education about physical activity, diet, smoking and medication compliance (without individual counselling).

The core components delivered in both groups are presented in table 2.

Outcomes, measures and follow-up

The primary outcome is recurrent cardiovascular events, a composite of cardiovascular mortality (defined as death by stroke, myocardial infarction or heart failure) and hospitalisation due to a cardiovascular cause (non-fatal stroke, non-fatal myocardial infarction, heart failure and need for revascularisation surgery). Study personnel will monitor death occurrence through review of public registries. The death certificate and any associated medical documentation will be copied for consideration by the adjudicating committee. Hospitalisation occurrence will

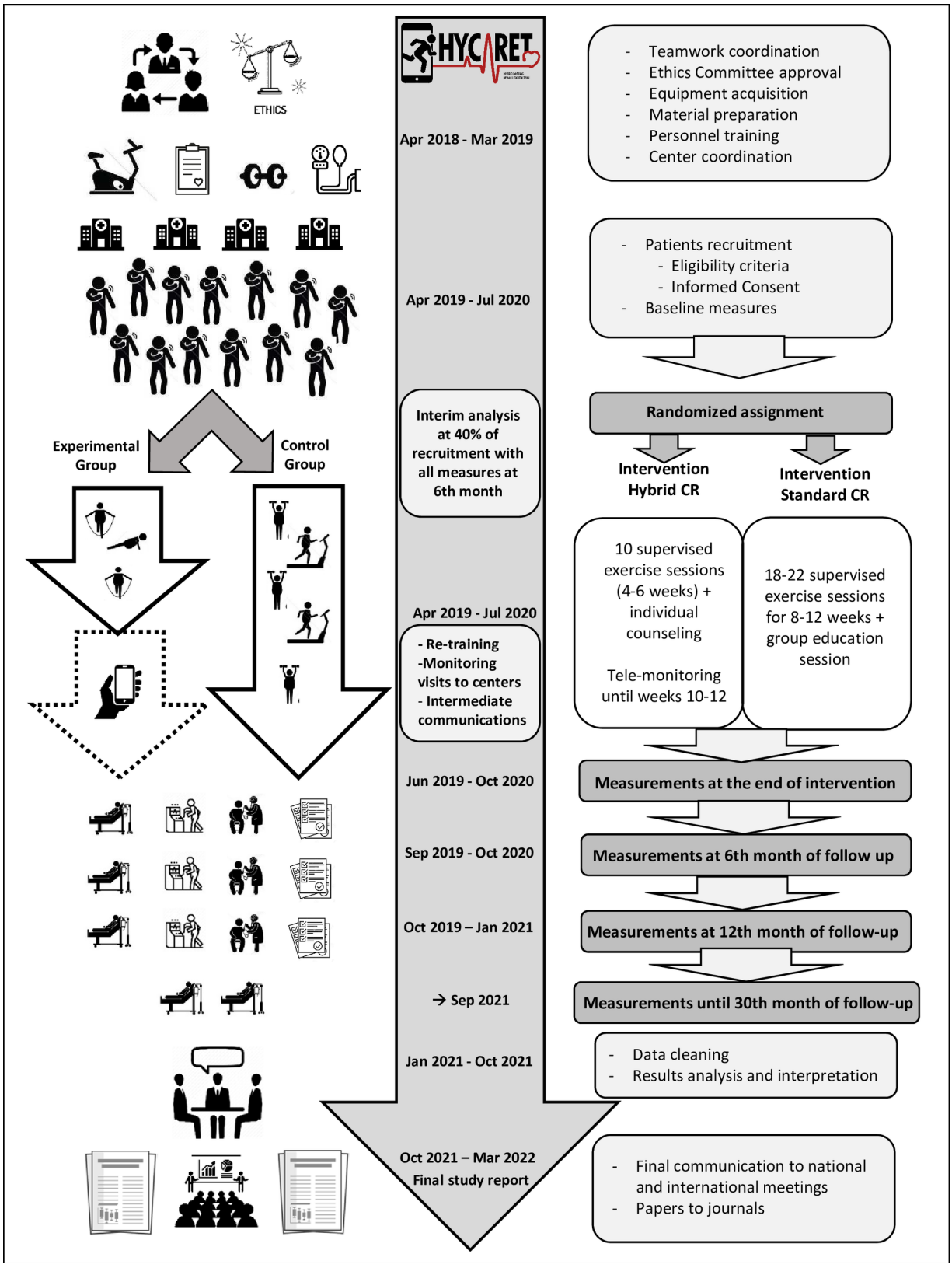

Figure 1 Flow chart, activities and timeline expected of the trial. CR, cardiac rehabilitation; HYCARET, Hybrid Cardiac Rehabilitation Trial.

