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Economic evaluation protocol for a multicentre randomised controlled trial to compare Smartphone Cardiac Rehabilitation, Assisted self-Management (SCRAM) versus usual care cardiac rehabilitation among people with coronary heart disease

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Title page

Title

Economic evaluation protocol for a multicentre randomised controlled trial to compare Smartphone Cardiac Rehabilitation, Assisted self-Management (SCRAM) versus usual care cardiac rehabilitation among people with coronary heart disease

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Abstract

Introduction

It is important to ascertain the cost-effectiveness of alternative services to traditional cardiac rehabilitation while the economic credentials of the Smartphone Cardiac Rehabilitation, Assisted self-Management (SCRAM) program among people with coronary heart disease (CHD) are unknown. This economic protocol outlines the methods for undertaking a trial-based economic evaluation of SCRAM in the real world setting in Australia.

Methods and analysis

The within-trial economic evaluation will be undertaken alongside a randomised controlled trial (RCT) designed to determine the effectiveness of SCRAM in comparison to usual care cardiac rehabilitation (UC) alone in people with CHD. Pathway analysis will be performed to identify all the costs related to the delivery of SCRAM and UC. Both a healthcare system and a limited societal perspective will be adopted to gauge all costs associated with health resource utilisation and productivity loss. Healthcare resource use over the six-month participation period will be extracted from administrative databases (i.e. Pharmaceutical Benefits Scheme and Medical Benefits Schedule). Productivity loss will be measured by absenteeism from work (valued by human capital approach). The primary outcomes for the economic evaluation are maximal oxygen uptake (VO_2max, ml·kg^{-1}·min^{-1}, primary RCT outcome) and Quality-adjusted life years estimated from health-related quality of life (HRQoL) as assessed by the Assessment of Quality of Life (AQoL-8D) instrument. The incremental cost-effectiveness ratio (ICER) will be calculated using the differences in costs and benefits (i.e. primary and secondary outcomes) between the two randomised groups from both perspectives with no discounting. All costs will be valued in Australian dollars for the year 2020.

Ethics and dissemination

The study protocol has been approved under Australia's National Mutual Acceptance agreement by the Melbourne Health Human Research Ethics Committee (HREC/18/MH/119). It is anticipated that SCRAM is a cost-effective cardiac telerehabiliation program for people

with CHD from both a healthcare and limited societal perspective in Australia. The evaluation will provide evidence to underpin national scale-up of the program to a wider population.

Trial registration

Australian New Zealand Clinical Trials Registry (ACTRN12618001458224)

Strengths and limitations of the study

- Health economics data will be collected prospectively along with a randomised controlled trial to reliably capture the individual-level health care resource use and changes in productivity.
- National administrative data collection (i.e. Medicare and Pharmaceutical Benefits Scheme Australia) will be extracted to source the healthcare resource utilisation over the trial duration.
- The economic evaluation is based on the sample size determined by the primary outcome of the SCRAM RCT, which may be underpowered to detect a difference in costs.

Introduction

Cardiac rehabilitation (CR) is an effective multifactorial secondary prevention intervention that is typically delivered in centre-based (i.e. face-to-face) settings. Centre-based CR reduces recurrent ischaemic events, improves health-related quality of life and long-term prognosis for coronary heart disease (CHD) patients [1-3]. CR programs have also been reported to reduce overall premature mortality (relative risk (RR) 0.87, 95% confidence interval (CI): 0.75-0.99) and cardiac deaths (RR 0.74 (95%CI 0.63-0.87) in comparison with no CR. [4] Despite effectiveness of CR, many people with CHD do not engage in such programs.[5] For instance, CR utilisation is low in Australia; uptake (attended ≥1 session) and completion rates have been estimated at 25% to 60% and 19% to 42%, respectively, across the country; uptake rates as low as 10% have been reported in Victoria.[6-9] Reasons underlying poor participation are complex, but accessibility barriers such as limited program availability, transport restrictions, conflicting domestic/occupational responsibilities, and geographic isolation are key contributors. [10-13]

For these reasons, clinicians and researchers have been prompted to seek novel strategies for delivering CR programs to facilitate greater uptake and adherence rates. Telerehabilitation—defined as rehabilitation services that are delivered remotely through information and communication technologies—has received increasing attention as it can overcome key accessibility barriers that limit participation in centre-based CR. The effectiveness of telerehabilitation, which commonly includes telephone, internet and videoconference communication between participants and healthcare practitioners,[14] has been demonstrated. Systematic reviews have consistently shown that telerehabilitation services improve CVD risk factors (i.e. total cholesterol, blood pressure, high- and low-density lipoprotein), compared to controls[10 15]; and comparisons of traditional centre-based CR with telerehabilitation have shown them to be equivalent in terms of mortality, exercise capacity and quality of life outcomes[16]. The effectiveness of CR interventions delivered via telephone, internet, and videoconference has been well established; however, few trials have capitalised on opportunities to augment intervention design and delivery by using rapidly advancing mobile communication and device technologies (i.e. mobile broadband and smartphones; mHealth).

Four randomised-controlled trials (RCT) have compared mHealth CR with traditional centre-based programs. One study showed improved uptake and completion rate in comparison to the control group [17], two indicated mHealth and centre-based CR had comparable effects on maximal oxygen uptake (i.e. exercise capacity),[18 19] while the fourth suggested mHealth CR led to improvements in maximal oxygen uptake and quality of life[20]. The results from existing economic evaluations of mHealth intervention are not consistent[18 19 21 22].

We are currently undertaking a multi-centre RCT of a smartphone-based platform to support remotely delivered CR called Smartphone Cardiac Rehabilitation, Assisted self-Management (SCRAM). Unlike its predecessor REMOTE-CR[18], SCRAM extends beyond a single behaviour (exercise) to include other secondary prevention self-management behaviours (medication adherence, physical activity and sedentary behaviour, healthy eating, stress management, and smoking cessation). To establish the economic credentials of the SCRAM program in the Australian setting, an economic evaluation will be conducted to examine the balance between health effects and costs of health technologies (i.e. SCRAM program, medications, diagnostic tests, medical services, etc.) to inform efficient allocation of limited healthcare funding. In response to the transparent reporting of clinical trials, this paper outlines the methods of the prospective within-trial economic evaluation to be undertaken alongside the RCT[23], to provide important evidence for policy decision-making around the provision of cardiac rehabilitation services. It will include both cost-effectiveness and cost-utility analysis with a view to informing resource allocation, practice change and investment in the SCRAM program.

Methods

Design

The details of the study design are reported elsewhere[23]. Briefly, SCRAM is a multicentre investigator-, assessor-, and statistician-blinded parallel two-arm RCT comparing effects and costs of the 24-week SCRAM intervention with usual care CR. A process evaluation is also being undertaken. Participants are randomised (1:1) to receive either SCRAM (intervention) or usual care CR (control).

The study protocol was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12618001458224) on 30/08/2018 and adheres to the SPIRIT 2013 statement.[24] The intervention has been described according to recommendations in the TIDieR and CONSORT (eHealth extension) statements. Reporting of trial outcomes will adhere to the CONSORT statement and its eHealth extension.[25-27]

The economic evaluation will be undertaken from both an Australian healthcare system plus a limited societal perspective, incorporating all health care costs subsidised by state and Commonwealth governments in Australia. In addition, participant absenteeism from work due to CHD will be monetised and the associated cost will be included in the estimation from the limited societal perspective. The reporting of this economic evaluation will adhere to the Consolidated Health Economics Evaluation Reporting Standards (CHEERS) guidelines[28].

Study population

A total of 220 participants (N=110 per randomised group) diagnosed with CHD within the previous six months, are being recruited from hospitals, outpatient clinics, and cardiac rehabilitation services in Sunshine, Geelong, and Bendigo, Victoria, Australia. As study centres provide treatment to ~1.5 million individuals across broad catchment areas the trial cohort is anticipated to include a geographically diverse mix of metropolitan-, regional- and rural-dwelling participants.

Participants are randomised (1:1) to receive the SCRAM program (intervention) or usual care CR (control), stratified by sex and study centre. Key inclusion criteria at baseline are: aged over 18 years; diagnosed CHD within the previous six months (angina, myocardial infarction, or coronary revascularisation); outpatients who have been clinically stable for at least 6 weeks; able to perform exercise; and can understand and write English. Exclusion criteria include: New York Heart Association (NYHA) Functional class III/IV heart failure; terminal disease; significant non-CHD exercise limitations; contraindications for maximal exercise testing.

Patient and public involvement

There is not patient and public involvement.

Sample size

The target sample will provide 90% power at a 5% significance level (two-sided) to detect a clinically meaningful difference of 2.0 ml·kg^{-1}·min^{-1} in $\dot{V}O_2$max at 24 weeks (primary RCT outcome) between the control and intervention groups, assuming a standard deviation of 6.75, a correlation of 0.8 between the pre- and post-intervention measures, and 20% loss-to-follow-up. Minimum detectable differences in secondary RCT outcomes are outlined in the main trial protocol[23].

Baseline assessment

Prior to randomisation, researchers collect the following information: sociodemographic and clinical (diagnostic, smoking, alcohol history, medication) characteristics, ehealth literacy (a questionnaire), $\dot{V}O_2$max, and secondary outcomes (detailed below).

Randomisation

Treatment allocation follows a computer-generated schedule prepared by a biostatistician who is not involved with recruitment, treatment allocation, or outcome assessment[23]. Investigators, outcome assessors, and the statistician remain blinded to the group allocation over the course of the trial.

Treatment arms

Usual care cardiac rehabilitation

Usual care CR typically includes face-to-face support/education to adhere to medical treatment and health-promoting lifestyle behaviours as well as supervised exercise training. Specific program components vary across Australian healthcare providers but most offer education and exercise components;[29] stratification of treatment allocation by trial centre will ensure variation is balanced across treatment groups.

Usual care CR is not delivered as part of this trial. All participants retain access to usual care CR—regardless of treatment allocation—as it is unethical to withhold evidence-based

treatment. Participants randomised to the control group have access to usual care CR alone, as offered by their local CR provider, without further support.

