Ecologically Optimizing Exercise Maintenance in Men and Women Post-Cardiac Rehabilitation: Protocol for a Randomized Controlled Trial of Efficacy with Economics (ECO-PCR)

Authors: Robert Reid, MBA, PhD[1]; Chris M. Blanchard, PhD[2]; Evyanne Wooding, BSc[1];

Jennifer Harris, BScPT[1]; Murray Krahn, MSc MD[3]., Andrew Pipe, MD[1]; Caroline Chessex, MD[4], Sherry L. Grace, PhD[4,5] (corresponding author)

[1]University of Ottawa Heart Institute
40 Ruskin Street; Ottawa, ON Canada. K1Y 4W7
breid@ottawaheart.ca; EWooding@ottawaheart.ca; jharris@ottawaheart.ca; apipe@ottawaheart.ca

[2]Dalhousie University
5790 University Avenue; Halifax, Nova Scotia Canada. B3H 1V7
chris.blanchard@Dal.Ca

[3]University of Toronto
144 College Street, Toronto ON, Canada. M5S 3M2
murray.krahn@theta.utoronto.ca

[4,]University Health Network
399 Bathurst Street, Toronto, ON Canada. M5T 2S8
caroline.chessex@uhn.ca

[5]York University – Bethune 368
4700 Keele St. Toronto, ON Canada. M3J 1P3
sgrace@yorku.ca

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Abstract

Background: Exercise-based cardiac rehabilitation (CR) participation results in increased cardio-metabolic fitness, which is associated with reduced mortality. However, many graduates fail to maintain exercise post-program. ECO-PCR investigates the efficacy and cost-effectiveness of a social ecologically-based intervention to increase long-term exercise maintenance following the completion of CR.

Methods/Design: A three-site, 2-group, parallel randomized controlled trial is underway. 412 male and 192 female (N=604) supervised CR participants are being recruited just before CR graduation. Participants are randomized (1:1 concealed allocation) to intervention or usual care. A 50-week exercise facilitator intervention has been designed to assist CR graduates in the transition from structured, supervised exercise to self-managed home- or community-based (e.g., Heart Wise Exercise programs) exercise. The intervention consists of 8 telephone contacts over the 50 week period: 3 individual and 5 group.

Assessments occur at CR graduation, and 26, 52 and 78 weeks post-randomization. The primary outcome is change in minutes of accelerometer-measured moderate to vigorous-intensity physical activity (MVPA) from CR graduation to 52 weeks post-randomization. Secondary measures include exercise capacity, quality of life, and cardiovascular risk factors. Analyses will be undertaken based on intention-to-treat. For the primary outcome, an analysis of variance will be computed to test the change in minutes of MVPA in each group between CR graduation and 52 week follow-up (2 [arm] x 2 [time]). Secondary objectives will be assessed using mixed-model repeated measures analyses to compare differences between groups over time. Mean costs and quality-adjusted life years for each arm will be estimated.

Keywords: exercise, physical; heart diseases; rehabilitation; health care economics

Background

While cardiovascular disease is the leading cause of death globally [1], with advances in acute revascularization procedures, there are many patients surviving myocardial infarctions. Appropriate long-term management can reduce or eliminate the high risk of further acute coronary events and other complications in these patients. Clinical outcomes are dependent on improvements in cardio-metabolic fitness mediated by appropriate health behaviour and pharmacological interventions[2]. Exercise is one of the most important health behaviour interventions; guidelines recommend 30-60 minutes of moderate to vigorous-intensity physical activity (MVPA) on most days of the week for patients with cardiovascular disease [3].

Participation in cardiac rehabilitation (CR) is the recognized standard of supporting cardiovascular disease patients in developing an exercising lifestyle[4]. Indeed, approximately 70-85% of participants achieve guideline-recommended levels of PA while participating in CR[5,6]. Accordingly, participation in exercise-based CR is associated with mortality reductions of 20-26%[7].

Long-term maintenance of exercise behaviour remains a challenge, however; only 38-56% of CR participants are adequately active 1 year after CR completion[8,9]. The challenge is even greater among women, who report PA levels that are significantly lower than men both during and after CR[6,10]. On average, only 21% of women meet exercise guidelines 1 year post-CR[6].

While many CR programs address long-term PA maintenance, most lack systematic, effective and efficient methods for supporting successful transition from supervised exercise to self-managed home and/or community-based exercise. Effective post-CR transition, focused on

maintaining and enhancing gains in levels of PA achieved during CR, would protect and augment the investment in exercise adoption; that is the focus of our trial.

There have been 10 published randomized, controlled studies of interventions to improve exercise maintenance after CR[11–20]; 8 have shown positive results[11-13,16-20]. Only one such study was undertaken in Canada where the current trial is being undertaken; and while results were positive in the short-term, there was no significant effect on exercise maintenance 1 year later[19]. A trial among women only by Johnson et al., showed maintenance of PA declined in all participants, but the decline was significantly greater in the control arm[14]. Interventions demonstrating beneficial effects on post-CR exercise maintenance employed: brief self-regulatory skills training focused on exercise planning[16]; exercise implementation planning[20]; exercise consultation[12]; an exercise diary and quarterly group meetings[11]; a home walking program with daily activity log[14]; written action and coping plans[17,18]; and self-monitoring of weight, blood pressure, heart rate, and pedometer-measured PA with personal feedback[13].

There are substantial limitations to the trials in this area. First, and perhaps the most critical, is an over-reliance on self-reported PA. Second, many interventions were only evaluated over a short period (i.e., 2 to 8 months) post-CR[13,17,20]. Third, no trials to date have examined separately the potential differential effects of exercise maintenance interventions for men and women. Fourth, there has been minimal consideration of the home, neighbourhood and community environments in which long-term exercise behaviour will take place. Previous investigations have not considered incorporating community resources and safe environments for exercise to facilitate sustainability and cost-effectiveness, and have not done so in a theoretically-

informed manner. Finally and correspondingly, economic analyses of exercise maintenance interventions have not been reported.