be assessed by study personnel through chart review, with all associated tests and exam reports to be extracted, at each participating centre; this will be supplemented by phone calls to participants every 2 months, using a standardised script, in case they received care at another centre.

A central adjudication committee will review all materials. This committee will be composed of three clinician

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
► Age 18 year old or over. ► Patient with coronary artery disease, including acute coronary syndrome (unstable angina, myocardial infarction with or without ST elevation) or stable coronary vessel disease diagnosed by angiography or a stress test. ► Patient treated medically (ie, medication only) or by thrombolysis, angioplasty or revascularisation surgery. ► Patient with physician referral, that can start CR between 2 weeks and 2 months from their event, diagnosis or procedure. ► Patient able to attend the health centre almost twice a week over 3 months. ► Patient owns a mobile phone. ► Patient that consents to participate in the study through signing an informed consent form.	► Patient has a planned repeat cardiac or other procedure in next 12 months. ► Explicit contraindication to perform exercise based on American College of Sport Medicine guidelines.[53] ► Patients with comorbidities that would interfere with ability to engage in CR such as dementia, blindness, deafness, serious mental illness, or frailty. ► Musculoskeletal disease that precludes the patient from performing exercise.

CR, cardiac rehabilitation.

scientists (at least one will be a cardiology specialist) blinded to participant allocation. Members will make the final decision whether the event is definitive, possible, probable, or if it is rejected, and specify the final death cause or hospitalisation diagnosis with corresponding International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) code.

Secondary outcomes are:

- Health-related QoL: Trained personnel will administer the HeartQol instrument, a disease-specific questionnaire for patients with ischaemic heart disease validated across 22 countries and 15 languages.[33] Additionally, the widely-used, generic EuroQol five-dimensional three-level (EQ-5D-3L) instrument will be administered; it has been validated, and the utility values have been established for the Chilean population.[34]
- Functional exercise capacity: This will be evaluated through the 6 min walk test (6MWT); the protocol will be administered by trained personnel. The 6MWT will be performed using a 30 m internal flat corridor with two cones marking the distance limits. Patients will be instructed to walk (no running or jogging) as much as possible for 6 min. Rest pauses will be allowed as many times as necessary, but the participant will be encouraged to resume walking as soon as possible. Total distance covered during the test will be recorded. All the procedures will be conducted in accordance with the American Thoracic Society Statement.[35]
- Muscle strength: This will be evaluated through a grip strength protocol administered by trained personnel, using a Jamar dynamometer, according to a standardised method. Patients will be instructed to sit in a chair with armrests with the shoulder adducted, elbow articulation flexed at 90° angle, forearm in neutral position and wrist between 0° and 30° of dorsiflexion. In this position, participants will be asked to perform three maximal effort trials with each hand; the highest value will be considered.[36 37] This is an important outcome because a reduction of 5 kg in grip strength is inversely associated with all-cause mortality. In addition, reduction in grip strength is inversely associated with cardiovascular mortality, non-cardiovascular mortality, myocardial infarction and stroke.[36]
- Adherence to physical activity recommendations: WHO recommends that adults (including those with CVD) 18 years old or over perform 150 min of moderate-intensity aerobic activity or 75 min of vigorous activity per week, or a combination of both. The activity must be in bouts >10 min to be considered. The International Physical Activity Questionnaire will be administered by trained personnel, which has been validated and used in the local setting.[38 39] This instrument assesses physical activity of moderate and vigorous intensity in activities related to work, domestic labour, active transportation and leisure time, and hence can quantify the energy spent in metabolic equivalent per