Intervention: SCRAM program

Participants randomised to the intervention group receive the 24-week dual-phase SCRAM intervention, which is described in detail in the main trial protocol[23]. Briefly, during an initial 12-week intensive phase, participants receive real-time remotely prescribed, supervised and coached exercise training from accredited exercise physiologists as well as a modular multifactorial library of evidence- and theory-based behaviour change support push notifications. This phase is designed to provide intensive support for exercise and lifestyle behaviour uptake and adherence. During a subsequent 12-week maintenance phase, participants receive reduced frequency and intensity of exercise and behaviour change support. This phase is designed to provide tapered support that transitions participants towards long-term self-determined adherence to exercise and health-promoting lifestyle behaviours. Participants receive all intervention components via the bespoke SCRAM software platform, using an Android smartphone.

Comparator

It is important for the economic evaluation to be able to ascertain whether the planned intervention is conducted in addition to existing practices, or as a replacement to them. Consistent with the RCT design[23], SCRAM intervention will be compared to usual care CR (i.e. traditional centre-based CR).

Measurement of clinical endpoints

Outcome measures for the within-trial economic evaluation

Primary outcomes for the economic evaluation will be maximal oxygen uptake ($\dot{V}O_2$max, $ml \cdot kg^{-1} \cdot min^{-1}$, primary RCT outcome)—measured during an individualised treadmill cardiopulmonary exercise test—and health-related quality of life (HRQoL)—measured using the Assessment of Quality of Life-8D (AQoL-8D). $\dot{V}O_2$max is measured at baseline and 24-week follow-up, whilst HRQoL is assessed at baseline, 12-weeks, and 24-weeks. Secondary

outcomes, including modifiable cardiovascular risk factors and adverse events, are described in the main trial protocol[23].

Measurement of costs

Direct cost of delivering the SCRAM program

In identifying relevant costs, the following principles will be adhered to:

- Identification of costs to be included, using 'pathway analysis' (Figure 1), where activities in all stages of the roll out of the SCRAM project are fully specified; A healthcare system perspective and steady state operation of the intervention will be assumed (intervention is up and running, and start-up costs, like development of SCRAM app will be excluded). Costs will largely relate to the time costs of the remote exercise physiologists and project staff (using opportunity cost principles). Any administrative resources used at the program management level also will be identified and included.

- Measurement of the resources consumed in natural units (number of hours spent by remote exercise physiologists to deliver the intervention, etc.);

- Valuation of these resources in monetary units (Australian dollars), using 2020 as the reference year.

Direct health costs of participants

Beside intervention cost, healthcare-related costs including inpatient and outpatient care associated with CHD are documented. The cost of inpatient care over the 24-week participation period (e.g. emergency department (ED) visits and rehospitalisations will be estimated from self-reported adverse events documented throughout the trial. Complementary approaches will be utilised to calculate the cost for each hospitalisation episode: first, the cost per hospital admission from the National Hospital Cost Data Collection (actual cost per AR-DRG) will be used; second the National Efficient Price (projected cost) according the AR-DRG code[30] will be used to value the per hospitalisation episode adjusted for the length of hospital stay. The cost of outpatient care (e.g. outpatient consultations,

examinations) and medication use over the 24-week participation period will be estimated from MBS and PBS data, respectively.

Productivity cost (absenteeism from work)

Absence from work (i.e. days of sick leave) due to CHD is self-reported by participants of working age (i.e. ≤65 years old; people post working age do not attract productivity loss from a societal perspective) using a pre-designed questionnaire at baseline and 24-week follow up. The human capital approach will be used to value the productivity cost[31].

Exclusion of trial costs

Research-driven activities will be separated from the activities that would be carried out should the program be adopted by the healthcare system. Costs associated with trial administration, data collection, and RCT outcome assessment will be excluded.

Data analysis

Within-trial economic evaluation

The within-trial economic evaluation will be based on the intention-to-treat population as per the primary outcome of the RCT[23]. All evaluation results will be expressed as incremental results over and above the comparator case. In other words, the additional cost/saving of the intervention (SCRAM) compared to current practice will be expressed as a ratio by dividing by the net benefits derived. The following formula represents the calculation of the incremental cost-effectiveness ratio (ICER):

$$ICER = C_i\text{-}C_{UC}/B_i\text{-}B_{UC}$$

where C=costs, B=benefits, i=SCRAM intervention, UC=usual care CR

For the cost-effectiveness analysis (CEA), the incremental cost per unit increase in benefits for both the primary and secondary outcomes will be calculated if significant between-group differences are observed. For the cost-utility analysis (CUA), the quality-adjusted life year (QALY) will be estimated from HRQoL assessed by AQoL-8D by intervention group (Table 2).

A plot on the cost effectiveness plane will be drawn to illustrate the distribution of costs and effectiveness. A cost-effectiveness acceptability curve will also be plotted in order to assess the degree of uncertainty associated with the conclusion using a predetermined empirical willingness-to-pay (WTP) threshold for the QALY outcome (i.e. AU$50,000/QALY)[32].

Bootstrap simulation of the ICER will be used to simulate the study results over 2,000 iterations. This technique is used when data are skewed (cost data are nearly always highly skewed) and the confidence interval of a ratio using skewed data is required. The within-trial economic analysis will be undertaken using STATA 15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

Long-term modelling

For the long-term modelling that is beyond the trial duration, benefits observed in the trial will be translated into health benefits (e.g., avoided morbidity/mortality outcomes, and calculated in terms of QALY gained). The modelled economic evaluation will simulate the impact of increased maximal oxygen uptake on the overall well-being/survival of the cohort over its lifetime compared with the control group. A Markov model consisting of health states associated with CHD (i.e. recurrent myocardial infarction, angina, revascularisation, stroke or death) will be used to accrue costs and benefits over the lifetime horizon. The long-term improved outcomes may translate into the cost savings due to avoided ED visit and rehospitalisation. Long-term modelling will be performed in TreeAge Pro 2019.

Sensitivity analysis

Uncertainty analyses will be conducted based on Monte Carlo simulations. The between-group differences in both costs and QALY will be bootstrapped to estimate the probability of the SCRAM program being cost-effective regardless of the significance in between-group difference[33]. A series of one-way sensitivity analyses will be undertaken to examine robustness of the base-case ICER, for example, alternative costing approach for rehospitalisation (unit costs derived from Independent Hospital Pricing Authority, Australia; Australian Institute of Health and Wellbeing), labours (unit costs sourced from Australia Bureau of Statistics, PayScale), and SCRAM intervention delivery (varying the quantity and unit cost of the resource utilised).

Ethics approval

The study protocol has been approved under Australia's National Mutual Acceptance agreement by the Melbourne Health Human Research Ethics Committee (HREC/18/MH/119). Ethics approval has been ratified by the Deakin University Human Research Ethics Committee (2018-251). All participants provide written informed consent prior to undertaking baseline assessments. Separate consent is sought to extract MBS/PBS data for the purpose of this study.

Discussion

This paper details the protocol of a trial-based economic evaluation that purports to assess the cost-effectiveness of the SCRAM telerehabilitation program among people with CHD. It has a number of methodological strengths, the key one being that the economic evaluation will be undertaken alongside a prospective RCT. This has the advantage of being efficient and timely in terms of the data collected. In addition, the RCT design provides credibility through high internal validity, minimisation of bias, and tight protocol control. The SCRAM RCT aims to minimise the predictable sources of bias and confounding via allocation concealment, blinded outcome assessment and intention-to-treat analysis. The primary costing data will be sourced from administrative databases including MBS, PBS, and hospital costing system data; this allows for maximum accuracy of the data collected and enhances the capture of effects and outcomes. Furthermore, this RCT is recruiting participants from metropolitan, regional and rural areas of Victoria, Australia, allowing for broader representativeness of participants that will maximise generalisability of the results. Lastly, HRQoL will be assessed by the AQoL-8D, a 35-item questionnaire, which has been widely applied in measuring HRQoL for Australia-based studies[34-37]. It has increased measurement sensitivity, especially in the psychosocial dimensions, compared with existing instruments [i.e. EuroQol-5D-5L (EQ-5D-5L), Quality of Wellbeing (QWB), Health Utilities Index Mark 3 (HUI3), and 15D] that vary greatly and report inconsistent utility scores [38].

The economic credentials of traditional centre-based CR versus no CR have long been established. A systematic review of 19 CEAs of such interventions concluded that the majority reported traditional CR was cost-effective versus no CR (ICER ranged from US$1065 to

US$71755/QALY), especially with exercise as a component[39 40]. Specifically in relation to cardiac telerehabiliation (not involving a smartphone-based remote CR component), studies are varied in terms of their results. Whilst one within-trial economic evaluation reported that such an intervention (offering the flexibility of having the CR at hospital, healthcare centre, or call centre) was not cost-effective given its high cost (ICER €400,000 per QALY)[21], others have demonstrated more positive outcomes. A trial-based economic analysis home-based CR was associated with non-significantly lower costs and a high probability of being cost-effective[19]. Another CUA showed that the mean cost per patient in a telemonitoring program was €564 lower than in the control group, but with higher QALY gains (0.026), thereby making the intervention dominant (lower costs but higher benefits)[22]. Another CEA of home-based telerehabilitation, delivered through online videoconferencing for patients with heart failure, concluded that it was associated with significantly lower costs (-AU$1590, 95%CI -$2822 to -$359) during the 6 month participation period[41]. Our previous economic evaluation alongside a non-inferiority RCT in New Zealand indicated the REMOTE-CR smartphone-based cardiac telerehabilitation program—a precursor to SCRAM—was associated with cost-saving (-NZ$4615/participant) and comparable benefits[18].

Some methodological limitations are worth mentioning: first of all, the economic evaluation is based on the sample size determined by the primary outcome of the SCRAM RCT. It may be underpowered to detect a difference in costs. Second, whilst the gold standard is to undertake economic evaluations from a societal perspective (which captures all costs falling on patients, their carers, and families), the current study only considers a limited societal perspective (i.e. including only productivity costs); the costs borne by carers and families are excluded. However, it is believed that the health care system plus the limited societal perspectives will provide sufficient information to inform decision-making around investment in the SCRAM program in Australia and elsewhere.