The theoretical perspective taken by this trial is socio-ecological[21]; this encompasses 'individual' (e.g. knowledge, attitudes, skills), 'social-environmental' (e.g. friends, family, and social networks) and 'physical-environmental' (e.g. home, neighbourhood and community characteristics; climate) factors that are deemed to influence exercise behaviour[22,23]. Each factor operates both independently and interdependently. Ecological correlates of exercise behaviour in patients with cardiovascular disease following CR were reviewed by Petter et al.[24]. Modifiable barriers and facilitators of exercise maintenance at each of these levels have been identified and serve as targets for intervention.

The objective of this trial is to test the hypothesis that patients completing CR who receive support over a 50-week period from a trained exercise facilitator will be engaging in more MVPA 52 weeks following the completion of CR compared to usual care. Secondary objectives are to evaluate the effect of the intervention on: exercise capacity, quality of life; cardiovascular risk factors (e.g., blood pressure, and waist circumference) and enrollment in community-based exercise programs (e.g., Heart Wise Exercise programs). These outcomes will enable us to validate that improvement in exercise maintenance translate into improvements in cardio-metabolic fitness. We hypothesize that the intervention will be superior to usual care in each of these dimensions. A tertiary objective is to determine whether theoretically-based individual, social-environmental and physical-environmental factors mediate the relationship between the intervention and PA level. The final objective is to test whether community-based exercise facilitation post-CR is cost-effective.

Methods

Design

This is a three-site, randomized (1:1), allocation-concealed, controlled, 2-group, parallel, single-blind superiority study (Figure 1) evaluating the efficacy of the exercise facilitator intervention for improving long-term exercise maintenance in patients graduating from CR compared to usual care. The intervention is 50 weeks in duration, and assessments occur post-CR as well as 26, 52 and 78 weeks later.

The Ecologically-Optimizing exercise maintenance in men and women Post-Cardiac Rehabilitation (ECO-PCR) trial is registered with clinicaltrials.gov (Identifier: NCT01658683). The protocol has been approved by the Research Ethics Boards at participating institutions. Trial oversight is ensured through quarterly calls of the steering committee, bi-annual site monitoring visits, and the use of standard operating procedures for data management and handling.

Participants

Male and female CR participants will be recruited for the trial just before graduation from 1 of 3 medically-supervised programs in Toronto and Ottawa, Canada. The inclusion criteria are: (1) patient participated in an on-site CR program of ≥ 8-week duration; (2) patient graduates from CR; (3) patient has a documented diagnosis of coronary artery disease; (4) patient is 18 years of age or older; and (5) patient is able to walk unaided at 2 mph. The exclusion criteria are: (1) patient has New York Heart Association class III or IV heart failure[25]; (2) patient is pregnant, lactating or planning to become pregnant during the study period; (3) patient is unable to read and understand English or French; (4) patient is planning to leave the province or region in the next 12 months; (5) member of the patient's household is already participating in the

study; and (6) the patient is unable, in the opinion of the qualified investigator, to participate in unsupervised exercise.

Sample size justification

PASS software (NCSS, Kaysville, Utah) was used for power analysis and sample size calculation. The primary outcome used in the calculation was the change in number of minutes of MVPA per week, as measured by accelerometer, from CR completion to 52 weeks later. The trial was powered to examine effects of the intervention in men and women separately. With regard to the former, with 288 men assigned in a 1:1 fashion to the two groups, we will have 80% power to detect a difference of 45 minutes between the groups, assuming the mean change in number of minutes of MVPA in the usual care group is 77 and the standard deviation of the outcome measure is 136 (two-sided test; alpha = 0.05). A 45-minute decrease in the number of minutes of MVPA per week would be considered clinically important, and is based on previous studies of exercise maintenance interventions[11,15]. We will use an 'intention-to-treat' strategy in our primary analysis, however we adjusted our sample size upward to account for a planned 30% loss to follow-up to allow a secondary analysis using only men with complete outcome data (i.e., per protocol analysis). We therefore plan to randomize 412 men in the trial.

With 166 women assigned in a 1:1 fashion to the two groups, we will have 80% power to detect a difference of 45 minutes between the groups, assuming the mean change in number of minutes of MVPA is 81 in the usual care group and the standard deviation of the outcome measure is 103 minutes per week. Again, we will use an 'intent-to-treat' strategy in our primary analysis, however we adjusted our sample size upward to account for loss to follow-up to allow a

secondary analysis using only women with complete outcome data. We therefore plan to randomize 412 men and 192 women in the trial (N=604).

Study Arms

Intervention

The intervention was developed using a systematic process known as 'intervention mapping', in which knowledge regarding barriers to, and facilitators of, change is used in program design [30]. Development was also undertaken in accordance with the Medical Research Council's guidance on developing complex interventions [31]. The intervention was pilot-tested.

Participants assigned to the exercise facilitator arm receive a workbook containing information and activities to be completed during the intervention. They are also provided with a pedometer and an activity diary to record the date, time, location, mode, duration and intensity of their physical activities. Table 2 outlines the exercise facilitator intervention and the format, duration, timing, and content of the contacts to be completed over the 50-week intervention period. The intervention employs a single face-to-face introduction between the participant and facilitator, small group counseling teleconferences, personal telephone contacts, and community exercise program demonstrations (where desired).

The face-to-face introduction will occur within 2 weeks of randomization. Participants will be formed into small groups (~5 participants), organized by a trained exercise facilitator. The first group counseling teleconference will occur 3 weeks after the participant has been randomized to the intervention. During the teleconference, the importance of ongoing exercise training as a means to maintain/improve cardiometabolic fitness will be emphasized. The

recommended standard for exercise maintenance in patients with cardiovascular disease will be reiterated (i.e., 150 minutes of MVPA/week). The facilitator will help participants develop plans for adhering to this exercise standard. Methods for mapping out walking routes around home and recommendations regarding home exercise equipment will be discussed.

Subsequent small group counseling teleconferences will be held 3, 13, 26, 39 and 50 weeks after randomization. At each session, participants will review their activity diaries, identify barriers to exercise maintenance experienced to date and brainstorm solutions as a group.

The facilitator will contact participants individually by telephone 20, 34 and 45 weeks after CR program completion. During each telephone call, the facilitator will review the participant's activity diary and assess their confidence and motivation with respect to exercise maintenance. Barriers and solutions will be discussed as appropriate.

