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Exercise-based cardiac rehabilitation for patients with stable angina (Protocol)

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Cochrane Database of Systematic Reviews 2017, Issue 9. Art. No.: CD012786.
DOI: 10.1002/14651858.CD012786.

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[Intervention Protocol]

Exercise-based cardiac rehabilitation for patients with stable angina

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Editorial group: Cochrane Heart Group.
Publication status and date: New, published in Issue 9, 2017.

Citation: Anderson L, Dewhirst AM, He J, Gandhi M, Taylor RS, Long L. Exercise-based cardiac rehabilitation for patients with stable angina. *Cochrane Database of Systematic Reviews* 2017, Issue 9. Art. No.: CD012786. DOI: 10.1002/14651858.CD012786.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of exercise-based CR for patients with stable angina compared to usual care.

BACKGROUND

Description of the condition

Angina pectoris is traditionally defined as a pain, discomfort or tightness, most commonly felt in the chest, that may radiate to the neck, jaw and arms. It is typically gradual in onset and offset and may be associated with breathlessness and nausea. Angina occurs when the coronary arteries become narrowed and myocardial oxygen demand exceeds oxygen supply. This leads to reversible myocardial ischaemia or hypoxia, particularly when oxygen demands are high, such as during exercise and stress. The complex mechanisms leading to symptoms of angina are not entirely understood. Importantly, acidosis results from myocardial ischaemia, causing the release of metabolites such as adenosine and bradykinin that stimulate the sympathetic afferent nerve pathway, eventually transmitting the painful stimuli to the brain (Crea 1990; Foreman 1999).

It was estimated in 2013 that over 1.3 million people were living with angina in the UK (BHF 2014); and it was thought to affect approximately 112 million people, or 1.6% of the population worldwide in 2010 (Vos 2012). Data suggest an annual incidence of uncomplicated angina of 1.0% in Western men aged 45 to 65 years, with a slightly higher incidence in women in this age bracket (Hemingway 2006; NHLBI 2012). Incidence increases with age in both men and women aged 75 to 84 years, reaching almost 4% (Hemingway 2006). However, age standardised angina prevalence decreased globally from 21.9 to 20.3 per 100,000 in males and from 17.7 to 15.9 in females between 1990 and 2010 (Moran 2014)

Angina is considered stable when there is no increase in frequency or severity of symptoms (NICE 2011). However, the transition from stable to unstable angina is, in reality, a continuum and without clear boundaries (Montalescot 2013). We define stable angina as chest pain and associated symptoms of cardiovascular disease precipitated by some activity (running, walking etc.) with minimal or non-existent symptoms at rest. We define unstable angina as

chest pain and other symptoms of cardiovascular disease which are of new onset (within the prior 4 to 6 weeks), worsening, becoming more frequent or occurring at rest (or with minimal exertion). Despite the term 'stable', a diagnosis of stable angina is a chronic medical condition associated with a low but appreciable incidence of acute coronary events and increased mortality. Management options include lifestyle advice, drug therapy and revascularisation, which aim to minimise symptoms, and improve quality of life and long-term morbidity and mortality.

Although it can be precipitated by a number of conditions, stable angina is considered to be a symptom of coronary heart disease (CHD), which is the single most common cause of global mortality, and accounts for approximately one-third of all deaths worldwide, placing a major economic and resource burden on health systems (WHO 2014).

Description of the intervention

As previously described (Anderson 2016a), many definitions of cardiac rehabilitation (CR) have been proposed (for example, Balady 2011; BACPR 2012; WHO 1993). The following definition encompasses the key concepts of CR: "The coordinated sum of activities required to influence favourably the underlying cause of cardiovascular disease, as well as to provide the best possible physical, mental and social conditions, so that the patients may, by their own efforts, preserve or resume optimal functioning in their community and through improved health behaviour, slow or reverse progression of disease" (BACPR 2012). Cardiac rehabilitation is a complex intervention that may involve a variety of therapies, including exercise, risk factor education, behaviour change, psychological support, and strategies that are aimed at targeting traditional risk factors for cardiovascular disease. Cardiac rehabilitation is an essential part of contemporary heart disease care and is considered a priority in countries with a high prevalence of CHD. Based on evidence from previous meta-analyses and systematic reviews, exercise-based CR following a cardiac event is a Class I recommendation from the American College of Cardiology/American Heart Association (Balady 2011; Kulik 2015), and the European Society of Cardiology (Roffi 2015; Smith 2011; Steg 2012). Service provision, though predominantly hospital-based, varies markedly; and referral, enrolment and completion are sub-optimal, especially among women and older people (Beswick 2004; Clark 2012). Home-based CR programmes have been increasingly introduced to widen access and participation (Taylor 2010), and interventions aimed at improving patient uptake and adherence to CR programmes have been adopted (Karmali 2014).

