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Cardiac rehabilitation meta-analysis of trials in patients with coronary heart disease using individual participant data (CaReMATCH): Project protocol

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ABSTRACT

Background: Exercise-based cardiac rehabilitation (CR) has long been a cornerstone in the secondary prevention of coronary heart disease (CHD). Despite meta-analyses of randomised trials demonstrating a positive impact of CR on cardiovascular mortality, hospitalisation, exercise capacity and health related quality of life, the impact of CR on all-cause mortality remains uncertain, especially in the context of contemporary clinical practice. This CR meta-analysis of trials in patients with coronary heart disease using individual participant data (IPD) (CaReMATCH) seeks to (1) provide definitive estimates of the effectiveness of CR in terms of all-cause mortality, cardiovascular mortality, hospitalisation and health-related quality of life, and (2) determine the influence of individual patient characteristics (e.g. age, sex, risk factors) on the effectiveness of CR to inform a personalised CR-approach.

Methods: Randomised controlled trials will be identified that were performed in the last decade, to ensure that CR was performed in combination with contemporary medical care (2010–2020). For our first aim, outcomes of interest include all cause- and CVD-related mortality and hospitalisations. To answer our second research question, we will collect data on exercise capacity, health-related quality of life, and patient baseline demographic and clinical data. Original IPD will be requested from the authors of all eligible trials; we will check original data and compile a master dataset. IPD meta-analyses will be conducted using a one-step meta-analysis approach where the IPD from all studies are modelled simultaneously whilst accounting for the clustering of participants within studies.

Discussion: Findings from CaReMATCH will inform future (inter)national clinical and policy decision-making on the (personalised) application of exercise-based CR for patients with CHD.

1. Introduction

Cardiovascular diseases (CVDs), including coronary heart disease (CHD), are a leading cause of global mortality and morbidity, responsible for approximately one third of total deaths and 20% of the worldwide disease burden [1]. Reducing physical inactivity and sedentary behaviour are potent, well advocated, non-pharmacological, primary and secondary preventative strategies for CHD [2–4]. Although there is a lack of global consensus on exercise mode and intensity for cardiac rehabilitation (CR), the application of CR promotes secondary prevention of CVD and is an essential component of routine care for cardiac patients [5,6]. Exercise-based CR is recommended (with the highest level of scientific evidence - class I) by the European Society of Cardiology (ESC) [7], the American Heart Association (AHA) and the American College of Cardiology (ACC) [8]. Core components of exercise-based CR include patient assessment, physical activity counselling, exercise programme, nutrition counselling, weight management, lipid management, blood pressure management, smoking cessation and psychological support [7].

These global recommendations for CR are supported by studies that find CR-related improvements in exercise capacity, health-related quality of life, and reductions in hospital admissions [9,10,11]. Findings related to mortality, however, are less ubiquitous. In contrast to early Cochrane meta-analyses [9,10], the most recent Cochrane review [11], did not observe a statistically significant reduction in all-cause mortality following exercise-based CR

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in CHD patients. The loss of a protective effect of CR on all-cause mortality in the most recent meta-analysis may be due to improved medical management of CVD in recent years. Another possible explanation may be the heterogeneity of the CHD populations included in most recent studies. Moreover, randomized controlled trials (RCT) to date have lacked representation of the elderly, females, and those from low socio-economic backgrounds [10],[12]. Therefore, substantial differences in individual patient responses to CR may be present, and it is unknown whether the benefits of CR are moderated by participant characteristics. Better insight into these topics may clarify the impact of CR on all-cause mortality and contribute to a personalised approach of CR for individual patients with CHD.

By performing a CR meta-analysis on patients with coronary heart disease using individual-participant data (IPD) (CaReMATCH), it is possible to provide definitive estimates on outcomes of CR (mortality, hospitalisation, exercise capacity, health-related quality of life) with higher power compared to individual RCTs. Thereby, the higher sample size of the pooled IPD provides the ability to study underlying mediators of an effect on CR outcomes. Improved insight into whether patient or exercise (e.g. fitness, amount, type, or location of exercise) characteristics affect all-cause mortality or hospitalisation following CR, will ultimately enhance the benefits of CR.

CaReMATCH is an international collaboration with the goal of undertaking IPD meta-analysis of RCTs that investigate the impact of CR in CHD based on a systematic review of contemporary RCT evidence. The information gained from the CaReMATCH project will help inform future (inter)national clinical and policy decision-making on the use of exercise-based CR in CHD. The primary objectives of the CaReMATCH IPD meta-analysis is to:

1. Provide definitive estimates of the effectiveness of CR in CHD versus control on all-cause mortality, cardiovascular mortality, hospitalisation and health-related quality of life.
2. Analyse the influence of pre-randomisation patient characteristics on the effectiveness of CR in CHD, including age, sex, diagnosis (post-myocardial infarction only, revascularisation only, angina only, mixed CHD population) and exercise capacity.
3. Perform an exploratory analysis to assess whether the change in exercise capacity mediates the effectiveness of the CR on all-cause mortality, hospitalisation and health-related quality of life.
4. Perform an exploratory analysis to assess the importance of factors on effectiveness of CR in CHD, including the amount of exercise prescribed, the setting in which exercise is undertaken (centre versus home), and the provision of additional interventional elements such as psychological or educational support.