Conclusion

The results of this economic evaluation will fill the evidence gap for the cost-effectiveness of this mHealth CR program versus usual care CR alone, given that the current economic credentials of a pre-cursor intervention are based on a non-inferiority RCT[18]. Results will assist policy makers, healthcare managers and other healthcare service providers to inform

decisions regarding the ongoing use or future implementation of the SCRAM program. If the economic evaluation finds the SCRAM program to be cost-effective, then it can be recommended at the national or even international level as a complementary alternative CR delivery model that may meet the needs of many people who are unable or unwilling to participate in traditional centre-based CR services.

Contributorship statement

All the authors contributed to the study design and the protocol of the economic analysis. LG drafted the initial manuscript. All the other authors reviewed, edited and approved the final manuscript.

Competing interests

None declared.

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Tables

Table 1 Identified cost items according to pathway analysis

Process to be costed	Identification of costs	Measurement of costs	Valuation of costs	Who records cost data & how is it collected
Recruitment of participants	Researcher	minutes/hours	Salary costs	Researcher records time taken
Training				
Training/induction session for participants	Project team time	hours	Salary costs	Project team records time taken
Training/induction session for accredited exercise physiologist	Project team time	hours	Salary costs	Project team records time taken
Capital				
Leasing of venue for training/induction sessions	Cost of leasing	Unit cost	Market price	Research team to record
Leasing of venues for cardiac rehabilitation professionals to deliver the SCRAM program	Cost of leasing	Unit cost	Market price	Research team to record

Wearable sensor devices	Cost of sensor device	Unit cost	Market price	Research team to record
Smartphone	Cost of smartphone	Unit cost	Market price	Research team to record
Computers (desktop or laptop)	Cost of computer	Unit cost	Market price	Research team to record
Staffing				
CR professional	CR professional time	Hours	Salary costs	CR professional records time taken
Administrative support	Project staff time	Hours	Salary costs	Project staff records time taken
Miscellaneous costs				
Mobile phone/internet access	Cost of mobile phone, internet access	Unit cost	Market price	Research team to record
Stationery	Cost of stationery	Unit cost	Market price	Research team to record
Utilities (i.e. electricity)	Cost of utility	Unit cost	Market price	Research team to record
Hosting (server)	Cost of server	Unit cost	Market price	Research team to record

Handouts (flyer, information sheet, etc.)	Cost of printing	Unit cost	Market price	Research team to record

Abbreviation: CR, cardiac rehabilitation.

Table 2. Expected outcomes of the economic analysis

Analysis	Incremental costs	Incremental effectiveness	Incremental cost-effectiveness
Incremental cost-effectiveness analysis	AUD	Maximal oxygen uptake (VO_2max, ml·kg^{-1}·min^{-1})	Cost of per unit improvement in VO_2max
	AUD	Anthropometry (i.e. body weight, BMI, waist/hip circumference, etc.*)	Cost of per unit improvement in anthropometry outcomes
	AUD	Blood lipid and glucose concentrations, blood pressure	Cost per unit improvement in biomedical outcomes
Incremental cost-utility analysis	AUD	Quality-adjusted life year gained	Cost per additional quality-adjusted life year gained

*complete list of secondary outcomes could be found in the trial protocol[23].

AUD: Australian dollar; BMI: body mass index

Figures

Figure 1 Pathway analysis for identifying the cost associated with SCRAM program delivery

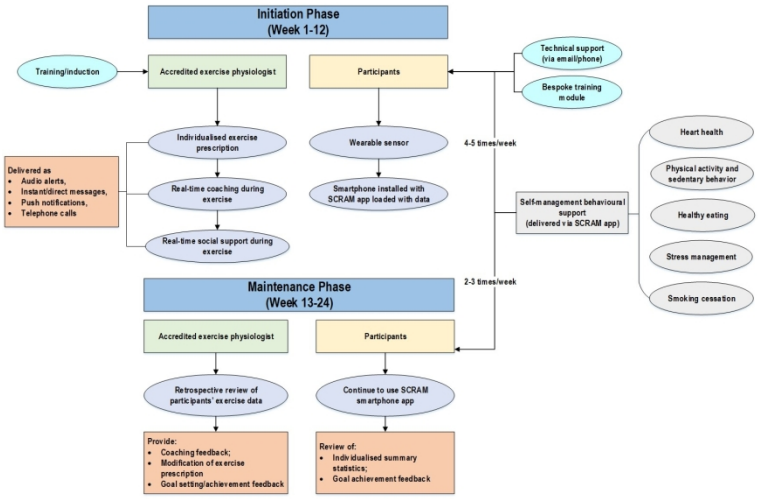

Figure 1 Pathway analysis for identifying the cost associated with SCRAM program delivery

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Economic evaluation protocol for a multicentre randomised controlled trial to compare Smartphone Cardiac Rehabilitation, Assisted self-Management (SCRAM) versus usual care cardiac rehabilitation among people with coronary heart disease

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Title page

Title

Economic evaluation protocol for a multicentre randomised controlled trial to compare Smartphone Cardiac Rehabilitation, Assisted self-Management (SCRAM) versus usual care cardiac rehabilitation among people with coronary heart disease

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Abstract

Introduction

It is important to ascertain the cost-effectiveness of alternative services to traditional cardiac rehabilitation while the economic credentials of the Smartphone Cardiac Rehabilitation, Assisted self-Management (SCRAM) program among people with coronary heart disease (CHD) are unknown. This economic protocol outlines the methods for undertaking a trial-based economic evaluation of SCRAM in the real world setting in Australia.

Methods and analysis

The within-trial economic evaluation will be undertaken alongside a randomised controlled trial (RCT) designed to determine the effectiveness of SCRAM in comparison to usual care cardiac rehabilitation (UC) alone in people with CHD. Pathway analysis will be performed to identify all the costs related to the delivery of SCRAM and UC. Both a healthcare system and a limited societal perspective will be adopted to gauge all costs associated with health resource utilisation and productivity loss. Healthcare resource use over the six-month participation period will be extracted from administrative databases (i.e. Pharmaceutical Benefits Scheme and Medical Benefits Schedule). Productivity loss will be measured by absenteeism from work (valued by human capital approach). The primary outcomes for the economic evaluation are maximal oxygen uptake (VO_2max, ml·kg^{-1}·min^{-1}, primary RCT outcome) and Quality-adjusted life years estimated from health-related quality of life (HRQoL) as assessed by the Assessment of Quality of Life (AQoL-8D) instrument. The incremental cost-effectiveness ratio (ICER) will be calculated using the differences in costs and benefits (i.e. primary and secondary outcomes) between the two randomised groups from both perspectives with no discounting. All costs will be valued in Australian dollars for the year 2020.

Ethics and dissemination

The study protocol has been approved under Australia's National Mutual Acceptance agreement by the Melbourne Health Human Research Ethics Committee (HREC/18/MH/119). It is anticipated that SCRAM is a cost-effective cardiac telerehabiliation program for people

with CHD from both a healthcare and limited societal perspective in Australia. The evaluation will provide evidence to underpin national scale-up of the program to a wider population.

Trial registration

Australian New Zealand Clinical Trials Registry (ACTRN12618001458224)

Strengths and limitations of the study

- Health economics data will be collected prospectively along with a randomised controlled trial to reliably capture the individual-level health care resource use and changes in productivity.
- National administrative data collection (i.e. Medicare and Pharmaceutical Benefits Scheme Australia) will be extracted to source the healthcare resource utilisation over the trial duration.
- The economic evaluation is based on the sample size determined by the primary outcome of the SCRAM RCT, which may be underpowered to detect a difference in costs.

Introduction

Cardiac rehabilitation (CR) is an effective multifactorial secondary prevention intervention that is typically delivered in centre-based (i.e. face-to-face) settings. Centre-based CR reduces recurrent ischaemic events, improves health-related quality of life and long-term prognosis for coronary heart disease (CHD) patients [1-3]. CR programs have also been reported to reduce overall premature mortality (relative risk (RR) 0.87, 95% confidence interval (CI): 0.75-0.99) and cardiac deaths (RR 0.74 (95%CI 0.63-0.87) in comparison with no CR. [4] Despite effectiveness of CR, many people with CHD do not engage in such programs.[5] For instance, CR utilisation is low in Australia; uptake (attended ≥1 session) and completion rates have been estimated at 25% to 60% and 19% to 42%, respectively, across the country; uptake rates as low as 10% have been reported in Victoria.[6-9] Reasons underlying poor participation are complex, but accessibility barriers such as limited program availability, transport restrictions, conflicting domestic/occupational responsibilities, and geographic isolation are key contributors. [10-13]

For these reasons, clinicians and researchers have been prompted to seek novel strategies for delivering CR programs to facilitate greater uptake and adherence rates. Telerehabilitation—defined as rehabilitation services that are delivered remotely through information and communication technologies—has received increasing attention as it can overcome key accessibility barriers that limit participation in centre-based CR. The effectiveness of telerehabilitation, which commonly includes telephone, internet and videoconference communication between participants and healthcare practitioners,[14] has been demonstrated. Systematic reviews have consistently shown that telerehabilitation services improve CVD risk factors (i.e. total cholesterol, blood pressure, high- and low-density lipoprotein), compared to controls[10 15]; and comparisons of traditional centre-based CR with telerehabilitation have shown them to be equivalent in terms of mortality, exercise capacity and quality of life outcomes[16]. The effectiveness of CR interventions delivered via telephone, internet, and videoconference has been well established; however, few trials have capitalised on opportunities to augment intervention design and delivery by using rapidly advancing mobile communication and device technologies (i.e. mobile broadband and smartphones; mHealth).

Four randomised-controlled trials (RCT) have compared mHealth CR with traditional centre-based programs. One study showed improved uptake and completion rate in comparison to the control group [17], two indicated mHealth and centre-based CR had comparable effects on maximal oxygen uptake (i.e. exercise capacity),[18 19] while the fourth suggested mHealth CR led to improvements in maximal oxygen uptake and quality of life[20]. The results from existing economic evaluations of mHealth intervention are not consistent[18 19 21 22].