During the intervention period, or as requested by the participant, exercise facilitators will recurrently conduct community exercise program demonstrations for interested participants (see supplemental Appendix A for checklist). The Heart Wise Exercise program (http://heartwise.ottawaheart.ca/) aims to bridge clinical and existing community-based exercise programs which meet specific safety criteria, to optimize CR graduate exercise maintenance (see supplemental appendix B)[32]. Participants will be informed of the date and time of all demonstrations via e-mail or telephone.

Intervention Delivery, Fidelity and Cost

The intervention is delivered by physiotherapists or exercise specialists (including trainees). Facilitators receive training prior to participant recruitment.

Scripts and checklists have been developed to ensure the intervention is delivered as originally conceptualized; these elements have been codified in a treatment manual. A random sub-sample of 10% of phone sessions are audio-recorded to assess standardization and fidelity across facilitators and sites. Facilitators participate in quarterly case discussions and booster sessions to maintain skill over time.

Attendance records are kept for all contacts. Facilitators record the actual amount of contact time during in-person and telephone interactions to enable intervention cost calculations.

Control Condition

Usual care consists of practices currently in place at the participating CR programs to transition patients to self-care upon program completion. Patients in each program are provided with an updated exercise prescription and a home-based exercise program prior to program completion. Exercise maintenance strategies are reviewed with program exercise staff. Patients are provided with a list of community-based exercise facilities recommended by the program. The CR programs in Toronto offer maintenance CR once per week on a fee-for-service basis.

Procedure

Recruitment and baseline assessment

Patients who have indicated willingness to consider the trial are being approached to solicit written informed consent. The site coordinator will abstract clinical information from the patient CR chart using a standardized Case Report Form. Resting heart rate, blood pressure, body height and weight, as well as waist circumference will be measured using standardized procedures.

Participants will be asked to complete questionnaires assessing quality of life [26], current leisure-time PA [5], and potential mediators of the intervention - exercise relationship based on the socio-ecological model (Table 1). Participants will be fitted with an accelerometer that they will wear for a 9-day recording period, and will be provided with a log to track when they wore the device.

Randomization and Blinding

Participants will be stratified by recruitment site and sex and randomized in a 1:1 ratio to either the exercise facilitator or usual care arm using a random sequence that was computer-generated by a statistical consultant in permuted blocks of 4, 8, and 10. Sequences were placed in opaque, numbered envelopes which were sealed to ensure that treatment allocation is concealed until after baseline data collection. Study coordinators allocate the next available number on study entry, and maintain a log of all randomizations.

To reduce study costs, graded exercise tests (required for secondary outcomes) will only be performed on a random subset of participants. A sample of 208 participants for graded exercise testing will give us 93% power to detect a minimal clinically-important difference of 1 metabolic equivalent of task (MET) from post-CR to 52 weeks later[27,28]. Therefore, after initial randomization to treatment group, participants will be stratified by treatment group and randomly assigned to one of two exercise testing conditions: graded exercise tests required (n=208); or graded exercise tests not required (n=396).

Research assistants blinded to the participants' treatment allocation will conduct follow-up assessments 26, 52 and 78 weeks after study enrollment. Data will only be identifiable by a research identification number for confidentiality. Study investigators and research assistants

performing measurements, but not patients, research coordinators and exercise facilitators, will be blind to group allocation.

Follow-up data collection

All participants will be called and asked to return to the study centres for follow-up assessments. The time points coincide with the mid-point (26 weeks) and end-point (52 weeks) of the exercise facilitator intervention, and six months after the last treatment contact (78 weeks) in the intervention group. Resting heart rate, blood pressure, body weight, and waist circumference will again be measured by blinded research assistants using standardized procedures. Participants will be instructed to bring any medications they are currently taking, and medication information will be recorded. Any new cardiac events reported by patients are reviewed by the qualified clinical investigator to ascertain whether patients require a modified exercise prescription, specific guidance, and / or can safely continue in the study.

Participants will again be asked to complete questionnaires to measure leisure-time MVPA, quality of life, and use of community exercise programs. Participants will be fitted with an accelerometer that they will wear for a 9-day recording period and will be provided with a log to record when they put on and take off the device each day. Follow-up response rates will be optimized through the Dillman method of repeated and personalized contacts[29].

Measures

Sociodemographic characteristics were assessed in the initial survey. Clinical data extracted form CR charts included medical history, risk factors, disease severity indicators, co-morbidities, and medications.

Primary Outcome: Exercise maintenance

The primary outcome measure will be change in minutes of accelerometer-measured MVPA from CR graduation to 52 weeks post-randomization. MVPA will be measured at baseline, 26, 52 and 78 weeks from randomization. PA will be measured directly by having participants wear the Actigraph GT3X+ accelerometer (Actigraph, Pensacola, Florida) over the right hip for a 9-day recording period, excluding periods when they are sleeping, swimming, or bathing. The activity monitor provides activity counts, energy expenditure, and step counts, in addition to activity intensity levels. Data will be recorded in 5-second epochs over the recording period. The vector magnitude, a composite measure of all 3 axes from the accelerometer, will be used. The Actigraph GT3X+ has been shown to be valid and reliable using treadmill walking at known speed and a laboratory shaker[33].

We will also gather self-report exercise data. A modified and validated version[5] of the Godin Leisure-Time Exercise Questionnaire [35] will be used to gather data concerning average weekly PA. Participants will be asked "How many days in a typical week in the past six months did you do moderate (e.g., fast walking, easy bicycling, easy swimming, dancing) PA for at least 10 minutes at a time?" and, "On the days when you did moderate PA, how many minutes on average did you spend per day doing this activity?" The same two questions will assess the frequency and duration of vigorous (e.g., running, jogging) activities. Minutes of MVPA per week will be summed.

Secondary Outcomes

A random sub-sample of participants (n=208) will complete a symptom-limited graded exercise test with electrocardiographic monitoring on a treadmill at baseline and at 52 weeks.