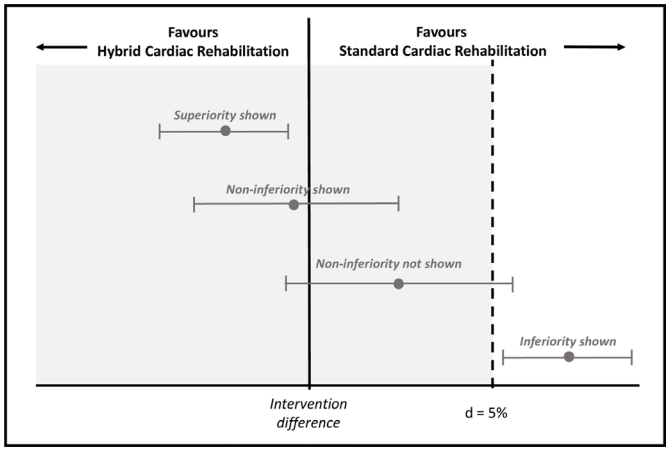

Figure 2 Possible scenarios of observed intervention differences with sample size calculation. d= non-inferiority limit.

Table 2 Components and differences in experimental and control groups

	Hybrid cardiac rehabilitation	Standard cardiac rehabilitation
Initial comprehensive assessment	Includes evaluation of physical activity, diet, tobacco consumption, overweight/obesity, blood pressure, self-efficacy and medications. Additionally, lipids and glycaemia levels will be extracted from the clinical chart. Exercise testing with a 6 min walk test (6MWT) will be performed at the beginning of the programme to develop an individualised exercise prescription.	Includes evaluation of physical activity, diet, tobacco consumption, overweight/obesity, blood pressure, self-efficacy and medications. Additionally, lipids and glycaemia levels will be extracted from the clinical chart. 6MWT will be performed as with the experimental group.
Lifestyle risk factor management	Physical activity, diet, smoking and medication compliance counselling, will be provided by the physiotherapist individually across exercise sessions, using a perceived self-efficacy approach and strategic planning, according to the Health Action Process Approach theoretical model.[54] A booklet was designed with patient involvement to support the counselling. If applicable, a referral to the mental health department will be made.	Group education sessions about physical activity, diet, smoking and medication compliance, as usually performed in each centre by a multiprofessional team.
Exercise sessions	10 supervised exercise sessions over 4–6 weeks of aerobic and resistance training will ensue, supervised by a physiotherapist. Exercise sessions are 10 min in duration at the beginning of the programme, and are progressed to 60 min by the end as tolerated. Intensity of exercise will be moderate.	18–22 supervised exercise sessions are delivered over the 8–12 weeks programme supervised by a physiotherapist. These sessions include aerobic and resistance training and a similar progression of duration as the experimental group. Intensity of exercise will be moderate.
Transition to unsupervised phase	After 6 weeks, all patients will be transitioned to unsupervised delivery, through mobile technology. Delivery modes will include calls biweekly, and text messaging three times per week for 6 weeks. The content is designed to promote patients to follow the same exercise prescription, eat a healthy diet, and adhere to medication.	Not applicable

minute and weeks (minutes/week) for categorisation in accordance with WHO recommendation.

- Adherence to diet recommendations: trained personnel will administer the Mediterranean Dietary Index for the Chilean population. Participants will be asked to recall the frequency of consumption of 14 food groups. This instrument had been validated. Scores range from 0 to 14 points, indicating absence and maximum adherence, respectively.[40]
- Return-to-work: Work status just before or at the time of the cardiac event, diagnosis or procedure and desired work status (ie, participant is retired) will be assessed at baseline. At the follow-up evaluations, the participants will again be questioned about their work status, and if they are working, the date of return-to-work will be recorded. Concordance between desired and actual work status at the final assessment will serve as the outcome of interest.
- Cardiovascular risk factor: the routine lipid and glycaemia test results will be extracted from charts, using the standard methods in each centre. Blood pressure will be assessed by trained personnel, assessing it three times at 30 s intervals using the standard digital sphygmomanometer with the appropriate cuff size.[41] Weight will be measured with a standing scale supported on a steady surface with participants wearing only underwear. Height will be measured on the Frankfort plane positioned at a 90° angle against a metric tape mounted on a wall. These will be used to compute body mass index, and hence obesity. Waist circumference will be measured in the midpoint between the lowest rib and the iliac crest.
- Adherence: attendance at each supervised session and also adherence to the calls in the intervention group will be recorded.
- Exercise-related adverse events: adverse events during exercise, such as myocardial ischaemia or malignant arrhythmias, will be recorded and communicated to the monitor of the study. Serious adverse event, such as death in the exercise session, will be recorded and reported to the corresponding ethics committee and monitor. All events will be recorded for the interim and final analysis.