We are currently undertaking a multi-centre RCT of a smartphone-based platform to support remotely delivered CR called Smartphone Cardiac Rehabilitation, Assisted self-Management (SCRAM). Unlike its predecessor REMOTE-CR[18], SCRAM extends beyond a single behaviour (exercise) to include other secondary prevention self-management behaviours (medication adherence, physical activity and sedentary behaviour, healthy eating, stress management, and smoking cessation). To establish the economic credentials of the SCRAM program in the Australian setting, an economic evaluation will be conducted to examine the balance between health effects and costs of health technologies (i.e. SCRAM program, medications, diagnostic tests, medical services, etc.) to inform efficient allocation of limited healthcare funding. In response to the transparent reporting of clinical trials, this paper outlines the methods of the prospective within-trial economic evaluation to be undertaken alongside the RCT[23], to provide important evidence for policy decision-making around the provision of cardiac rehabilitation services. It will include both cost-effectiveness and cost-utility analysis with a view to informing resource allocation, practice change and investment in the SCRAM program. This planned economic evaluation aims to provide the evidence around the cost-effectiveness of tele-cardiac rehabilitation, assessing its value-for-money in Australia context.

Methods

Design

The details of the study design are reported elsewhere[23]. Briefly, SCRAM is a multicentre investigator-, assessor-, and statistician-blinded parallel two-arm RCT comparing effects and costs of the 24-week SCRAM intervention with usual care CR. A process evaluation is also being undertaken. Participants are randomised (1:1) to receive either SCRAM (intervention) or usual care CR (control).

The study protocol was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12618001458224) on 30/08/2018 and adheres to the SPIRIT 2013 statement.[24] The intervention has been described according to recommendations in the TIDieR and CONSORT (eHealth extension) statements. Reporting of trial outcomes will adhere to the CONSORT statement and its eHealth extension.[25-27]

The economic evaluation will be undertaken from both an Australian healthcare system plus a limited societal perspective, incorporating all health care costs subsidised by state and Commonwealth governments in Australia. In addition, participant absenteeism from work due to CHD will be monetised and the associated cost will be included in the estimation from the limited societal perspective. The reporting of this economic evaluation will adhere to the Consolidated Health Economics Evaluation Reporting Standards (CHEERS) guidelines[28].

Study population

A total of 220 participants (N=110 per randomised group) diagnosed with CHD within the previous six months, are being recruited from hospitals, outpatient clinics, and cardiac rehabilitation services in Sunshine, Geelong, and Bendigo, Victoria, Australia. As study centres provide treatment to ~1.5 million individuals across broad catchment areas the trial cohort is anticipated to include a geographically diverse mix of metropolitan-, regional- and rural-dwelling participants.

Participants are randomised (1:1) to receive the SCRAM program (intervention) or usual care CR (control), stratified by sex and study centre. Key inclusion criteria at baseline are: aged over 18 years; diagnosed CHD within the previous six months (angina, myocardial infarction, or coronary revascularisation); outpatients who have been clinically stable for at least 6 weeks; able to perform exercise; and can understand and write English. Exclusion criteria include: New York Heart Association (NYHA) Functional class III/IV heart failure; terminal disease; significant non-CHD exercise limitations; contraindications for maximal exercise testing.

Patient and public involvement

There is not patient and public involvement.

Sample size

The target sample will provide 90% power at a 5% significance level (two-sided) to detect a clinically meaningful difference of 2.0 ml·kg^{-1}·min^{-1} in $\dot{V}O_2$max at 24 weeks (primary RCT outcome) between the control and intervention groups, assuming a standard deviation of 6.75, a correlation of 0.8 between the pre- and post-intervention measures, and 20% loss-to-follow-up. Minimum detectable differences in secondary RCT outcomes are outlined in the main trial protocol[23].

Baseline assessment

Prior to randomisation, researchers collect the following information: sociodemographic and clinical (diagnostic, smoking, alcohol history, medication) characteristics, ehealth literacy (a questionnaire), $\dot{V}O_2$max, and secondary outcomes (detailed below).

Randomisation

Treatment allocation follows a computer-generated schedule prepared by a biostatistician who is not involved with recruitment, treatment allocation, or outcome assessment[23]. Investigators, outcome assessors, and the statistician remain blinded to the group allocation over the course of the trial.

Treatment arms

Usual care cardiac rehabilitation

Usual care CR typically includes face-to-face support/education to adhere to medical treatment and health-promoting lifestyle behaviours as well as supervised exercise training. Specific program components vary across Australian healthcare providers but most offer education and exercise components;[29] stratification of treatment allocation by trial centre will ensure variation is balanced across treatment groups. It is unclear how many participants will opt for both SCRAM and usual care CR; nevertheless, widespread low uptake of centre-based CR suggests very few patients randomised to SCRAM program will seek to complete

both programs[13]. To explore impact on trial outcomes, self-reported usual care CR utilisation for patients assigned to SCRAM program will be assessed.

Usual care CR is not delivered as part of this trial. All participants retain access to usual care CR—regardless of treatment allocation—as it is unethical to withhold evidence-based treatment. Participants randomised to the control group have access to usual care CR alone, as offered by their local CR provider, without further support.

Intervention: SCRAM program

Participants randomised to the intervention group receive the 24-week dual-phase SCRAM intervention, which is described in detail in the main trial protocol[23]. Briefly, during an initial 12-week intensive phase, participants receive real-time remotely prescribed, supervised and coached exercise training from accredited exercise physiologists as well as a modular multifactorial library of evidence- and theory-based behaviour change support push notifications. This phase is designed to provide intensive support for exercise and lifestyle behaviour uptake and adherence. During a subsequent 12-week maintenance phase, participants receive reduced frequency and intensity of exercise and behaviour change support. This phase is designed to provide tapered support that transitions participants towards long-term self-determined adherence to exercise and health-promoting lifestyle behaviours. Participants receive all intervention components via the bespoke SCRAM software platform, using an Android smartphone.

Comparator

It is important for the economic evaluation to be able to ascertain whether the planned intervention is conducted in addition to existing practices, or as a replacement to them. Consistent with the RCT design[23], SCRAM intervention will be compared to usual care CR (i.e. traditional centre-based CR).

Measurement of clinical endpoints

Outcome measures for the within-trial economic evaluation

Primary outcomes for the economic evaluation will be maximal oxygen uptake ($\dot{V}O_2$max, ml·kg^{-1}·min^{-1}, primary RCT outcome)—measured during an individualised treadmill cardiopulmonary exercise test—and health-related quality of life (HRQoL)—measured using the Assessment of Quality of Life-8D (AQoL-8D). The Australian tariff for AQoL-8D will be used to estimate the QALY gains for individual participant [30]. $\dot{V}O_2$max is measured at baseline and 24-week follow-up, whilst HRQoL is assessed at baseline, 12-weeks, and 24-weeks. Secondary outcomes, including modifiable cardiovascular risk factors and adverse events, are described in the main trial protocol[23].

Measurement of costs

Direct cost of delivering the SCRAM program

In identifying relevant costs, the following principles will be adhered to:

- Identification of costs to be included, using 'pathway analysis' (Figure 1), where activities in all stages of the roll out of the SCRAM project are fully specified; A healthcare system perspective and steady state operation of the intervention will be assumed (intervention is up and running, and start-up costs, like development of SCRAM app will be excluded). Costs will largely relate to the time costs of the remote exercise physiologists and project staff (using opportunity cost principles). Any administrative resources used at the program management level also will be identified and included.

- Measurement of the resources consumed in natural units (number of hours spent by remote exercise physiologists to deliver the intervention, etc.);

- Valuation of these resources in monetary units (Australian dollars), using 2020 as the reference year.

Direct health costs of participants

Beside intervention cost, healthcare-related costs including inpatient and outpatient care associated with CHD are documented. The cost of inpatient care over the 24-week

participation period (e.g. emergency department (ED) visits and rehospitalisations will be estimated from self-reported adverse events documented throughout the trial. Complementary approaches will be utilised to calculate the cost for each hospitalisation episode: first, the cost per hospital admission from the National Hospital Cost Data Collection (actual cost per AR-DRG) will be used; second the National Efficient Price (projected cost) according the AR-DRG code[31] will be used to value the per hospitalisation episode adjusted for the length of hospital stay. The cost of outpatient care (e.g. outpatient consultations, examinations) and medication use over the 24-week participation period will be estimated from MBS and PBS data, respectively. Cost items are summarised in Table 1.

Productivity cost (absenteeism from work)

Absence from work (i.e. days of sick leave) due to CHD is self-reported by participants of working age (i.e. ≤65 years old; people post working age do not attract productivity loss from a societal perspective) using a pre-designed questionnaire at baseline and 24-week follow up. The human capital approach will be used to value the productivity cost[32].

Exclusion of trial costs

Research-driven activities will be separated from the activities that would be carried out should the program be adopted by the healthcare system. Costs associated with trial administration, data collection, and RCT outcome assessment will be excluded.

Data analysis

Within-trial economic evaluation

The within-trial economic evaluation will be based on the intention-to-treat population as per the primary outcome of the RCT[23]. In particular, completers data will be used for the base case analysis, whereas the imputed data analysis (using multiple missing data imputation approach, with the assumption that missingness is at random) will be undertaken to examine the robustness of base case results. All evaluation results will be expressed as incremental results over and above the comparator case. In other words, the additional cost/saving of the

intervention (SCRAM) compared to current practice will be expressed as a ratio by dividing by the net benefits derived. The following formula represents the calculation of the incremental cost-effectiveness ratio (ICER):

$ICER = C_i\text{-}C_{UC}/B_i\text{-}B_{UC}$

where C=costs, B=benefits, i=SCRAM intervention, UC=usual care CR

For the cost-effectiveness analysis (CEA), the incremental cost per unit increase in benefits for both the primary and secondary outcomes will be calculated if significant between-group differences are observed. For the cost-utility analysis (CUA), the quality-adjusted life year (QALY) will be estimated from HRQoL assessed by AQoL-8D by intervention group (Table 2). A plot on the cost effectiveness plane will be drawn to illustrate the distribution of costs and effectiveness. A cost-effectiveness acceptability curve will also be plotted in order to assess the degree of uncertainty associated with the conclusion using a predetermined empirical willingness-to-pay (WTP) threshold for the QALY outcome (i.e. AU$50,000/QALY)[33].