Cardiovascular risk factors will also be assessed at each time point. Height and weight will be measured for the determination of body mass index. Waist circumference will be measured using a non-stretchable standard tape measure according to the World Health Organization protocol [36]. Blood pressure and heart rate will be measured in a seated position after a five-minute rest period using an automated, non-invasive BPTru [37].

3.9.5 Enrollment in community-based exercise programs

Investigator-generated items are included in the follow-up surveys to assess location and modality of exercise. Enrollment in community-based and "Heart Wise Exercise" programs will be queried in the follow-up surveys.

Socio-Ecological Correlates as Potential Mediators of Intervention Effect

Several potential mediators will be measured at baseline and at follow-up to provide insight into the process by which facilitator intervention may work to improve long-term exercise maintenance (Table 1). This will facilitate understanding the change process related to the complex aspects of the intervention. PA history will be assessed by an investigator-generated item. PA self-regulation will be measured using the 12-item PA self-regulation scale [38]. Action planning will be measured using a 6-item Action Planning scale[5]. Intentions to exercise will be measured using Blanchard's 6-item scale[5]. Beliefs about the benefits of and barriers to exercise will be measured using the 43-item Exercise Benefits/Barriers scale[39]. Task self-efficacy will be measured using Blanchard's 7-item scale [5]. Barrier self-efficacy will be measured using the 14-item scale developed by Plotnikoff et al.[40]. Social support from family and friends will be measured using Sallis et al's 13-item scale [41]. Autonomy support derived from health care providers will be measured using the 6-item Health Care Climate scale [42].

Home exercise equipment, neighbourhood environmental attributes of walkability and access to recreation facilities will be measured using the 17-item PA Neighbourhood Environment Scale [43]. All scales have been psychometrically-validated, pilot-tested in CR samples in our respective programs, and have demonstrated adequate validity and reliability.

Cost-effectiveness and Cost-Utility

Quality of life will be measured using the EuroQoL (EQ-5D-3L) [26]. The EQ-5D is the current gold standard measure of generic quality of life, comprising the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. EQ-5D health states can be converted into single index value by applying a weighting formula based on the level in each dimension. The index can then be calculated by deducting the appropriate weights from 1; scores range from 0 (death) to 1 (perfect health). Scores can be converted to quality-adjusted life years (QALYs) to support cost evaluation.

For costing purposes, participants will be asked to complete a survey assessing time for counselling and physical activities, out-of-pocket expenses (e.g., exercise-related products and services, taxi fares, parking fees), as well as items related to productivity, including lost work days, and home care expenses due to reduced function or disability associated with their cardiac conditions, through items adapted from Oliveira et al. [44]. This information will be self-reported at each follow-up assessment point.

From linked administrative databases, we will obtain health care resources consumed by the participants, including emergency department visits, hospitalizations, day procedures, generalist and specialist visits. We will collect data on resources used to deliver the intervention, including training time for facilitators; phone equipment and long distance charges for

teleconference counselling, and travel costs for community program demonstrations. We will derive costs by multiplying the quantities of resources used by their appropriate unit costs.

Statistical analysis

The analyses will be performed once, at the end of the trial. Baseline clinical and sociodemographic characteristics will be compared between groups to identify any chance differences that may have occurred despite random assignment. The pattern of missing data will be assessed to determine whether multiple imputation is warranted. Outcome variables will be screened to determine whether they meet assumptions of normally-distributed random variables with equal variances, and a descriptive examination will be performed, including plotting of relationships by condition. Retention rate will be computed.

Prior to conducting the primary analyses, the accelerometer data will be prepared. Wear time will be determined by subtracting non-wear time from 24 hours. Non-wear time will be defined as an interval of at least 60 consecutive minutes of zero activity intensity counts, with allowance for 1-2 minutes of counts between 0 and 100[45]. A valid day will be defined as ≥10 hours of wear time, and participants will be required to have a minimum of 4 days to be retained in the analyses[46] . For participants with >7 valid days, the first day will be removed (to minimize reactivity), and the subsequent 7 days used for the average. The amount of PA will be examined as the time spent in PA of moderate or vigorous intensity, separately and combined. We will use cut-points of 2690 counts per minute to indicate moderate activity (≈ 3 METS) and 6167 counts per minute to indicate vigorous activity (≈ 6 METS)[47,48]. Time spent in activity of a defined intensity (moderate, vigorous, or moderate and vigorous combined) will be determined by summing minutes in a day where the count met the criterion for that intensity.

We will also examine, each day, the duration of activity occurring. Weekly averages will be calculated by multiplying the daily average (minutes/day) by 7.

For the primary analysis of the effect of the intervention on exercise maintenance, we will use a t-test to compare the change in MVPA in each group between CR graduation and 52 weeks later (2 [arm] x 2 [time]). Separate analyses will be conducted for men and women to compare trial arms. To explore maintenance of PA across the year and a half of the trial, hierarchical linear modeling analyses [49] will be used given the nested nature of the data (i.e. 4 repeated measurement occasions nested within the individual). A model will be fitted such that the intercept will be allowed to vary randomly (i.e., baseline PA will vary across patients) and the slope for a linear trend (i.e., the potential change in PA) will be constrained to be fixed (i.e., the same across patients) or random at Level-1 based on model selection criteria (i.e., Akaike Information Criterion and/or Bayesian Information Criterion). Subsequent analyses will then include a quadratic term if warranted, after which the need to allow the linear and potential quadratic slopes to vary randomly will be determined. Once completed, the moderating influence of arm at Level-2 (i.e. intervention vs. usual care) on the intercept and linear trend (and potentially quadratic trend) at Level-1 will be examined controlling for potentially important demographic characteristics (i.e., gender) or clinical confounders identified in preliminary analyses at Level-2.

To assess the secondary objectives related to the effects of the intervention on exercise capacity, quality of life, and continuous cardiovascular risk factors (i.e., body mass index, waist circumference, blood pressure), the same hierarchical analytical approach will be used. However, binomial tests will be used to test the effects of the intervention on categorical variables (i.e. enrollment in Heart Wise Exercise programs).