Exercise-based CR in selected patient groups is remarkably safe. An observational study of more than 25,000 patients who underwent CR following cardiac surgery, recent percutaneous coronary intervention (PCI) or with other coronary and noncoronary conditions, reported one cardiac event for 50,000 hours of exercise training, equivalent to 1.3 cardiac arrests per million patient-hours (Pavy 2006). An earlier study reported one case of ventricular fibrillation per 111,996 patient-hours of exercise and one myocardial infarction (MI) per 294,118 patient-hours (Van Camp 1986). However, patients with unstable angina, uncontrolled ventricular arrhythmia, and severe heart failure (New York Heart Association level 4) have been considered at high risk, and careful assessment by an experienced clinician is recommended before they engage in the exercise component of CR (BACPR 2012). Historically, CR has often not been routinely offered to people with stable angina. Indeed, 20% of all CR programmes included in the 2009 UK national audit of CR actively excluded stable angina (Lewin 2010). In the latest UK audit, angina referrals accounted for less than 4% of the 82,000 patients receiving CR, although 27% of all patients were reported as having co-morbid angina at the point of entry to their CR programme (Doherty 2015).

How the intervention might work

As previously described by the authors, the precise mechanisms by which exercise training improves mortality in CHD patients have not been fully elucidated (Anderson 2016a; Taylor 2006). Exercise training has been shown to have direct benefits on the heart and coronary vasculature, including myocardial oxygen demand, endothelial function, autonomic tone, coagulation and clotting factors, inflammatory markers, and the development of coronary collateral vessels (Clausen 1976; Hambrecht 2000; Lavie 2015). However, it has been suggested that approximately half of the 28% reduction in cardiac mortality in patients with CHD may also be mediated via the indirect effects of exercise through improvements in the risk factors for atherosclerotic disease (i.e. total cholesterol, smoking and blood pressure) (Taylor 2006). Further reductions in mortality may be attributed to reductions in psychological stress, including depression, anxiety and hostility (Lavie 2011).

Why it is important to do this review

The American College of Cardiology/American Heart Association give a Class I recommendation that medically supervised CR programs and physician-directed, home-based programmes are offered to at-risk patients with stable CHD including those with stable angina, at first diagnosis (Fihn 2012). Similarly, the European Society of Cardiology recommends that patients with stable CHD, including stable angina, should undergo "moderate-to-vigorous intensity aerobic exercise training $\geq$ 3 times a week and for 30 min per session" (Montalescot 2013). Meanwhile, the British Association for Cardiovascular Prevention and Rehabilitation (BACPR) recommend CR for people following a cardiac event, with heart failure, and to those with other established forms of cardiovascular disease, including stable angina (BACPR 2012). Yet despite these guidelines, the current National Institute for Health and Care Excellence (NICE) guideline for the manage-

ment of stable angina (CG126) states that there is "no evidence to suggest that CR is clinically or cost effective for managing stable angina" (NICE 2011). NICE reports that while there has been limited research on short-term outcomes such as a change in diet or exercise levels, the effect on morbidity and mortality has not been studied, and they highlight research into CR for this patient population as one of their key research recommendations (NICE 2011).