Bootstrap simulation of the costs and ICER will be used to simulate the study results over 2,000 iterations. This technique is used when data are skewed (cost data are nearly always highly skewed) and the confidence interval of a ratio using skewed data is required. The within-trial economic analysis will be undertaken using STATA 15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

Long-term modelling

Model-based long-term cost-effectiveness analysis of SCRAM versus usual care CR will be undertaken if the primary outcome (VO2 max) from the RCT is proven to significantly increase. The VO2 max will be converted to the reduction in overall mortality (i.e. odds ratio in mortality for 1 Metabolic Equivalents increase). The difference (if any, observed from the RCT) in the incidence of recurrent CVD post the index MI will also be used to model the long-term health and cost outcomes associated with the application of the two modes of CR. Benefits observed in the trial will be translated into health benefits (e.g., avoided morbidity/mortality outcomes, and calculated in terms of QALY gained). The modelled economic evaluation will simulate the impact of increased maximal oxygen uptake on the overall well-being/survival of the cohort over its lifetime compared with the control group. A Markov model consisting of health states associated with CHD (i.e. recurrent myocardial infarction, angina, revascularisation, stroke or

death) will be used to accrue costs and benefits over the lifetime horizon. The long-term improved outcomes may translate into the cost savings due to avoided ED visit and rehospitalisation. Long-term modelling will be performed in TreeAge Pro 2019.

Sensitivity analysis

Uncertainty analyses will be conducted based on Monte Carlo simulations. The between-group differences in both costs and QALY will be bootstrapped to estimate the probability of the SCRAM program being cost-effective regardless of the significance in between-group difference[34]. A series of one-way sensitivity analyses will be undertaken to examine robustness of the base-case ICER, for example, alternative costing approach for rehospitalisation (unit costs derived from Independent Hospital Pricing Authority, Australia; Australian Institute of Health and Wellbeing), labours (unit costs sourced from Australia Bureau of Statistics, PayScale), and SCRAM intervention delivery (varying the quantity and unit cost of the resource utilised).

Ethics approval

The study protocol has been approved under Australia's National Mutual Acceptance agreement by the Melbourne Health Human Research Ethics Committee (HREC/18/MH/119). Ethics approval has been ratified by the Deakin University Human Research Ethics Committee (2018-251). All participants provide written informed consent prior to undertaking baseline assessments. Separate consent is sought to extract MBS/PBS data for the purpose of this study.

Discussion

This paper details the protocol of a trial-based economic evaluation that purports to assess the cost-effectiveness of the SCRAM telerehabilitation program among people with CHD. It has a number of methodological strengths, the key one being that the economic evaluation will be undertaken alongside a prospective RCT. This has the advantage of being efficient and timely in terms of the data collected. In addition, the RCT design provides credibility through high internal validity, minimisation of bias, and tight protocol control. The SCRAM RCT aims

to minimise the predictable sources of bias and confounding via allocation concealment, blinded outcome assessment and intention-to-treat analysis. The primary costing data will be sourced from administrative databases including MBS, PBS, and hospital costing system data; this allows for maximum accuracy of the data collected and enhances the capture of effects and outcomes. Furthermore, this RCT is recruiting participants from metropolitan, regional and rural areas of Victoria, Australia, allowing for broader representativeness of participants that will maximise generalisability of the results. Lastly, HRQoL will be assessed by the AQoL-8D, a 35-item questionnaire, which has been widely applied in measuring HRQoL for Australia-based studies[35-38]. It has increased measurement sensitivity, especially in the psychosocial dimensions, compared with existing instruments [i.e. EuroQol-5D-5L (EQ-5D-5L), Quality of Wellbeing (QWB), Health Utilities Index Mark 3 (HUI3), and 15D] that vary greatly and report inconsistent utility scores [39]. Further, undertaking both completers and imputed data analyses for the trial-based economic evaluation will increased the validity of the results given the potential significant proportion of missingness in follow up cost and QALY data. The trial-based economic evaluation only has a short 24 week timeframe and was based on the trial under strictly controlled research conditions. It cannot answer the long term cost-effectiveness of SCRAM program which is pivotal for the reimbursement decision-making. The model-based economic evaluation that extrapolates the short-term trial outcome to the lifetime horizon and a real-world setting will inform the cost-effectiveness of the proposed program in the Australian context.

The economic credentials of traditional centre-based CR versus no CR have long been established. A systematic review of 19 CEAs of such interventions concluded that the majority reported traditional CR was cost-effective versus no CR (ICER ranged from US$1065 to US$71755/QALY), especially with exercise as a component[40 41]. Specifically in relation to cardiac telerehabiliation (not involving a smartphone-based remote CR component), studies are varied in terms of their results. Whilst one within-trial economic evaluation reported that such an intervention (offering the flexibility of having the CR at hospital, healthcare centre, or call centre) was not cost-effective given its high cost (ICER €400,000 per QALY)[21], others have demonstrated more positive outcomes. A trial-based economic analysis home-based CR was associated with non-significantly lower costs and a high probability of being cost-effective[19]. Another CUA showed that the mean cost per patient in a telemonitoring program was €564

lower than in the control group, but with higher QALY gains (0.026), thereby making the intervention dominant (lower costs but higher benefits)[22]. Another CEA of home-based telerehabilitation, delivered through online videoconferencing for patients with heart failure, concluded that it was associated with significantly lower costs (-AU$1590, 95%CI -$2822 to -$359) during the 6 month participation period[42]. Our previous economic evaluation alongside a non-inferiority RCT in New Zealand indicated the REMOTE-CR smartphone-based cardiac telerehabilitation program—a precursor to SCRAM—was associated with cost-saving (-NZ$4615/participant) and comparable benefits[18].

Some methodological limitations are worth mentioning: first of all, the economic evaluation is based on the sample size determined by the primary outcome of the SCRAM RCT. It may be underpowered to detect a difference in costs. Second, whilst the gold standard is to undertake economic evaluations from a societal perspective (which captures all costs falling on patients, their carers, and families), the current study only considers a limited societal perspective (i.e. including only productivity costs); the costs borne by carers and families are excluded. However, it is believed that the health care system plus the limited societal perspectives will provide sufficient information to inform decision-making around investment in the SCRAM program in Australia and elsewhere.

Conclusion

The results of this economic evaluation will fill the evidence gap for the cost-effectiveness of this mHealth CR program versus usual care CR alone, given that the current economic credentials of a pre-cursor intervention are based on a non-inferiority RCT[18]. Results will assist policy makers, healthcare managers and other healthcare service providers to inform decisions regarding the ongoing use or future implementation of the SCRAM program. If the economic evaluation finds the SCRAM program to be cost-effective, then it can be recommended at the national or even international level as a complementary alternative CR delivery model that may meet the needs of many people who are unable or unwilling to participate in traditional centre-based CR services.

Contributorship statement

All the authors (LG, RM, JR, KB, BO, CC, SAM, KL, JA, VN, CN, SC, and MM) contributed to the study design and the protocol of the economic analysis. LG drafted the initial manuscript. All the other authors (RM, JR, KB, BO, CC, SAM, KL, JA, VN, CN, SC, and MM) reviewed, edited and approved the final manuscript.

Competing interests

None declared.

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Tables

Table 1 Identified cost items according to pathway analysis

Process to be costed	Identification of costs	Measurement of costs	Valuation of costs	Who records cost data & how is it collected
Recruitment of participants	Researcher	minutes/hours	Salary costs	Researcher records time taken
Training				
Training/induction session for participants	Project team time	hours	Salary costs	Project team records time taken
Training/induction session for accredited exercise physiologist	Project team time	hours	Salary costs	Project team records time taken
Capital				
Leasing of venue for training/induction sessions	Cost of leasing	Unit cost	Market price	Research team to record
Leasing of venues for cardiac rehabilitation professionals to deliver the SCRAM program	Cost of leasing	Unit cost	Market price	Research team to record

Wearable sensor devices	Cost of sensor device	Unit cost	Market price	Research team to record
Smartphone	Cost of smartphone	Unit cost	Market price	Research team to record
Computers (desktop or laptop)	Cost of computer	Unit cost	Market price	Research team to record
Staffing				
CR professional	CR professional time	Hours	Salary costs	CR professional records time taken
Administrative support	Project staff time	Hours	Salary costs	Project staff records time taken
Miscellaneous costs				
Mobile phone/internet access	Cost of mobile phone, internet access	Unit cost	Market price	Research team to record
Stationery	Cost of stationery	Unit cost	Market price	Research team to record
Utilities (i.e. electricity)	Cost of utility	Unit cost	Market price	Research team to record
Hosting (server)	Cost of server	Unit cost	Market price	Research team to record

Handouts (flyer, information sheet, etc.)	Cost of printing	Unit cost	Market price	Research team to record

Abbreviation: CR, cardiac rehabilitation.