For the evaluation of potential mediators of the intervention → exercise behaviour relationships, the time spent in MVPA (i.e., a continuous variable) will serve as the dependent variable, and the mediation procedure proposed by Krull and MacKinnon [50] for lower-level mediation in hierarchical models will be followed. MVPA will be regressed onto a given ecological mediator (i.e., which will be treated as a time varying covariate at Level-1) controlling for the linear trend at Level-1 and the potential demographic / clinical and past MVPA covariates at Level-2. Next, the mediator from the previous analysis will be treated as the dependent variable and be regressed onto a linear trend at Level-1, condition at Level-2, and a linear trend x condition interaction term controlling for the same aforementioned covariates. To establish mediation, the ecological variable coefficient from regression #1 will be multiplied by the linear trend x condition interaction coefficient from regression #2 and be statistically examined via the Sobel test [51].

Economics

We will conduct a cost-effective analysis and a cost-utility analysis according to the intention-to-treat principle [52]. Health effects will be measured in terms of overall survival time; event-free time from myocardial infarction, revascularization or death; and QALYs. The frequency and time to these events will be determined from linked administrative database analysis. The analysis will take the societal perspective, with a time horizon of 78 weeks, the duration of the follow-up period of the trial. Average overall survival time and event-free time gained from the intervention will be estimated from the proportional hazard method, adjusting for disease risk and ecological factors [53].

QALYs will be derived for all participants to reflect any mortality and morbidity differences in health-related quality of life according to the EQ-5D questionnaire [54]. We will derive health-related quality of life weights from participants' responses to the EQ-5D at baseline, 26, 52 and 78 weeks [55]. By using area under the curve method which effectively weights time by quality-of-life values, we will calculate QALYs over each participant's period of follow-up [56]. In estimating mean QALYs in each arm, we will use analysis of covariance to adjust for differences in quality-of-life weights at baseline [57].

Mean costs and mean QALYs for each intervention will be estimated using methods to adjust for censored data [58,59]. Ninety-five percent confidence intervals will be calculated using the bias corrected and accelerated bootstrap method to account for skewness in cost data[60]. Relative to usual care, incremental costs and incremental QALYs associated with the intervention will be derived, with incremental cost effectiveness ratios calculated as appropriate[61]. Sensitivity analyses will be conducted to assess the impact of various parameters and assumptions on results of the cost-effectiveness analysis[62].

A recent systematic review shows that exercise-based CR reduces overall and cardiovascular mortality[63]; the expected health effects of the intervention may extend beyond the duration of the trial. We therefore will consider the lifetime effectiveness and cost-effectiveness of the intervention using a decision model in which CR patients receive usual care or the intervention and experience health events whose likelihood depend on their exercise status. We will extrapolate the intermediate survival endpoints and QALYs observed in the trial to death (testing the various assumptions used in the extrapolation). We will assess the potential impact of the intervention on the post-CR population in Canada and the feasibility of scaling the intervention up so as to be delivered nationally.

Discussion

Several strategies have been built into the protocol to protect against sources of bias. The primary bias relates to the nature of the exercise facilitator intervention, such that it is not possible to blind participants to arm. However, randomization with allocation concealment will be used to assign participants to group. Consecutive patients who are eligible and provide consent will be enrolled using the strict inclusion and exclusion criteria outlined herein. Second, to reduce measurement bias: (1) research assistants administering questionnaires or performing objective measurements will be blinded to random assignment, and (2) validated measures, instruments and techniques will be used to assess all outcomes. Participants who elect to discontinue the intervention will be asked to return for the final assessment and will be included in the intent-to-treat analysis.

This protocol is not without limitations. In particular, attentional bias will threaten attribution of positive findings to the intervention. The usual care control participants will not receive contacts over the first year of the study. Moreover, the Toronto CR sites offer a maintenance CR program which may contaminate findings. It would be unethical not to offer the program to trial participants.

Positive results will yield a new intervention that can be incorporated into CR practice guidelines and widely disseminated to programs. Knowledge of the individual, social-environmental, and physical-environmental factors that mediate the effect of the intervention will inform refinement and tailoring of the intervention for specific patient needs (e.g., by sex). Should the intervention be shown to be efficacious and cost-effective, we will make a business

case for CR program funding and present this to health care decision-makers. Indeed, we have included such decision-makers as members of the investigative team.

Trial Status

Recruitment for the trial commenced September 2012 and will be completed December 2016.

References

[1] Mendis S, Puska P, Norrving B, Mendis, S; Puska, P; Norrving B. Global Atlas on cardiovascular disease prevention and control. Geneva, Switzerland: World Health Organization; 2011. doi:NLM classification: WG 120.

[2] Stone JA, Arthur HM, Stone JA, Suskin N, et al. Canadian guidelines for cardiac rehabilitation and cardiovascular disease prevention: Translating knowledge into action. 3rd ed. Winnipeg, MB: Canadian Association of Cardiac Rehabilitation; 2009.

[3] Tremblay MS, Warburton DER, Janssen I, Paterson DH, Latimer AE, Rhodes RE, et al. New Canadian Physical Activity Guidelines. Appl Physiol Nutr Metab 2011;36:36–46.

[4] Smith SC, Benjamin EJ, Bonow RO, Braun LT, Creager MA, Franklin BA, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. J Am Coll Cardiol 2011;58:2432–46. doi:10.1016/j.jacc.2011.10.824.

[5] Blanchard CM, Reid RD, Morrin LI, McDonnell L, McGannon K, Rhodes RE, et al. Demographic and clinical determinants of moderate to vigorous physical activity during home-based cardiac rehabilitation: the home-based determinants of exercise (HOME) study. J Cardiopulm Rehabil Prev 2010;30:240–5. doi:10.1097/HCR.0b013e3181d0c4ae.

[6] Reid RD, Morrin LI, Pipe AL, Dafoe WA, Higginson L a J, Wielgosz AT, et al. Determinants of physical activity after hospitalization for coronary artery disease: the Tracking Exercise After Cardiac Hospitalization (TEACH) Study. Eur J Cardiovasc Prev Rehabil 2006;13:529–37. doi:10.1097/01.hjr.0000201513.13343.97.

[7] Anderson LJ, Taylor RS. Cardiac rehabilitation for people with heart disease : An overview of Cochrane systematic reviews. Int J Cardiol 2014;177:348–61. doi:10.1016/j.ijcard.2014.10.011.