Previous Cochrane Reviews have looked at the effect of exercise-based CR in patients with CHD (Anderson 2016a), heart failure (Taylor 2014), and after heart valve surgery (Sibilitz 2016). A meta-analysis of 63 trials, which randomised 14,486 patients with CHD (including those with angina) to exercise-based CR or a no-exercise control, showed that exercise-based CR led to a reduction in cardiovascular mortality (relative risk (RR) 0.74, 95% confidence interval (CI) 0.64 to 0.86), hospital admissions (RR 0.82, 95% CI 0.70 to 0.96) and an increase in health-related quality of life (HRQL) (Anderson 2016a). However, many trials in this review were in a mixed population of CHD patients (Anderson 2016a). Given the NICE key research recommendations, we believe there is a good case for separating out the evidence for CR in stable angina. Our scoping searches have confirmed that no systematic review has been conducted which has specifically assessed the impact of CR in a population in patients with stable angina.

OBJECTIVES

To assess the effects of exercise-based CR for patients with stable angina compared to usual care.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) with a parallel group, cluster-randomised, or cross-over design, which compare the independent effects of exercise-based CR versus a usual care or no-exercise comparator. We will only include RCTs with a follow-up period of at least six months, in order to reflect current practice of guideline and policy writing which are driven by long-term health benefits (NICE 2010; SIGN 2007).

Types of participants

We will include adult men and women (≥ 18 years) who have stable angina and have been diagnosed with coronary heart disease. We will include people who have presented with stable or exertional angina (effort-induced chest discomfort), who are being treated with medical antianginal therapy and who may have had a previous myocardial infarction (MI), coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI). However, we will exclude people in the immediate period following such an event, i.e. within 3 months of MI, PCI or CABG. We will also exclude people with unstable angina (pain at rest) and those with refractory angina for whom revascularisation is planned.

We will include studies with a mixed population of patients with CHD, where the data for those with stable angina and without any confounding co-morbidities are reported separately. We will also include studies where the majority of the participant sample (50% or more) are reported to have stable angina, regardless of whether data for this sub-population are reported separately.

Types of interventions

Exercise-based CR is defined as a supervised or unsupervised inpatient, outpatient, centre- or home-based intervention which includes some form of exercise training that is applied to a cardiac patient population. The intervention could be exercise training alone or exercise training in addition to psychosocial or educational interventions, or both (i.e. 'comprehensive CR').

The comparator group could include usual or standard medical care, such as drug therapy, but without any form of structured exercise training or advice. We will include studies designed to assess the independent effect of exercise (e.g. exercise plus usual care versus usual care alone; exercise, usual care and education versus usual care and education alone). However, we will also include studies which compare exercise to an active intervention such as education, behavioural or psychological interventions or surgery.

Types of outcome measures

Primary outcomes

1. All-cause mortality.
2. Morbidity - myocardial infarction (MI), revascularisation (CABG or PCI) or all-cause hospital admissions, or combinations thereof.
3. Health-related quality of life (HRQoL) assessed using validated instruments (e.g. 36-Item Short Form Health Survey (SF-36), EQ-50).
4. Exercise capacity assessed by validated outcome measure (e.g. VO_2 peak, 6-minute walk test).
5. Cardiovascular-related hospital admissions.

Secondary outcomes

1. Severity of angina, assessed using validated instruments (e.g. Canadian Cardiovascular Society grading of angina pectoris; New York Heart Association Functional Classification of Angina).
2. Reported adverse events (clinical events relating to CR e.g. skeletomuscular injuries or arrhythmias or withdrawal from the intervention, or combinations thereof).
3. Return to work.
4. Costs.

Reporting one of more of the outcomes listed here in the trial is not an inclusion criterion for the review.

Search methods for identification of studies

Electronic searches

We will identify trials through systematic searches of the following bibliographic databases.

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library.
- MEDLINE (Ovid) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE daily and MEDLINE.
- Embase Classic and Embase (Ovid).
- CINAHL Plus (EBSCO).
- Database of Abstracts of Reviews of Effects (DARE).
- Health Technology Assessment (HTA).
- Web of Science Core Collection (Thomson Reuters).

We will design the search strategies with reference to those of a previous and related Cochrane Review of exercise-based CR (Anderson 2016b). We will search the databases using a strategy combining selected MeSH terms and free-text terms relating to exercise-based rehabilitation and stable angina, with filters applied to limit to RCTs. We will use the Cochrane sensitivity-maximising RCT filter for MEDLINE, and apply terms recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* for Embase (Lefebvre 2011). We will apply adaptations of this filter to CINAHL and Web of Science. We will translate the MEDLINE (Ovid) search strategy (Appendix 1) for use with the other databases using the appropriate controlled vocabulary as applicable. We will search all databases from their inception to the present, we will impose no restriction on language of publication and will give consideration to variations in terms used and spellings of terms in different countries so that the search strategy will not miss studies because of such variations.