Table 2. Expected outcomes of the economic analysis

Analysis	Incremental costs	Incremental effectiveness	Incremental cost-effectiveness
Incremental cost-effectiveness analysis	AUD	Maximal oxygen uptake (VO_2max, ml·kg^{-1}·min^{-1})	Cost of per unit improvement in VO_2max
	AUD	Anthropometry (i.e. body weight, BMI, waist/hip circumference, etc.*)	Cost of per unit improvement in anthropometry outcomes
	AUD	Blood lipid and glucose concentrations, blood pressure	Cost per unit improvement in biomedical outcomes
Incremental cost-utility analysis	AUD	Quality-adjusted life year gained	Cost per additional quality-adjusted life year gained

*complete list of secondary outcomes could be found in the trial protocol[23].
AUD: Australian dollar; BMI: body mass index

Figures

Figure 1 Pathway analysis for identifying the cost associated with SCRAM program delivery

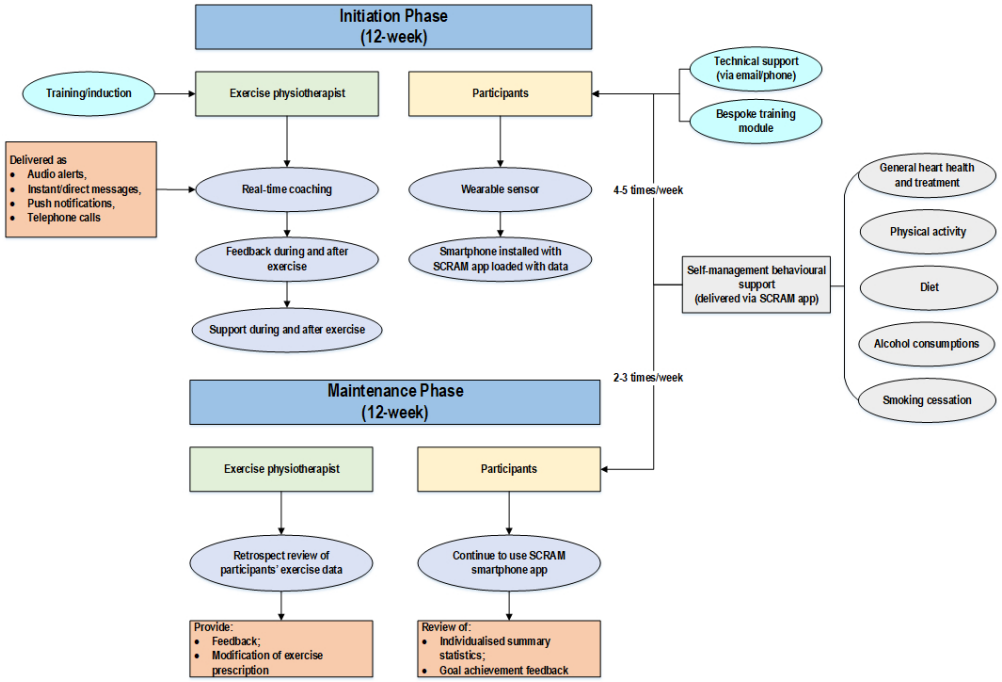

Figure 1 Pathway analysis for identifying the cost associated with SCRAM program delivery

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Economic evaluation protocol for a multicentre randomised controlled trial to compare Smartphone Cardiac Rehabilitation, Assisted self-Management (SCRAM) versus usual care cardiac rehabilitation among people with coronary heart disease

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Title page

Title

Economic evaluation protocol for a multicentre randomised controlled trial to compare Smartphone Cardiac Rehabilitation, Assisted self-Management (SCRAM) versus usual care cardiac rehabilitation among people with coronary heart disease

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Abstract

Introduction

It is important to ascertain the cost-effectiveness of alternative services to traditional cardiac rehabilitation while the economic credentials of the Smartphone Cardiac Rehabilitation, Assisted self-Management (SCRAM) program among people with coronary heart disease (CHD) are unknown. This economic protocol outlines the methods for undertaking a trial-based economic evaluation of SCRAM in the real world setting in Australia.

Methods and analysis

The within-trial economic evaluation will be undertaken alongside a randomised controlled trial (RCT) designed to determine the effectiveness of SCRAM in comparison to usual care cardiac rehabilitation (UC) alone in people with CHD. Pathway analysis will be performed to identify all the costs related to the delivery of SCRAM and UC. Both a healthcare system and a limited societal perspective will be adopted to gauge all costs associated with health resource utilisation and productivity loss. Healthcare resource use over the six-month participation period will be extracted from administrative databases (i.e. Pharmaceutical Benefits Scheme and Medical Benefits Schedule). Productivity loss will be measured by absenteeism from work (valued by human capital approach). The primary outcomes for the economic evaluation are maximal oxygen uptake (VO_2max, $ml \cdot kg^{-1} \cdot min^{-1}$, primary RCT outcome) and Quality-adjusted life years estimated from health-related quality of life (HRQoL) as assessed by the Assessment of Quality of Life (AQoL-8D) instrument. The incremental cost-effectiveness ratio (ICER) will be calculated using the differences in costs and benefits (i.e. primary and secondary outcomes) between the two randomised groups from both perspectives with no discounting. All costs will be valued in Australian dollars for the year 2020.

Ethics and dissemination

The study protocol has been approved under Australia's National Mutual Acceptance agreement by the Melbourne Health Human Research Ethics Committee (HREC/18/MH/119). It is anticipated that SCRAM is a cost-effective cardiac telerehabiliation program for people with CHD from both a healthcare and limited societal perspective in Australia. The evaluation

will provide evidence to underpin national scale-up of the program to a wider population. Results of the economic analysis will be submitted for publication in a peer-reviewed journal.

Trial registration

Australian New Zealand Clinical Trials Registry (ACTRN12618001458224)

Strengths and limitations of the study

- Health economics data will be collected prospectively along with a randomised controlled trial to reliably capture the individual-level health care resource use and changes in productivity.
- National administrative data collection (i.e. Medicare and Pharmaceutical Benefits Scheme Australia) will be extracted to source the healthcare resource utilisation over the trial duration.
- The economic evaluation is based on the sample size determined by the primary outcome of the SCRAM RCT, which may be underpowered to detect a difference in costs.

Introduction

Cardiac rehabilitation (CR) is an effective multifactorial secondary prevention intervention that is typically delivered in centre-based (i.e. face-to-face) settings. Centre-based CR reduces recurrent ischaemic events, improves health-related quality of life and long-term prognosis for coronary heart disease (CHD) patients [1-3]. CR programs have also been reported to reduce overall premature mortality (relative risk (RR) 0.87, 95% confidence interval (CI): 0.75-0.99) and cardiac deaths (RR 0.74 (95%CI 0.63-0.87) in comparison with no CR. [4] Despite effectiveness of CR, many people with CHD do not engage in such programs.[5] For instance, CR utilisation is low in Australia; uptake (attended ≥1 session) and completion rates have been estimated at 25% to 60% and 19% to 42%, respectively, across the country; uptake rates as low as 10% have been reported in Victoria.[6-9] Reasons underlying poor participation are complex, but accessibility barriers such as limited program availability, transport restrictions, conflicting domestic/occupational responsibilities, and geographic isolation are key contributors. [10-13]

For these reasons, clinicians and researchers have been prompted to seek novel strategies for delivering CR programs to facilitate greater uptake and adherence rates. Telerehabilitation—defined as rehabilitation services that are delivered remotely through information and communication technologies—has received increasing attention as it can overcome key accessibility barriers that limit participation in centre-based CR. The effectiveness of telerehabilitation, which commonly includes telephone, internet and videoconference communication between participants and healthcare practitioners,[14] has been demonstrated. Systematic reviews have consistently shown that telerehabilitation services improve CVD risk factors (i.e. total cholesterol, blood pressure, high- and low-density lipoprotein), compared to controls[10 15]; and comparisons of traditional centre-based CR with telerehabilitation have shown them to be equivalent in terms of mortality, exercise capacity and quality of life outcomes[16]. The effectiveness of CR interventions delivered via telephone, internet, and videoconference has been well established; however, few trials have capitalised on opportunities to augment intervention design and delivery by using rapidly advancing mobile communication and device technologies (i.e. mobile broadband and smartphones; mHealth).

Four randomised-controlled trials (RCT) have compared mHealth CR with traditional centre-based programs. One study showed improved uptake and completion rate in comparison to the control group [17], two indicated mHealth and centre-based CR had comparable effects on maximal oxygen uptake (i.e. exercise capacity),[18 19] while the fourth suggested mHealth CR led to improvements in maximal oxygen uptake and quality of life[20]. The results from existing economic evaluations of mHealth intervention are not consistent[18 19 21 22].

We are currently undertaking a multi-centre RCT of a smartphone-based platform to support remotely delivered CR called Smartphone Cardiac Rehabilitation, Assisted self-Management (SCRAM). Unlike its predecessor REMOTE-CR[18], SCRAM extends beyond a single behaviour (exercise) to include other secondary prevention self-management behaviours (medication adherence, physical activity and sedentary behaviour, healthy eating, stress management, and smoking cessation). To establish the economic credentials of the SCRAM program in the Australian setting, an economic evaluation will be conducted to examine the balance between health effects and costs of health technologies (i.e. SCRAM program, medications, diagnostic tests, medical services, etc.) to inform efficient allocation of limited healthcare funding. In response to the transparent reporting of clinical trials, this paper outlines the methods of the prospective within-trial economic evaluation to be undertaken alongside the RCT[23], to provide important evidence for policy decision-making around the provision of cardiac rehabilitation services. It will include both cost-effectiveness and cost-utility analysis with a view to informing resource allocation, practice change and investment in the SCRAM program. This planned economic evaluation aims to provide the evidence around the cost-effectiveness of tele-cardiac rehabilitation, assessing its value-for-money in Australia context.

Methods

Design

The details of the study design are reported elsewhere[23]. Briefly, SCRAM is a multicentre investigator-, assessor-, and statistician-blinded parallel two-arm RCT comparing effects and costs of the 24-week SCRAM intervention with usual care CR. A process evaluation is also being undertaken. Participants are randomised (1:1) to receive either SCRAM (intervention) or usual care CR (control).

The study protocol was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12618001458224) on 30/08/2018 and adheres to the SPIRIT 2013 statement.[24] The intervention has been described according to recommendations in the TIDieR and CONSORT (eHealth extension) statements. Reporting of trial outcomes will adhere to the CONSORT statement and its eHealth extension.[25-27]

The economic evaluation will be undertaken from both an Australian healthcare system plus a limited societal perspective, incorporating all health care costs subsidised by state and Commonwealth governments in Australia. In addition, participant absenteeism from work due to CHD will be monetised and the associated cost will be included in the estimation from the limited societal perspective. The reporting of this economic evaluation will adhere to the Consolidated Health Economics Evaluation Reporting Standards (CHEERS) guidelines[28].