[8] Bock BC, Carmona-Barros RE, Esler JL, Tilkemeier PL. Program Participation and Physical Activity Maintenance after Cardiac Rehabilitation. Behav Modif 2003;27:37–53. doi:10.1177/0145445502238692.

[9] Izawa KP, Yamada S, Oka K, Watanabe S, Omiya K, Iijima S, et al. Long-term exercise maintenance, physical activity, and health-related quality of life after cardiac rehabilitation. Am J Phys Med Rehabil 2004;83:884–92.

[10] Moore SM, Dolansky MA, Ruland CM, Pashkow FJ, Blackburn GG. Predictors of women's exercise maintenance after cardiac rehabilitation. J Cardiopulm Rehabil 2003;23:40–9.

[11] Arrigo I, Brunner-LaRocca H, Lefkovits M, Pfisterer M, Hoffmann A. Comparative outcome one year after formal cardiac rehabilitation: the effects of a randomized intervention to improve exercise adherence. Eur J Cardiovasc Prev Rehabil 2008;15:306–11. doi:10.1097/HJR.0b013e3282f40e01.

[12] Hughes AR, Mutrie N, Macintyre PD. Effect of an exercise consultation on maintenance

of physical activity after completion of phase III exercise-based cardiac rehabilitation. Eur J Cardiovasc Prev Rehabil 2007;14:114–21. doi:10.1097/HJR.0b013e3280116485.

[13] Izawa KP, Watanabe S, Omiya K, Hirano Y, Oka K, Osada N, et al. Effect of the Self-Monitoring Approach on Exercise Maintenance During Cardiac Rehabilitation. Am J Phys Med Rehabil 2005;84:313–21. doi:10.1097/01.PHM.0000156901.95289.09.

[14] Johnson NA, Lim LL-Y, Bowe SJ. Multicenter randomized controlled trial of a home walking intervention after outpatient cardiac rehabilitation on health-related quality of life in women. Eur J Cardiovasc Prev Rehabil 2009;16:633–7. doi:10.1097/HJR.0b013e32832e8eba.

[15] Moore SM, Charvat JM, Gordon NH, Pashkow F, Ribisl P, Roberts BL, et al. Effects of a CHANGE Intervention to Increase Exercise Maintenance Following Cardiac Events. Ann Behav Med 2006;31:53–62. doi:10.1207/s15324796abm3101_9.

[16] Scholz U, Knoll N, Sniehotta FF, Schwarzer R. Physical activity and depressive symptoms in cardiac rehabilitation: long-term effects of a self-management intervention. Soc Sci Med 2006;62:3109–20. doi:10.1016/j.socscimed.2005.11.035.

[17] Sniehotta FF, Scholz U, Schwarzer R. Action plans and coping plans for physical exercise: A longitudinal intervention study in cardiac rehabilitation. Br J Health Psychol 2006;11:23–37. doi:10.1348/135910705X43804.

[18] Sniehotta FF, Scholz U, Schwarzer R, Fuhrmann B, Kiwus U, Völler H. Long-term effects of two psychological interventions on physical exercise and self-regulation following coronary rehabilitation. Int J Behav Med 2005;12:244–55. doi:10.1207/s15327558ijbm1204_5.

[19] Lear SA, Ignaszewski A, Linden W, Brozic A, Kiess M, Spinelli JJ, et al. The Extensive Lifestyle Management Intervention (ELMI) following cardiac rehabilitation trial. Eur Heart J 2003;24:1920–7. doi:10.1016/j.ehj.2003.08.015.

[20] Luszczynska A. An implementation intentions intervention, the use of a planning strategy, and physical activity after myocardial infarction. Soc Sci Med 2006;62:900–8. doi:10.1016/j.socscimed.2005.06.043.

[21] McLaren L, Hawe P. Ecological perspectives in health research. J Epidemiol Community Health 2005;59:6–14. doi:10.1136/jech.2003.018044.

[22] Trost SG, Owen N, Bauman AE, Sallis JF, Brown W. Correlates of adults' participation in physical activity: review and update. Med Sci Sports Exerc 2002;34:1996–2001. doi:10.1249/01.MSS.0000038974.76900.92.

[23] Spence JC, Lee RE. Toward a comprehensive model of physical activity. Psychol Sport Exerc 2003;4:7–24. doi:10.1016/S1469-0292(02)00014-6.

[24] Petter M, Blanchard C, Kemp KAR, Mazoff AS, Ferrier SN. Correlates of exercise among coronary heart disease patients: review, implications and future directions. Eur J Cardiovasc Prev Rehabil 2009;16:515–26. doi:10.1097/HJR.0b013e3283299585.

[25] Dolgin M, The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston,

Massachusetts, Massachusetts: Little, Brown & Co.; 1994.

[26] Rabin R, Oemar MO. EQ-5D-3L User Guide. Rotterdam: EuroQoL Group 2011.

[27] Kavanagh T, Mertens DJ, Hamm LF, Beyene J, Kennedy J, Corey P, et al. Prediction of long-term prognosis in 12 169 men referred for cardiac rehabilitation. Circulation 2002;106:666–71.

[28] Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med 2002;346:793–801. doi:10.1056/NEJMoa011858.

[29] Hoddinott SN, Bass MJ. The dillman total design survey method. Can Fam Physician 1986;32:2366–8.

[30] Van Bokhoven M, Kok G, Van der Weijden T. Designing a quality improvement intervention: a systematic approach. Qual Saf Health Care 2003;12:215–20.

[31] Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ 2008;337:a1655–a1655. doi:10.1136/bmj.a1655.

[32] Reed JL, Harris J, Midence L, Yee EB, & Grace SL. Evaluating the Heart Wise Exercise Program: A model for safe community exercise programming. BMC Public Health 2016;(in press).

[33] Slootmaker SM, Chin A Paw MJ, Schuit J, Van Mechelen W, Koppes LL. Concurrent validity of the PAM accelerometer relative to the MTI Actigraph using oxygen consumption as a reference. Scand J Med Sci Sports 2009;19:36–43. doi:10.1111/j.1600-0838.2007.00740.x.