Searching other resources

We will handsearch reference lists, and conduct forward citation searching, of all primary studies and review articles for additional references not identified by the electronic searches. We will conduct a search of World Health Organization International Clinical Trials Registry Platform (WHO ICTRP; www.who.int/ictrp/en) and ClinicalTrials.gov (ClinicalTrials.gov)) for ongoing clinical trials. We will also contact experts in the field for unpublished and ongoing trials and will contact trial authors where necessary for any additional information. We will also examine any relevant retraction statements and errata for included studies.

Data collection and analysis

Selection of studies

Two review authors will independently screen titles and abstracts for inclusion of all the potential studies we identify as a result of the search and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. If there are any disagreements, a third author will be asked to arbitrate. We will retrieve the full-text study reports/publication and two review authors will independently screen the full text and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third person. We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table.

Data extraction and management

We will use a data collection form for study characteristics and outcome data which has been piloted on at least one study in the review. One review author will extract study characteristics from included studies. We will extract the following study characteristics.

1. Methods: study design, total duration of study, number of study centres and location, study setting, withdrawals, and date of study.
2. Participants: N, mean age, age range, gender, severity of condition, diagnostic criteria, inclusion criteria, and exclusion criteria.
3. Interventions: intervention, comparison, and co-interventions.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial, and notable conflicts of interest of trial authors.

Two review authors will independently extract outcome data from included studies. We will resolve disagreements by consensus or by involving a third person. One review author will transfer data into the Review Manager 5 file (Review Manager 2014). We will double-check that data is entered correctly by comparing the data presented in the systematic review with the study reports. A second review author will check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreements by discussion or by involving another author. We will assess the risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of outcome assessment.
4. Incomplete outcome data.
5. Selective outcome reporting.
6. Other (specifically sources of funding and conflicts of interest).

We will also assess two further quality criteria: whether the study groups were balanced at baseline; and if the study groups received comparable care (apart from the exercise component of the intervention). These criteria, agreed upon in advance by the review authors, have not been validated but have been used to assess quality in previous CR reviews (Anderson 2016a; Anderson 2016b; Brown 2011; Sibilitz 2016; Taylor 2014; Taylor 2015). We will assess these two further quality criteria as follows.

Groups balanced at baseline

- *Low risk of bias*: The characteristics of the participants in the intervention and control groups at baseline are reported to be comparable or can be judged to be comparable (e.g. baseline data reported in Table 1) in terms of likely main prognostic factors.
- *Unclear risk of bias*: Whether the characteristics of the participants in the intervention and control groups are balanced at baseline is not reported, and reported information is inadequate to assess this (e.g. no Table 1).
- *High risk of bias*: There is evidence of substantive imbalance in the baseline characteristics of the intervention and control groups with regard to likely major prognostic factors.

Groups received comparable treatment (except exercise)

- *Low risk of bias*: All co-interventions were delivered equally across intervention and control groups.
- *Unclear risk of bias*: Information to assess whether co-interventions were delivered equally across groups was insufficient.
- *High risk of bias:* The co-interventions were not delivered equally across intervention and control groups.

We will grade each potential source of bias as high, low, or unclear and provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We will summarise the 'Risk of bias' judgements across different studies for each of the domains listed. Where information on risk of bias relates to unpublished data or correspondence with an author, we will note this in the 'Risk of bias' table.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and will report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data as risk ratios with 95% confidence intervals and continuous data as mean difference with 95% confidence intervals. For any outcomes which are measured by studies in a variety of ways (for example, some studies may measure exercise capacity using VO_{2peak}, and others using the 6-minute walk test), the standardised mean difference with 95% confidence intervals will be used as the summary statistic. We will enter data presented as a scale with a consistent direction of effect.

We will narratively describe skewed data reported as medians and interquartile ranges.