2. Methods

2.1. Search methods for identification of studies

Trials for inclusion in the CaReMATCH project were identified from the 2016 Cochrane review plus any eligible trials published since Anderson et al. [11], identified through a systematic search. In total, 63 Randomised controlled trials (RCTs) were included in the latest update of the CR Cochrane reviews. To reflect contemporary CHD medical management, this project will focus on the IPD from trials in CHD patients published since 2010. Specific rationale for 2010 cut-off included (1) digitisation of healthcare resulting in potential improvements in quality, efficiency, and population health [14], (2) in 1998/2000 the American Heart Association set a decade-long goal to reduce CHD and stroke risk by 25% by 2010, which was realised [15], and (3) publications from 2010 onwards include data predating 2010, thus this cut-off ensures included data is at least within the last 20 years. For the updated systematic search, the 2016 Cochrane search was reproduced with time period included from July 2014 onwards. The following databases were searched CENTRAL (Cochrane Central Register of Controlled Trials), DARE (Database of Abstracts of Reviews of Effects), HTA (Health Technology Assessment), MEDLINE and Medline in Process (Ovid), EMBASE (Ovid), and CINAHL (Cumulative Index to Nursing and Allied Health Literature) Plus (EBSCO).

Data from each RCT will be sought including (1) individual patient characteristics: age, sex, socio-economic status (employment and education level proxies), medication use, CVD risk factors, disease type, and exercise capacity; (2) individual outcomes of all-cause mortality, CV mortality, hospitalisations, myocardial infarction, revascularization, and health-related quality of life (HRQoL); and (3) CR characteristics: duration, single versus multi-component interventions, mode, and intensity (e.g. % of maximum heart rate, rating of perceived exertion).

2.2. Eligibility criteria for studies

We will include studies if they meet the following inclusion and exclusion criteria:

- *Study design:* RCTs with a minimum follow-up of 6 months. We excluded studies with a non-randomised allocation.
- *Population*: Patients with the diagnosis of a myocardial infarction, who had undergone revascularization (coronary artery bypass grafting [CABG]) or percutaneous coronary intervention (PCI) or who have angina pectoris or CHD defined by angiography.
- *Context:* Patients managed in any setting i.e. hospital, community facility or home.
- *Intervention:* Exercise-based CR was defined as a supervised or unsupervised inpatient, outpatient, community-based, or home-based intervention that included some form of exercise training, either alone or in addition to psychosocial and/or educational interventions.
- *Comparator:* The comparator could include standard medical care and psychosocial and/or educational interventions, but not any structured exercise training.
- *Sample size:* No restrictions on sample size were enforced to maximise available data.

Table 1 lists the characteristics of the [n = 8] studies included from the Cochrane 2016 review. As of July 2020, one investigator declined to provide data as the data was no longer available [20]. An updated Cochrane review [11], is currently ongoing [Led by RST], and any new randomised trials identified will inform this IPD meta-analysis.

2.3. Main outcomes

In accordance with the study research objectives we will seek IPD for the following outcomes from eligible trials:

- Mortality (all-cause, death due to CVD): incidence and time-to-event;
- Hospital admission/re-admission (all-cause, CVD specific): incidence and time-to-event;
- Disease specific health-related quality of life: outcome at baseline (pre-randomisation) and several post-randomisation follow-up time points; and
- Exercise capacity as a mediator (irrespective of assessment method): outcomes at baseline and at several post-randomisation follow-up time points.

Table 1
Characteristics of the [n = 8] studies included from the Cochrane 2016 review.