[34] Godin G, Shephard R. A simple method to assess exercise behaviour in the community. Can J Appl Sport Sci 1985;10:141–6.

[35] Godin G, Shephard R. Godin leisure-time exercise questionnaire. Med Sci Sports Exerc 1985;29:36.

[36] World Health Organization. Preventing and managing the global epidemic. World Health Organization; 1997.

[37] Mattu GS, Heran BS WJ. Overall accuracy of the BpTRU--an automated electronic blood pressure device. Blood Press Monit 2004;9:47–52.

[38] Umstattd MR, Motl R, Wilcox S, Saunders R, Watford M. Measuring physical activity self-regulation strategies in older adults. J Phys Act Health 2009;6 Suppl 1:S105–12.

[39] Sechrist KR, Walker SN, Pender NJ. Development and psychometric evaluation of the exercise benefits/barriers scale. Res Nurs Health 1987;10:357–65.

[40] Plotnikoff RC, Lippke S, Trinh L, Courneya KS, Birkett N, Sigal RJ. Protection motivation theory and the prediction of physical activity among adults with type 1 or type 2 diabetes in a large population sample. Br J Health Psychol 2010;15:643–61. doi:10.1348/135910709X478826.

[41] Sallis JF, Grossman RM, Pinski RB, Patterson TL, Nader PR. The development of scales to measure social support for diet and exercise behaviors. Prev Med (Baltim) 1987;16:825–36.

[42] Williams GC, Ryan RM DE. Self Determination Theory Questionnaire Packet 2010. http://www.selfdeterminationtheory.org/health-care-self-determination-theory/ (accessed February 16, 2016).

[43] Sallis JF, Kerr J, Carlson J a, Norman GJ, Saelens BE, Durant N, et al. Evaluating a brief self-report measure of neighborhood environments for physical activity research and surveillance: Physical Activity Neighborhood Environment Scale (PANES). J Phys Act Health 2010;7:533–40.

[44] De Oliveira C, Bremner KE, Ni A, Alibhai SM, Laporte A, Krahn MD. Patient time and out-of-pocket costs for long-term prostate cancer survivors in Ontario, Canada. J Cancer Surviv 2014;8:9–20. doi:10.1007/s11764-013-0305-7.

[45] Troiano RP, Berrigan D, Dodd KW, Mâsse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. Med Sci Sports Exerc 2008;40:181–8. doi:10.1249/mss.0b013e31815a51b3.

[46] Colley RC, Garriguet D, Janssen I et al. Physical activity of Canadian adults: accelerometer results from the 2007 to 2009 Canadian Health Measures Survey. Health Rep 2011;22:7–14.

[47] Stevenson TG, Riggin K, Nagelkirk PR, Hargens T a, Strath SJ, Kaminsky L a. Physical activity habits of cardiac patients participating in an early outpatient rehabilitation program. J Cardiopulm Rehabil Prev 2009;29:299–303. doi:10.1097/HCR.0b013e3181b4ca61.

[48] Freedson PS, Melanson E, Sirard J. Calibration of the Computer Science and Applications, Inc. accelerometer. Med Sci Sports Exerc 1998;30:777–81.

[49] Stephen W. Raudenbush ASB. Hierarchical Linear Models: Applications and Data Analysis Methods (Advanced Quantitative Techniques in the Social Sciences) 2003.

[50] Krull J, Mackinnon D. Multilevel Modeling of Individual and Group Level Mediated Effects. Mul 2010;36:249–77. doi:10.1207/S15327906MBR3602.

[51] Sobel M. A symptotic confidence intervals for indirect effects in structural models. Sociol Methodol 1982:290–312.

[52] Willan AR. Statistical analysis of cost-effectiveness data from randomized clinical trials. Expert Rev Pharmacoecon Outcomes Res 2006;6:337–46. doi:10.1586/14737167.6.3.337.

[53] Fleming TR, Lin DY. Survival Analysis in Clinical Trials: Past Developments and Future Directions. Biometrics 2000;56:971–83. doi:10.1111/j.0006-341X.2000.0971.x.

[54] Drummond M. Introducing economic and quality of life measurements into clinical studies. Ann Med n.d.;33:344–9.

[55] Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. Med Care 2005;43:203–20.

[56] Matthews JN, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. BMJ 1990;300:230–5. doi:10.1136/bmj.300.6719.230.

[57] Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. Health Econ 2005;14:487–96. doi:10.1002/hec.944.

[58] D. Y. Lin, E. J. Feuer RE and YW. Estimating Medical Costs from Incomplete Follow-Up Data on JSTOR. Biometrics 1997:419–34.

[59] Willan AR, Bingshu Chen E, Cook RJ LD. Incremental net benefit in randomized clinical trials with quality-adjusted survival. Stat Med 2003;22:353–62.

[60] Barber JA, Thompson SG. Analysis of cost data in randomized trials: an application of the non-parametric bootstrap. Stat Med 2000;19:3219–36.

[61] Drummond M et al. Methods for the economic evaluation of health care programmes. Oxford Press 1988.

[62] Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. Health Econ 2001;10:779–87.

[63] Anderson L, Oldridge N, Thompson DR, Zwisler A-D, Rees K, Martin N, et al. Exercise-Based Cardiac Rehabilitation for Coronary Heart Disease. Cochrane Systematic Review and Meta-Analysis 2016. doi:10.1016/j.jacc.2015.10.044.

Table 1. Socio-ecological correlates assessed in the ECO-PCR trial.

Level	Constructs
Individual	Sex, Racial/Ethnic Background, Work Status, Education Level, Income Level, Depressive Symptoms, Functional Status, Health Status: Comorbidities, Smoking Status, PA Self-regulation, PA Intention and Planning, Task Self-efficacy, Barrier Self-efficacy, Exercise Benefits and Barriers, Body Mass Index.
Social-environmental	Social Support: Participation, Rewards, and Punishment, Subjective Norm, Living Arrangements, Marital Status, Autonomy Support: Health Care Climate.
Physical-environmental	Neighbourhood Environment: Places to do PA, Home Environment: Home PA Equipment.
	Neighbourhood Characteristics: Aesthetics, Crime Rate, and Street Connectivity, Mixed-Land Use, Season.