Study population

A total of 220 participants (N=110 per randomised group) diagnosed with CHD within the previous six months, are being recruited from hospitals, outpatient clinics, and cardiac rehabilitation services in Sunshine, Geelong, and Bendigo, Victoria, Australia. As study centres provide treatment to ~1.5 million individuals across broad catchment areas the trial cohort is anticipated to include a geographically diverse mix of metropolitan-, regional- and rural-dwelling participants.

Participants are randomised (1:1) to receive the SCRAM program (intervention) or usual care CR (control), stratified by sex and study centre. Key inclusion criteria at baseline are: aged over 18 years; diagnosed CHD within the previous six months (angina, myocardial infarction, or coronary revascularisation); outpatients who have been clinically stable for at least 6 weeks; able to perform exercise; and can understand and write English. Exclusion criteria include: New York Heart Association (NYHA) Functional class III/IV heart failure; terminal disease; significant non-CHD exercise limitations; contraindications for maximal exercise testing.

Patient and public involvement

There is not patient and public involvement.

Sample size

The target sample will provide 90% power at a 5% significance level (two-sided) to detect a clinically meaningful difference of 2.0 ml·kg^{-1}·min^{-1} in $\dot{V}O_2$max at 24 weeks (primary RCT outcome) between the control and intervention groups, assuming a standard deviation of 6.75, a correlation of 0.8 between the pre- and post-intervention measures, and 20% loss-to-follow-up. Minimum detectable differences in secondary RCT outcomes are outlined in the main trial protocol[23].

Baseline assessment

Prior to randomisation, researchers collect the following information: sociodemographic and clinical (diagnostic, smoking, alcohol history, medication) characteristics, ehealth literacy (a questionnaire), $\dot{V}O_2$max, and secondary outcomes (detailed below).

Randomisation

Treatment allocation follows a computer-generated schedule prepared by a biostatistician who is not involved with recruitment, treatment allocation, or outcome assessment[23]. Investigators, outcome assessors, and the statistician remain blinded to the group allocation over the course of the trial.

Treatment arms

Usual care cardiac rehabilitation

Usual care CR typically includes face-to-face support/education to adhere to medical treatment and health-promoting lifestyle behaviours as well as supervised exercise training. Specific program components vary across Australian healthcare providers but most offer education and exercise components;[29] stratification of treatment allocation by trial centre will ensure variation is balanced across treatment groups. It is unclear how many participants will opt for both SCRAM and usual care CR; nevertheless, widespread low uptake of centre-based CR suggests very few patients randomised to SCRAM program will seek to complete

both programs[13]. To explore impact on trial outcomes, self-reported usual care CR utilisation for patients assigned to SCRAM program will be assessed.

Usual care CR is not delivered as part of this trial. All participants retain access to usual care CR—regardless of treatment allocation—as it is unethical to withhold evidence-based treatment. Participants randomised to the control group have access to usual care CR alone, as offered by their local CR provider, without further support.

Intervention: SCRAM program

Participants randomised to the intervention group receive the 24-week dual-phase SCRAM intervention, which is described in detail in the main trial protocol[23]. Briefly, during an initial 12-week intensive phase, participants receive real-time remotely prescribed, supervised and coached exercise training from accredited exercise physiologists as well as a modular multifactorial library of evidence- and theory-based behaviour change support push notifications. This phase is designed to provide intensive support for exercise and lifestyle behaviour uptake and adherence. During a subsequent 12-week maintenance phase, participants receive reduced frequency and intensity of exercise and behaviour change support. This phase is designed to provide tapered support that transitions participants towards long-term self-determined adherence to exercise and health-promoting lifestyle behaviours. Participants receive all intervention components via the bespoke SCRAM software platform, using an Android smartphone.

Comparator

It is important for the economic evaluation to be able to ascertain whether the planned intervention is conducted in addition to existing practices, or as a replacement to them. Consistent with the RCT design[23], SCRAM intervention will be compared to usual care CR (i.e. traditional centre-based CR).

Measurement of clinical endpoints

Outcome measures for the within-trial economic evaluation

Primary outcomes for the economic evaluation will be maximal oxygen uptake ($\dot{V}O_2$max, ml·kg^{-1}·min^{-1}, primary RCT outcome)—measured during an individualised treadmill cardiopulmonary exercise test—and health-related quality of life (HRQoL)—measured using the Assessment of Quality of Life-8D (AQoL-8D). The Australian tariff for AQoL-8D will be used to estimate the QALY gains for individual participant [30]. $\dot{V}O_2$max is measured at baseline and 24-week follow-up, whilst HRQoL is assessed at baseline, 12-weeks, and 24-weeks. Secondary outcomes, including modifiable cardiovascular risk factors and adverse events, are described in the main trial protocol[23].

Measurement of costs

Direct cost of delivering the SCRAM program

In identifying relevant costs, the following principles will be adhered to:

- Identification of costs to be included, using 'pathway analysis' (Figure 1), where activities in all stages of the roll out of the SCRAM project are fully specified; A healthcare system perspective and steady state operation of the intervention will be assumed (intervention is up and running, and start-up costs, like development of SCRAM app will be excluded). Costs will largely relate to the time costs of the remote exercise physiologists and project staff (using opportunity cost principles). Any administrative resources used at the program management level also will be identified and included. Cost items identified from pathway analysis are summarised in Table 1.

- Measurement of the resources consumed in natural units (number of hours spent by remote exercise physiologists to deliver the intervention, etc.);

- Valuation of these resources in monetary units (Australian dollars), using 2020 as the reference year.

Direct health costs of participants

Beside intervention cost, healthcare-related costs including inpatient and outpatient care associated with CHD are documented. The cost of inpatient care over the 24-week participation period (e.g. emergency department (ED) visits and rehospitalisations will be estimated from self-reported adverse events documented throughout the trial. Complementary approaches will be utilised to calculate the cost for each hospitalisation episode: first, the cost per hospital admission from the National Hospital Cost Data Collection (actual cost per AR-DRG) will be used; second the National Efficient Price (projected cost) according the AR-DRG code[31] will be used to value the per hospitalisation episode adjusted for the length of hospital stay. The cost of outpatient care (e.g. outpatient consultations, examinations) and medication use over the 24-week participation period will be estimated from MBS and PBS data, respectively.

Productivity cost (absenteeism from work)

Absence from work (i.e. days of sick leave) due to CHD is self-reported by participants of working age (i.e. ≤65 years old; people post working age do not attract productivity loss from a societal perspective) using a pre-designed questionnaire at baseline and 24-week follow up. The human capital approach will be used to value the productivity cost[32].

Exclusion of trial costs

Research-driven activities will be separated from the activities that would be carried out should the program be adopted by the healthcare system. Costs associated with trial administration, data collection, and RCT outcome assessment will be excluded.

Data analysis

Within-trial economic evaluation

The within-trial economic evaluation will be based on the intention-to-treat population as per the primary outcome of the RCT[23]. In particular, completers data will be used for the base case analysis, whereas the imputed data analysis (using multiple missing data imputation

approach, with the assumption that missingness is at random) will be undertaken to examine the robustness of base case results. All evaluation results will be expressed as incremental results over and above the comparator case. In other words, the additional cost/saving of the intervention (SCRAM) compared to current practice will be expressed as a ratio by dividing by the net benefits derived. The following formula represents the calculation of the incremental cost-effectiveness ratio (ICER):

$ICER = C_i\text{-}C_{UC}/B_i\text{-}B_{UC}$

where C=costs, B=benefits, i=SCRAM intervention, UC=usual care CR

For the cost-effectiveness analysis (CEA), the incremental cost per unit increase in benefits for both the primary and secondary outcomes will be calculated if significant between-group differences are observed. For the cost-utility analysis (CUA), the quality-adjusted life year (QALY) will be estimated from HRQoL assessed by AQoL-8D by intervention group (Table 2). A plot on the cost effectiveness plane will be drawn to illustrate the distribution of costs and effectiveness. A cost-effectiveness acceptability curve will also be plotted in order to assess the degree of uncertainty associated with the conclusion using a predetermined empirical willingness-to-pay (WTP) threshold for the QALY outcome (i.e. AU$50,000/QALY)[33].

Bootstrap simulation of the costs and ICER will be used to simulate the study results over 2,000 iterations. This technique is used when data are skewed (cost data are nearly always highly skewed) and the confidence interval of a ratio using skewed data is required. The within-trial economic analysis will be undertaken using STATA 15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

Long-term modelling

Model-based long-term cost-effectiveness analysis of SCRAM versus usual care CR will be undertaken if the primary outcome (VO2 max) from the RCT is proven to significantly increase. The VO2 max will be converted to the reduction in overall mortality (i.e. odds ratio in mortality for 1 Metabolic Equivalents increase). The difference (if any, observed from the RCT) in the incidence of recurrent CVD post the index MI will also be used to model the long-term health and cost outcomes associated with the application of the two modes of CR. Benefits observed in the trial will be translated into health benefits (e.g., avoided morbidity/mortality outcomes, and calculated in terms of QALY gained). The modelled economic evaluation will simulate the

impact of increased maximal oxygen uptake on the overall well-being/survival of the cohort over its lifetime compared with the control group. A Markov model consisting of health states associated with CHD (i.e. recurrent myocardial infarction, angina, revascularisation, stroke or death) will be used to accrue costs and benefits over the lifetime horizon. The long-term improved outcomes may translate into the cost savings due to avoided ED visit and rehospitalisation. Long-term modelling will be performed in TreeAge Pro 2019.

Sensitivity analysis

Uncertainty analyses will be conducted based on Monte Carlo simulations. The between-group differences in both costs and QALY will be bootstrapped to estimate the probability of the SCRAM program being cost-effective regardless of the significance in between-group difference[34]. A series of one-way sensitivity analyses will be undertaken to examine robustness of the base-case ICER, for example, alternative costing approach for rehospitalisation (unit costs derived from Independent Hospital Pricing Authority, Australia; Australian Institute of Health and Wellbeing), labours (unit costs sourced from Australia Bureau of Statistics, PayScale), and SCRAM intervention delivery (varying the quantity and unit cost of the resource utilised).