First author (year)	N = patients[1]	Trial location and site	Mean age	Male (%)	CHD Diagnosis[2]	Intervention/ Exercise type	Overall CR duration (weeks)	Exercise frequency (sessions/ week)	Mean session duration (minutes)	Overall exercise duration (minutes)	Exercise setting[3]	Longest follow-up (months)
Aronov (2010)	392	Russia Multicentre	52	94%	Mixed	Aerobic	52	3	45–60	8190	Centre	12
Houle (2012)	65	Canada Single centre	59	78%	Mixed	Aerobic (pedometer based increased stimulation of physical activity)	52	NA	NA	NA	Home	12
Maddison (2015)	170	New Zealand Multicentre	60	81%	Mixed	Aerobic (mobile phone intervention to stimulate physical activity)	24	NA	NA	NA	Home	6 (24 weeks)
Mutwalli (2012)	49	Saudi Arabia Single centre	57	100%	Revascularisation (CABG)	Aerobic (walking program)	NR	NR	NR	NR	Home	6
Oerkild (2012)	40	Denmark Single centre	77	58%	Mixed	Aerobic	6	6	45	1620	Centre	54
Reid (2012)	223	Canada Multicentre	56	84%	Mixed	Aerobic (internet-based stimulation to increase physical activity)	NA	NA	NA	NA	Home	12
Wang (2012)	160	China Multicentre	58	76%	Post-myocardial infarction	Aerobic	6	NR	NR	NR	Home	6
West (2012)	1813	United Kingdom Multicentre	64	74%	Post-myocardial infarction	Aerobic	6–8	1–2		1200	Centre	84–108 (7–9 years)

NA, not applicable; NR, not reported.
[1] Total number of participants randomised.
[2] Post-mycardial infarction only, revascularisation only, angina only or mixed CHD population.
[3] The delivery setting of cardiac rehabilitation; home, centre or both.

As exercise capacity may be collected using a variety of methods, standardisation procedures will be decided once all of the available data has been collected.

2.4. Collection of data

2.4.1. Investigator contact

We will initially email all trial investigative teams via the corresponding author as detailed in publications to tell them about our IPD meta-analysis, and to ask if they are willing to share their original IPD. As part of the review process we have previously been in contact with a number of investigators for the purpose of obtaining data and have received positive responses from several contact authors.

Members of this IPD meta-analysis project group have links with the majority of study investigators, so if we fail to receive a positive response to our initial email invitation, individual members of the project group will be assigned to make further contact by email or telephone. Study investigators still not responding or unwilling to contribute their study data will be sent a final note inquiring why they are unable to participate.

2.4.2. Data format

The procedure for collection and collation of data will be coordinated by the project lead [BB] based at the Liverpool Centre for Cardiovascular Science, University of Liverpool. Participating study authors will be asked to provide anonymised primary datasets corresponding to minimum data required to answer the primary research objectives. Where possible, electronic versions of datasets will be sought, together with written details of the coding of the variables. We will accept databases in all formats in order to minimise the amount of work for primary study authors; however, ideally the format will be a two-dimensional spreadsheet with one subject per row and variables listed by column.

2.4.3. Data transfer and storage

Methods of receiving raw data from investigators may vary depending on the security concerns of their host institutions. However, we anticipate that in most cases data transfer will be via an encrypted data file sent by email to the project lead [BB] or via the Liverpool Centre for Cardiovascular Science password-protected drop box facility. Once received, data will be stored in a secure computer server managed by the Executive Management Group. Each raw data set will be saved in its original format and then converted and combined into one overall dataset with standardised variables. We will work with individual trial authors to ensure standardisation of variables.

2.4.4. Data checking

We will: (1) evaluate data from each study and compare these with the available publication(s); (2) check each dataset for the range of included variables to make sure all values are reasonable;

(3) assess missing observations for each variable and check against the original publication; (4) attempt to replicate results reported in the original publication, including baseline characteristics and outcome data at each available follow-up period, by reproducing the statistical methods as reported by the study authors; (5) discuss and clarify any discrepancies or missing information between our results and those presented in each original publication with the original study authors.

Once data checks are complete and satisfactory, individual study datasets will be combined to form a new master dataset with a variable added to indicate the original study. Copies of the master data set will be held by the project statistician [RST]. Data from individual datasets will remain the property of the individual collaborators who have provided IPD.

2.5. Statistical analysis

Due to the complexity of the statistical analyses, the following section represents the planned principal analyses. A detailed statistical analysis plan will however be produced prior to any analyses being conducted. Analyses will be aligned to the latest guidance from the Cochrane Prospective Meta-Analysis Methods Group, existing recommendations for IPD meta-analyses [16], and underpinned by a previous IPD meta-analysis protocol [19].

2.5.1. Descriptive analysis

Both study and patient-level characteristics of included RCTs will be presented. We will also compare study-level and patient-level characteristics between the included studies and studies that were eligible but did not supply IPD, to determine if the included IPD studies are a representative (unbiased) sample of all eligible studies.

2.5.2. IPD meta-analysis

IPD will first be analysed comparing CR versus control in each separate study independently via linear regression models for continuous responses such as HRQoL, and Cox regressions for time to event data such as mortality. Individual trial data sets will then be combined, and a one-stage meta-analysis undertaken to compare CR and control. Appropriate regression models (linear, logistic, Cox) will be used, with a fixed effect on individual study and patient-level covariates, as well as a comparison of models with a fixed effect on intervention and random effects on intervention across trials. Continuous outcomes will be analysed with adjustments for baseline values. Heterogeneity will be assessed using the I^2 statistic.