Unit of analysis issues

In accordance with Section 16.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), we will aim to include data from both periods of any cross-over trials identified, assuming (i) there has been a wash-out period considered long enough to reduce carry-over, (ii) no irreversible events such as mortality have occurred, and (iii) appropriate statistical approaches have been used.

Dealing with missing data

We will contact investigators or study sponsors to verify key study characteristics and obtain missing numerical outcome data where possible (for example when a study is identified as abstract only). Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies on the overall assessment of results by a sensitivity analysis.

Assessment of heterogeneity

We will explore heterogeneity amongst included studies qualitatively (by comparing the characteristics of included studies) and quantitatively (using the Chi² test of heterogeneity and I² statistic). We will use a threshold of I² greater than 50% (considered to represent substantial heterogeneity (Deeks 2011)) for both dichotomous and continuous outcomes to determine the statistical model to be used for meta-analysis.

Assessment of reporting biases

If we are able to pool more than 10 trials, we will create and examine a funnel plot and the Egger test to explore possible small-study biases for the primary outcomes (Egger 1997).

Data synthesis

We will undertake meta-analyses only where this is meaningful, i.e. if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense.

Dichotomous outcomes for each comparison will be expressed as risk ratios with 95% confidence intervals. Continuous data will be expressed as mean difference with 95% confidence intervals, or, where an outcome is measured and reported in more than one way, as standardised mean difference with 95% confidence intervals. We will enter data presented as a scale with a consistent direction of effect. If there is a statistically significant absolute risk difference, we will aim to calculate the associated number needed to treat for an additional beneficial or harmful outcome.

Where appropriate, we will pool data from each study using a fixed-effect model, except where substantial heterogeneity exists. If possible, we will pool the results for HRQL using a standardised mean difference. If there is evidence of substantial statistical heterogeneity (P value less than 0.10, I² greater than 50%) associated with an effect estimate, we will apply a random-effects model, which provides a more conservative statistical comparison of the difference between intervention and control because a confidence interval around the effect estimate is wider than a confidence interval around a fixed-effect estimate. If a statistically significant difference is still present using the random-effects model, we will also report the fixed-effect pooled estimate and 95% confidence interval because of the tendency of smaller trials, which are more susceptible to publication bias, to be over-weighted with a random-effects analysis (Heran 2008a; Heran 2008b).

We will process data in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will complete data synthesis and analyses using Review Manager 5 software (Review Manager 2014). Meta-regression analysis will be conducted using the "metareg" command in Stata version 14.2 (Stata 2015).

'Summary of findings' table

We will employ the GRADE approach to interpret result findings (Schünemann 2011) and use GRADEpro GDT 2015 to import data from Review Manager 5 to create a 'Summary of findings table'. We will aim to create a 'Summary of findings' table using the following outcomes: all-cause mortality, myocardial infarction (MI), all-cause hospital admissions, HRQL, adverse events, return to work, and exercise capacity. We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data to the meta-analyses for the prespecified outcomes. We will use methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* using GRADEpro software (Higgins 2011). We will justify all decisions to downgrade the quality of studies using footnotes, and will make comments to aid readers' understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We anticipate length of follow-up to be a driver of intervention effect, with the size of effect for some outcomes being related to the length of the follow-up. We will therefore aim to stratify meta-analysis of each outcome according to the length of trial duration: i.e. 'short-term' follow-up (6 to 12 months); 'medium-term' follow-up (13 to 36 months); and 'long-term' follow-up (more than 36 months). We will also aim to undertake univariate meta-regression to explore heterogeneity and examine potential treatment effect modifiers. We will aim to test the following hypotheses regarding differences in the effect of exercise-based CR on all-cause mortality, morbidity, health-related quality of life and exercise capacity across particular subgroups (Anderson 2016a).

1. Type of CR (exercise-only CR versus comprehensive CR) (categorical variable).
2. 'Dose' of exercise intervention [dose = number of weeks of exercise training × average number of sessions/week × average duration of session in minutes] (dose ≥ 1000 units versus dose < 1000 units) (continuous variable).
3. Follow-up period (continuous variable).
4. Year of publication (≤1995 and >1995) (continuous variable) - timing reflects the introduction of modern-day drug therapy for the management of CHD.
5. Sample size (continuous variable).
6. Setting (home- or centre-based CR) (categorical variable).
7. Study location (continent) (categorical variable).
8. Mean age of participants (continuous variable).
9. Percentage of male participants (continuous variable).
10. Percentage of patients with previous MI, CABG surgery or PCI (continuous variables).