Ethics approval

The study protocol has been approved under Australia's National Mutual Acceptance agreement by the Melbourne Health Human Research Ethics Committee (HREC/18/MH/119). Ethics approval has been ratified by the Deakin University Human Research Ethics Committee (2018-251). All participants provide written informed consent prior to undertaking baseline assessments. Separate consent is sought to extract MBS/PBS data for the purpose of this study.

Discussion

This paper details the protocol of a trial-based economic evaluation that purports to assess the cost-effectiveness of the SCRAM telerehabilitation program among people with CHD. It has a number of methodological strengths, the key one being that the economic evaluation

will be undertaken alongside a prospective RCT. This has the advantage of being efficient and timely in terms of the data collected. In addition, the RCT design provides credibility through high internal validity, minimisation of bias, and tight protocol control. The SCRAM RCT aims to minimise the predictable sources of bias and confounding via allocation concealment, blinded outcome assessment and intention-to-treat analysis. The primary costing data will be sourced from administrative databases including MBS, PBS, and hospital costing system data; this allows for maximum accuracy of the data collected and enhances the capture of effects and outcomes. Furthermore, this RCT is recruiting participants from metropolitan, regional and rural areas of Victoria, Australia, allowing for broader representativeness of participants that will maximise generalisability of the results. Lastly, HRQoL will be assessed by the AQoL-8D, a 35-item questionnaire, which has been widely applied in measuring HRQoL for Australia-based studies[35-38]. It has increased measurement sensitivity, especially in the psychosocial dimensions, compared with existing instruments [i.e. EuroQol-5D-5L (EQ-5D-5L), Quality of Wellbeing (QWB), Health Utilities Index Mark 3 (HUI3), and 15D] that vary greatly and report inconsistent utility scores [39]. Further, undertaking both completers and imputed data analyses for the trial-based economic evaluation will increased the validity of the results given the potential significant proportion of missingness in follow up cost and QALY data. The trial-based economic evaluation only has a short 24 week timeframe and was based on the trial under strictly controlled research conditions. It cannot answer the long term cost-effectiveness of SCRAM program which is pivotal for the reimbursement decision-making. The model-based economic evaluation that extrapolates the short-term trial outcome to the lifetime horizon and a real-world setting will inform the cost-effectiveness of the proposed program in the Australian context.

The economic credentials of traditional centre-based CR versus no CR have long been established. A systematic review of 19 CEAs of such interventions concluded that the majority reported traditional CR was cost-effective versus no CR (ICER ranged from US$1065 to US$71755/QALY), especially with exercise as a component[40 41]. Specifically in relation to cardiac telerehabiliation (not involving a smartphone-based remote CR component), studies are varied in terms of their results. Whilst one within-trial economic evaluation reported that such an intervention (offering the flexibility of having the CR at hospital, healthcare centre, or call centre) was not cost-effective given its high cost (ICER €400,000 per QALY)[21], others have

demonstrated more positive outcomes. A trial-based economic analysis home-based CR was associated with non-significantly lower costs and a high probability of being cost-effective[19]. Another CUA showed that the mean cost per patient in a telemonitoring program was €564 lower than in the control group, but with higher QALY gains (0.026), thereby making the intervention dominant (lower costs but higher benefits)[22]. Another CEA of home-based telerehabilitation, delivered through online videoconferencing for patients with heart failure, concluded that it was associated with significantly lower costs (-AU$1590, 95%CI -$2822 to -$359) during the 6 month participation period[42]. Our previous economic evaluation alongside a non-inferiority RCT in New Zealand indicated the REMOTE-CR smartphone-based cardiac telerehabilitation program—a precursor to SCRAM—was associated with cost-saving (-NZ$4615/participant) and comparable benefits[18].

Some methodological limitations are worth mentioning: first of all, the economic evaluation is based on the sample size determined by the primary outcome of the SCRAM RCT. It may be underpowered to detect a difference in costs. Second, whilst the gold standard is to undertake economic evaluations from a societal perspective (which captures all costs falling on patients, their carers, and families), the current study only considers a limited societal perspective (i.e. including only productivity costs); the costs borne by carers and families are excluded. However, it is believed that the health care system plus the limited societal perspectives will provide sufficient information to inform decision-making around investment in the SCRAM program in Australia and elsewhere.

The results of this economic evaluation will fill the evidence gap for the cost-effectiveness of this mHealth CR program versus usual care CR alone, given that the current economic credentials of a pre-cursor intervention are based on a non-inferiority RCT[18]. Results will assist policy makers, healthcare managers and other healthcare service providers to inform decisions regarding the ongoing use or future implementation of the SCRAM program. If the economic evaluation finds the SCRAM program to be cost-effective, then it can be recommended at the national or even international level as a complementary alternative CR delivery model that may meet the needs of many people who are unable or unwilling to participate in traditional centre-based CR services.

Contributorship statement

All the authors (LG, RM, JR, KB, BO, CC, SAM, KL, JA, VN, CN, SC, and MM) contributed to the study design and the protocol of the economic analysis. LG drafted the initial manuscript. All the other authors (RM, JR, KB, BO, CC, SAM, KL, JA, VN, CN, SC, and MM) reviewed, edited and approved the final manuscript.

Competing interests

None declared.

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Tables

Table 1 Identified cost items according to pathway analysis

Process to be costed	Identification of costs	Measurement of costs	Valuation of costs	Who records cost data & how is it collected
Recruitment of participants	Researcher	minutes/hours	Salary costs	Researcher records time taken
Training				
Training/induction session for participants	Project team time	hours	Salary costs	Project team records time taken
Training/induction session for accredited exercise physiologist	Project team time	hours	Salary costs	Project team records time taken
Capital				
Leasing of venue for training/induction sessions	Cost of leasing	Unit cost	Market price	Research team to record
Leasing of venues for cardiac rehabilitation professionals to deliver the SCRAM program	Cost of leasing	Unit cost	Market price	Research team to record

Wearable sensor devices	Cost of sensor device	Unit cost	Market price	Research team to record
Smartphone	Cost of smartphone	Unit cost	Market price	Research team to record
Computers (desktop or laptop)	Cost of computer	Unit cost	Market price	Research team to record
Staffing				
CR professional	CR professional time	Hours	Salary costs	CR professional records time taken
Administrative support	Project staff time	Hours	Salary costs	Project staff records time taken
Miscellaneous costs				
Mobile phone/internet access	Cost of mobile phone, internet access	Unit cost	Market price	Research team to record
Stationery	Cost of stationery	Unit cost	Market price	Research team to record
Utilities (i.e. electricity)	Cost of utility	Unit cost	Market price	Research team to record
Hosting (server)	Cost of server	Unit cost	Market price	Research team to record

Handouts (flyer, information sheet, etc.)	Cost of printing	Unit cost	Market price	Research team to record

Abbreviation: CR, cardiac rehabilitation.

Table 2. Expected outcomes of the economic analysis

Analysis	Incremental costs	Incremental effectiveness	Incremental cost-effectiveness
Incremental cost-effectiveness analysis	AUD	Maximal oxygen uptake (VO_2max, ml·kg^{-1}·min^{-1})	Cost of per unit improvement in VO_2max
	AUD	Anthropometry (i.e. body weight, BMI, waist/hip circumference, etc.*)	Cost of per unit improvement in anthropometry outcomes
	AUD	Blood lipid and glucose concentrations, blood pressure	Cost per unit improvement in biomedical outcomes
Incremental cost-utility analysis	AUD	Quality-adjusted life year gained	Cost per additional quality-adjusted life year gained

*complete list of secondary outcomes could be found in the trial protocol[23].
AUD: Australian dollar; BMI: body mass index

Figures

Figure 1 Pathway analysis for identifying the cost associated with SCRAM program delivery

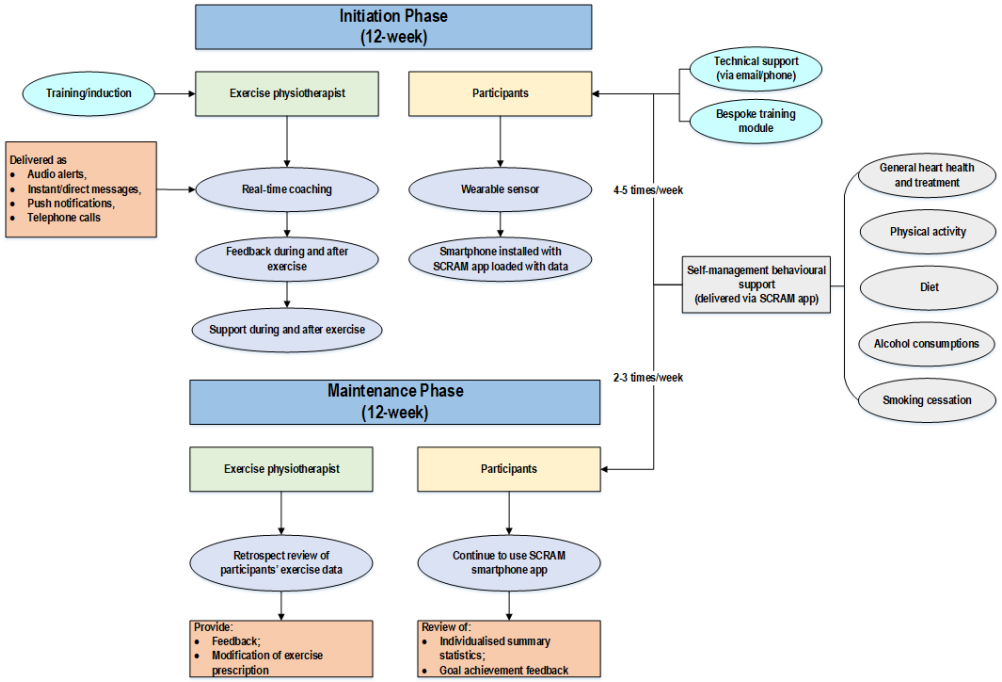

Figure 1 Pathway analysis for identifying the cost associated with SCRAM program delivery