All outcomes will be measured at the beginning of the programme, at the end of intervention (8–12 weeks), at 6 months and at 12 months of follow-up from recruitment to capture the acute and long-term impact of interventions. Hospitalisations and cardiovascular mortality follow-up will be a minimum of 1 year, and a maximum of 30 months for the participants recruited at the beginning of the study. The personnel assessing outcomes will be blinded to intervention assignment. Table 3 displays the

Table 3 Outcomes, measures and time point of assessments

Outcome		Measure/source	Time point BL	EI	6 m	12 m	24 m	30 m
Recurrent cardiovascular event*	Cardiovascular mortality Hospitalisation	Death certificate Clinical chart Medical documentation Patient report	X	X	X	X	X	X
Health-related quality of life		HeartQol and EQ-5D-3L	X	X	X	X		
Exercise capacity		6MWT	X	X	X	X		
Muscle strength		Grip strength	X	X	X	X		
Adherence to physical activity recommendations		IPAQ long version	X	X	X	X		
Adherence to diet recommendations		Chile MDI	X	X	X	X		
Return-to-work		Investigator-generated question		X	X	X		
Cardiovascular risk factors	Lipids and glycaemia	Clinical chart review	X	X	X	X		
	Blood pressure	Standard digital sphygmomanometer						
	Body mass index	Weight and height by standard procedure						
	Waist circumference	Standard procedure						
Adherence to exercise sessions		Checklist		X				
Exercise related adverse events		Checklist						

*To be adjudicated according ICD-10.
BL, Baseline; EI, end of intervention; EQ-5D-3L, EuroQol five-dimensional three level; IPAQ, International Physical Activity Questionnaire; 6 m, 6 months of follow-up; 12 m, 12 months of follow-up; 24 m, 24 months of follow-up; 30 m, 30 months of follow-up; MDI, Mediterranean Dietary Index; 6MWT, six-minute walk test.

outcomes, their associated measures and the assessment schedule.

Analysis plan

The analysis plan will include baseline data analysis in order to compare the distribution of sociodemographic and clinical characteristics of participants to test for homogeneity of groups with randomisation.

To test the primary hypothesis, differences in proportions of recurrent cardiovascular events will be estimated as absolute risk difference (ARD) and relative risk (RR). Additionally, Cox regression model will be used to compare primary outcome among study groups. For both, intention-to-treat (ITT) and per-protocol (PP) analysis will be performed, considering it is easier to establish non-inferiority with ITT and so the PP is considered a more conservative approach. Non-inferiority will be considered established if both ITT and PP analyses support it.[42]

To test the secondary outcomes, both, ARD and RR will be estimated for categorical outcomes, and mean differences will be calculated for continuous outcomes.

Generalised Estimating Equations will be used given the repeated measures and multicentre character of study. Analyses will be adjusted if imbalances in baseline characteristics are found or lost to follow-up is different between groups. Depending on the results, subgroup analysis (eg, sex) may be conducted to explain unexpected differences in outcomes.

An interim analysis for the primary outcome, when 40% of the sample has been recruited and followed up to 6 months, will be performed using an adjusted type I error rate according to the Lan and DeMets method.[43] Recruitment will be stopped if hybrid CR is shown to be less effective than standard CR.[44]

Management and monitoring

All trial procedures will be overseen by electronic and personal communication. Study data will be collected and managed using REDCap electronic data capture tools hosted at Universidad de La Frontera.[45 46] It is a secure web-based software platform designed to support data capture for research studies. REDCap's features enable entry and recording of data synchronously throughout all trial activities including: recruitment, randomisation and concealed allocation, baseline and follow-up measurements, documentation of exercise session adherence, documentation of voice calls and text messages, as well as event monitoring and adjudication.

A central management office will be established, responsible for overseeing all general processes for the study such as securing and managing ethical and regulatory approvals, document and questionnaire preparation, field personnel training, measurement standardisation and data entry monitoring. The general coordinator will be responsible for maintaining regular communication with participating centres, problem-solving and ensuring the overall integrity of the study.