Given the anticipated small ratio of trials to co-variates, meta-regression will be limited to univariate analysis (Higgins 2011).

However, given the anticipated small number of included studies, we recognise that it would be unlikely that meta-regression or a stratified meta-analysis will be possible.

We will aim to extract results of subgroup analyses, including participant-level subgroup analyses, if reported by individual included studies; for example, if a trial reports whether there was a difference in the effectiveness of CR between males and females.

Sensitivity analysis

We will compare meta-analysis results of including all studies versus only including those studies judged to have overall low risk of bias (low risk in $\geq$ four items).

Reaching conclusions

We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We will avoid making recommendations for practice and our implications for research will suggest priorities for future research and outline what the remaining uncertainties are in the area.

ACKNOWLEDGEMENTS

The authors acknowledge the support of the Cochrane Heart Group editorial team and the template protocol they made available.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Preliminary MEDLINE (Ovid) search strategy

MEDLINE

1 angina pectoris/ or angina, stable/
2 angina.tw.
3 stenocardia*.tw.
4 angor pectoris.tw.
5 1 or 2 or 3 or 4
6 exp Exercise Therapy/
7 Sports/
8 Physical Exertion/
9 rehabilitat*.tw.
10 (physical* adj5 (fit* or train* or therap* or activit*)).tw.
11 exp Exercise/
12 (train* adj5 (strength* or aerobic* or exercise*)).tw.
13 ((exercise* or fitness) adj3 (treatment or intervent* or program*)).tw.
14 exp Rehabilitation/
15 kinesiotherap*.tw.
16 "Physical Education and Training"/
17 Patient Education as Topic/
18 (patient* adj5 educat*).tw.
19 ((lifestyle or life-style) adj5 (interven* or program* or treatment*)).tw.
20 Self Care/
21 (self adj5 (manag* or care or motivate*)).tw.
22 exp Psychotherapy/
23 psychotherap*.tw.
24 (psycholog* adj5 intervent*).tw.
25 Counseling/
26 (counselling or counseling).tw.
27 ((behavior* or behaviour*) adj5 (modify or modificat* or therap* or change)).tw.
28 (psycho-educat* or psychoeducat*).tw.
29 (motivat* adj5 (intervention or interv*)).tw.
30 Health Education/
31 (health adj5 educat*).tw.
32 (psychosocial or psycho-social).tw.
33 (cognitive adj2 behav*).tw.
34 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35 randomized controlled trial.pt.
36 controlled clinical trial.pt.
37 randomized.ab.
38 placebo.ab.
39 drug therapy.fs.
40 randomly.ab.
41 trial.ab.
42 groups.ab.
43 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42
44 exp animals/ not humans.sh.
45 43 not 44
46 5 and 34 and 45

CONTRIBUTIONS OF AUTHORS

LA led the writing of the protocol, and approved the final manuscript.

AD contributed to the writing of the protocol.

JH provided clinical expertise and contributed to the writing of the protocol.

MG provided clinical expertise and edited the protocol..

RST contributed to the writing of the protocol..

LL contributed to the writing of the protocol.

DECLARATIONS OF INTEREST

LA is an author on a number of other Cochrane CR Reviews.

AD declares she has no conflicts of interest.

JH declares he has no conflicts of interest.

MG declares she has no conflicts of interest.

RST is an author on a number of other Cochrane CR Reviews and is currently the co-chief investigator on the programme of research with the overarching aims of developing and evaluating a home-based CR intervention for people with heart failure and their carers (PGfAR RP-PG-0611-12004).

LL declares she has no conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- University of Exeter Medical School, UK.

External sources

- The Cochrane Heart Group US Satellite is supported by intramural support from the Northwestern University Feinberg School of Medicine and the Northwestern University Clinical and Translational Science (NUCATS) Institute (UL1TR000150), USA.
- This project was supported by the National Institute for Health Research, via Cochrane Incentive funding to the Heart Group. The views and opinions expressed herein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health, UK.