If original data sets are not available for some RCTs, we will use methods to combine IPD with aggregate data where appropriate. The benefit of using aggregate data is to prevent bias due to lack of response of the lead author of a paper. For example, authors who are unwilling to provide access to datasets may be willing to run analyses to provide the necessary estimates for a 'two stage' analysis, or such data may be available from primary publications.

2.5.3. Subgroup and mediation analysis

Any modification of CR versus control effects across pre-defined patient subgroups (i.e., age, sex, socio-economic group, ethnicity, CHD aetiology, CHD risk factors, and exercise capacity), exercise programme duration, and trial geographical locality will be assessed by examining the significance of the subgroup by CR/control group interaction term within the model. Where available, the importance of the amount of exercise will be assessed by fitting the prescribed exercise duration as a continuous variable and examining the interaction with intervention.

Mediation analysis will be conducted to examine the association between changes in exercise capacity and health-related quality of life and clinical events [17].

2.5.4. Publication bias

Following published guidance, we will assess publication bias in this IPD meta-analysis in several ways [18]:

- Assess funnel plot asymmetry with and without studies using IPD.
- When IPD cannot be obtained, the impact on meta-analysis conclusions will be investigated by including the aggregate data from the studies lacking IPD.
- Where the inclusion of studies lacking IPD seem to have an important statistical or clinical impact, we will compare the characteristics of the studies with IPD and those without to see if there are key differences (e.g. quality, length of follow up, statistical methods).

2.6. Project management and ethics

The 'CaReMATCH Executive Management Group' refers to the core team of researchers who will oversee the strategic direction of the protocol; the '*CaReMATCH* Collaborators' refers to those linked to the project such as trial teams who provide data sets for the study. Members of the Project Executive Management and Collaborative groups are listed at the end of this protocol.

2.6.1. CaReMATCH executive management group

The roles of the CaReMATCH Executive Management Group are to:

- Agree the research questions addressed by the collaboration and develop the initial protocol;
- Agree the data collection proforma;
- Oversee arrangements for secure data handling;
- Review the publication strategy for the collaboration; and
- Ensure that data are only used, and any additional research (including updating of the combined data sets with emerging evidence) only proceeds, following consultation and agreement with the Collaborative Group.

2.6.2. CaReMATCH collaborative group

The Executive Management Group will act as a liaison between members of the Collaborative Group. The Collaborative Group will be composed of a representative from each of the included trials. We will invite new collaborators as new eligible studies are completed. Members of the collaborative group will be given opportunities to participate in decision making regarding the study design and analyses. We intend members of the collaborative group to have opportunities to network and identify future CaReMATCH research questions suitable for analysis with the IPD dataset. Once the Collaborative Group and initial dataset are established, we will develop mechanisms for communication and input on methodological issues.

2.6.3. Data ownership and confidentiality

Participants in the individual trials have previously consented to participation in their respective trial. Given that the analyses proposed are simply an extension of the core analysis of the constituent trials, we do not anticipate that additional ethical permission will be required. We will ensure that datasets shared as part of the project include no patient identifiable information (such as names and addresses), that all data storage is in accordance with the regulations governing research at the Liverpool Centre for Cardiovascular Science, University of Liverpool, and will obtain a

signed data sharing agreement with all authors to outline procedures for the transmission, storage, analysis and dissemination. The collaborators remain the custodians of their own data and retain the right to withdraw their data from the analysis at any time.

2.6.4. Publication policy

Requirements for authorship will follow those of the International Committee of Medical Journal Editors (http://www.icmje.org). A primary publication of the results of this review will be prepared by the Executive Management Group. This and all other CaReMATCH manuscript drafts will be circulated to the Collaborative Group for comment, revision and approval.

3. Discussion

CaReMATCH will establish a collaborative group and conduct an IPD meta-analysis of randomised controlled trials of exercise-based CR in CHD patients, focusing on studies that were published between 2010 and 2020 to understand the role of CR in contemporary medicine. A primary strength of an IPD approach is the ability to investigate treatment modifiers. Project findings will therefore provide clinicians and healthcare policy makers with definitive estimates and corresponding guidance on differential responses to CR across different CHD patient subgroups. This will improve understanding of the role of CR, including the role of personal characteristics in contemporary medicine.

CaReMATCH Executive Management Group

All authors are members of the CaReMATCH Executive Management Group.

CaReMATCH Collaborator Group (as of July 2020; pending 2020 Cochrane CR review update)

Ralph Maddison, National Institute for Health Innovation, University of Auckland, Auckland, New Zealand

David Aronov, State Research Center for Preventive Medicine. Petroverigsky, Moscow

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Registration. PROSPERO registration is being completed in parallel with this protocol.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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