Each centre will have a local coordinator in charge of trial activities such as recruitment, random assignment, coordination of assessments and data entry. The critical issues for which the local coordinator is responsible include ensuring assignment concealment and blinding of outcome assessments. Finally, a professional with documented training in Good Clinical Practice[47] will be engaged in order to monitor the conduct of the trial. They will verify the protection of the rights and well-being of participants that the data obtained will be accurate, complete and checked against source documents, that the study is being conducted consistently with the approved protocol, and is undertaken in accordance with the Good Clinical Practice guidelines and ethical requirements.

Patient and public involvement

The experimental intervention is based on by patients' perception and preferences, specifically a reduced attending in health centre and home-based exercise sessions are alternatives patient based, besides public health system based.

The booklet to support the counselling was designed with patients' revision and advices in aspects related with content, format and language.

Ethics, dissemination and impact

The study protocol and the Informed Consent form, were approved by the corresponding Ethics Committee at the Sponsor Institution: Comité Ético Científico (CEC) of Universidad de La Frontera. This approval was considered for the study implementation in two centres: Hospital San Juan de Dios and Hospital Regional de Antofagasta. In addition, the following Ethics Committees approved the protocol and a specific Informed Consent for implementation in their centres:

- Hospital San Borja Arriarán: CEC of Servicio de Salud Metropolitano Central.
- Hospital San José: CEC of Servicio de Salud Metropolitano Norte.
- Hospital Clínico Universidad de Chile: CEC of Hospital Clínico Universidad de Chile.
- Hospital Dr. Hernán Henríquez Aravena: CEC of Servicio de Salud Araucanía Sur.

In the design of this proposal, the fulfilment of ethical principles of the Belmont Report has been considered: the value of the research question, methodological rigour, that investigators are scientifically qualified, the protocol has been independently evaluated, and there is plan to ensure results will be published in a punctual and accurate way.

Amendments to the protocol will be reported in the trial registry.

The results will be reported in accordance with Consolidated Standards of Reporting Trials,[48] including the extensions for non-pharmacological treatment interventions,[49] non-inferiority and equivalence,[50] and pragmatic trials.[51] Research findings will be published in peer-reviewed journals in accordance with international recommendations of International Committee of Medical Journal Editors (ICMJE).[52] Additionally, scientific results and the corresponding CR service implications will be disseminated among stakeholders and national policy-makers.

There will be three types of manuscripts of the HYCARET: (1) Reports of the main outcomes of the study, (2) Reports addressing one aspect of the HYCARET, but in which data are derived from the entire study and (3) Reports of data derived from substudies or ancillary studies of HYCARET. There will be a publications committee (lead by the principal investigator, and including two coinvestigators, as well as trial coordinators at the participating centres) that will decide about the writing committees for each manuscript derived from HYCARET. Writing committees will comprise investigators and personnel from participating centres that contributed substantially to data collection, and meet all ICMJE authorship criteria.

We anticipate that if non-inferiority of the hybrid model is demonstrated, a feasible model of CR will be established for patients and the health system, in order to increase coverage, save resources, while improving cardiovascular health outcomes. It is also expected that findings will influence clinical practice guidelines.

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Contributors PS is the principal investigator for the trial, leading the protocol development and the research ethics application. PS, MJO and FL contributed fully to the study design. FL (cardiology), CR and GNM-N (physiotherapists), GM (nutritionist), SRM (biostatistics) and NS (Medical Technologist) provided discipline-specific expertise, and authored the relevant sections of the protocol. PS prepared the manuscript which was edited by SLG and MJO. All authors read and approved the final version of the manuscript.

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Disclaimer FONDECYT had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study protocol and the Informed Consent form (online supplementary file 1), were approved by the corresponding Ethics Committee at the Sponsor Institution: CEC of Universidad de La Frontera. Additionally by: CEC of Servicio de Salud Metropolitano Central, CEC of Servicio de Salud Metropolitano Norte, CEC of Hospital Clínico Universidad de Chile, and CEC of Servicio de Salud Araucanía Sur.

Provenance and peer review Not commissioned; externally peer reviewed.

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