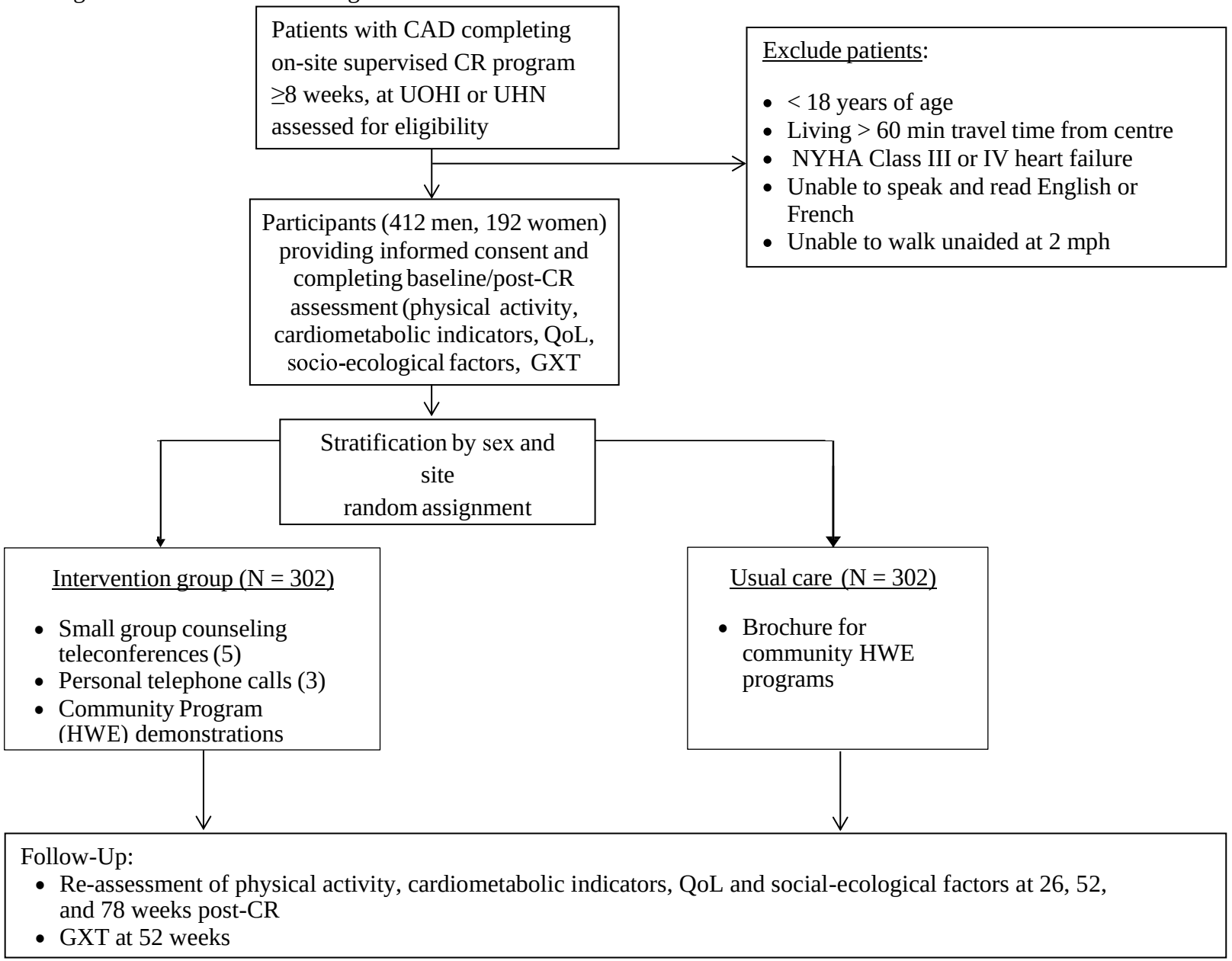
Table 2. Description of the ECO-PCR Exercise Facilitator Intervention

Contact Format	Duration (min)	Timing relative to randomization (weeks)	Content	Targeted barriers/facilitators
Introduction Session (in person)	60	1-2	• Introduction to intervention tools and counseling teleconferences • Establish exercise standards and identify potential barriers for adherence • Complete action/coping planning exercise (Goal Setting) • Complete exercise activity inventory • Provide activity diary (Self-Monitoring) • Provide pedometer (Self-Monitoring) • Create awareness for post-CR community programs and provide list for *HeartWise Exercise* programs in community • Exercise safety	• Knowledge/Awareness • Confidence • Motivation • Action planning • Linkages with approved community programs • Social Support • Home exercise equipment • Self-monitoring
Small group counseling teleconference	60	3, 13, 26, 39, 50	• Review activity diary • Identify barriers to exercise adherence experienced to date • Brainstorm solutions to barriers in group • Complete coping planning exercise • Discuss past successes and failures • Elicit personal views and discuss benefits of exercise for CAD management	• Confidence • Motivation • Action planning • Social support • Physical symptoms
Personal telephone call	15-30	20, 34, 45	• Review activity diary • Assess confidence and motivation • Discuss barriers and solutions • Elicit personal views and discuss benefits of exercise for CAD management	• Confidence • Motivation • Social support • Physical symptoms

Community Program Demonstrations (multiple opportunities) Suppl. Appendix B	60-90	Every 2-3 weeks for 52 weeks	• Facilitator-lead tour of community exercise facility and orientation to *HeartWise Exercise* programs occurring at that location • Demonstration of individual exercise opportunities using facility equipment • Overview of program registration procedures • Facilitation of physician referral for interested participants for program or facility enrollment • Discuss past successes and failures Elicit personal views and discuss benefits of exercise for CAD management	• Motivation • Social support • Convenient exercise options

CR=cardiac rehabilitation; CAD=coronary artery disease; min=minutes

Figure 1. ECO-PCR Flow Diagram



CAD= Coronary Artery Disease; CR= Cardiac Rehabilitation; QoL= Quality of Life; GXT=graded exercise test; HWE=Heart Wise Exercise; NYHA=New York Heart Association functional classification