Exercise Training Meta-Analysis of Trials for Chronic Heart Failure (ExTraMATCH II): An individual participant data meta-analysis of randomised controlled trials

NIHR-HTA Programme Funded (15/80/30)
Study Protocol

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Investigators

Prof Rod Taylor *(Chief Investigator*) - Prof of Health Services Research, University of Exeter Medical School, UK

Dr Fiona Warren - Lecturer in Medical Statistics. University of Exeter Medical School, UK

Dr Oriana Ciani - Postdoctoral Research Fellow. University of Exeter Medical School, UK

Professor Neil Smart - Associate Professor, University of New England, Australia

Professor Massimo Piepoli – Director, Department Heart Failure, Cardiology, Organisation Guglielmo da Saliceto Hospital, Italy

Mr Tim Eames - Medical Research Data Programmer, Exeter Clinical Trials Unit and NIHR Clinical Research Facility. University of Exeter Medical School, UK

International Steering Committee

Professor Andrew Coats, Monash University, Australia and University of Warwick, UK (Chair)
Professor Stephen Ellis, Duke Clinical Research Institute, North Carolina, USA
Dr Hayes Dalal, Research & Development, Knowledge Spa, Royal Cornwall Hospitals Trust, Truro & Primary Care Research Group, Exeter Medical School, UK
Dr Steven Keteyian, Division of Cardiovascular Medicine, Henry Ford Hospital, Detroit, USA
Professor Christopher O'Connor, Division of Cardiology and Clinical Pharmacology, Duke Heart Center, North Carolina, USA
Dr David Whellan, Duke Clinical Research Institute, North Carolina, USA
(And Taylor, Smart, Piepoli, Ciani, and Warren)

Collaborators

All lead trialists that have supplied individual patient data to the project:
Professor Romualdo Belardinelli, Cardiologia "GM Lancisi"-Ospedali Riuniti, Ancona, Italy
Dr Kathleen Dracup, UCSF School of Nursing, San Francisco, USA
Professor Rebecca Gary, Nell Hodgson Woodruff School of Nursing, Emory University, Atlanta, USA
Professor Pantaleo Giannuzzi, Istituto Scientifico di Veruno, Italy
Professor Reiner Hambrecht, Gesundheit Nord, Bremen, Germnay
Professor Kate Jolly, Department of Public Health & Epdemiology, University of Birmingham, UK
Professor Robert McKelvie, McMaster University, Canada
Dr Jonathan Meyers, VA Palo Alto Health Care System, Palo Alto, USA
Dr Brigitta Nilsson, Faculty of Medicine, University of Oslo, Norway
Dr Claudio Passino, Cardiovascular Medicine Department, CNR Institute of Clinical Physiology, Pisa, Italy

Dr Ronnie Wilenhheimer, Department of Cardiology, University Hospital, Malmö, Sweden.
Dr Miles Witham, University of Dundee, Dundee, UK
Prof Ann Dorthe Zwisler, CopenHeart, Copenhagen, Denmark
Dr Gloria Yeh, Department of Medicine, Beth Israel Deaconess Medical Center, Brookline, USA

This list will be updated with the identification of recent trials that meet the project inclusion criteria

1. Introduction

Heart failure (HF) is a generally progressive condition that is estimated to affects 900,000 people in United Kingdom (UK) (1). While survival after HF diagnosis has improved, prognosis is poor - 30 to 40% of patients die within a year of diagnosis (2). Those patients who live with HF, experience marked reductions in their exercise capacity which has detrimental effects on their activities of daily living, health-related quality of life, and risk of hospital admission rate and all-cause mortality (1, 3). It is estimated that the total annual cost of HF to the UK NHS is currently around £1 billion or around 2% of the total UK health budget; ~70% of this cost is due to hospitalisation (1,4). Hospital admissions due to HF are projected to rise by 50% over the next 25 years, largely due to ageing of the population (4).

With increasing numbers of people living longer with symptomatic HF, the effectiveness and accessibility of health services for heart failure patients have never been more important. Exercise-based cardiac rehabilitation programmes is recognised as integral to the comprehensive care of HF patients.

Cardiac rehabilitation is a process by which patients, in partnership with health professionals, are encouraged and supported to achieve and maintain optimal physical health (9). Whilst exercise training is at the centre of rehabilitation provision for HF it is accepted that programmes should be comprehensive in nature and include education and psychological input focusing on health and life-style behaviour change and psychosocial well-being (1-3, 9)

Previous systematic reviews and meta-analyses have shown exercise-based rehabilitation offers important health benefits for patients and their carers (9-12). Including 33 trials across 4740 HF patients, the 2014 Cochrane review (12) shows: no difference in pooled all-cause mortality with exercise-based rehabilitation (relative risk: 0.93; 95% CI 0.69 to 1.27), reduced risk of overall hospitalisation (relative risk: 0.75; 95% CI: 0.62 to 0.92) and HF-specific hospitalisation (relative risk: 0.61; 95% CI: 0.46 to 0.80); and a clinically important improvement in disease-specific health-related quality of life on the Minnesota Living with Heart Failure questionnaire (mean difference: -5.8 points, 95% CI: -9.2 to -2.4). Exercise rehabilitation for HF is therefore recommended by the National Institute of Health and Care Excellence (NICE) (1) and is a class I recommendation of the joint American College of Cardiology Foundation and the American Heart Association and the European Society of Cardiology guidelines (5-7). These guidelines do not differentiate by patient subgroup but, rather, recommend exercise rehabilitation to all HF patients ‘who are able to participate to improve functional status’ (7).

Despite this evidence and recommendation by clinical guidelines, the uptake of rehabilitation for HF is currently poor. Only 16% of UK rehabilitation centres have a specific rehabilitation programme for HF (14). The recently published European survey (ExtraHF) found that only 40% centres across 42 countries implemented an exercise programme for HF, concluding that ‘too many [HF] patients are still denied a highly recommended therapy’ (15).

Centres report lack of resources to the major barrier to providing rehabilitation services for HF, i.e., lack of finances, staff, and equipment (14, 15). A key potential solution (if supported by evidence) could be targeting exercise-based rehabilitation services to those HF patients who might experience the greatest benefit in outcomes. Such a differential effect of treatment across HF patients could improve the overall clinical and cost-effectiveness of rehabilitation for HF and drive improvements in patient uptake of rehabilitation.

Although meta-analyses demonstrate important health benefits with exercise-based rehabilitation, there is uncertainty whether there are differential effects across HF patient subgroups. Three data sources currently provide evidence on this issue but have weaknesses.

First, in 2004, the Exercise Training Meta-Analysis of Trials in Heart Failure (ExTraMATCH) Collaborative Group published an individual participant data meta-analysis based on 9 randomised trials in 801 HF patients, showing exercise rehabilitation reduced mortality (hazard ratio 0.65, 95% CI:, 0.46 to 0.92) and there were no subgroup (age, gender, HF aetiology, New York Heart Association (NYHA) class, ejection fraction, or exercise capacity) effects (16). Given the small number of trials, patients, and events (193 deaths) these subgroup analyses are likely to be underpowered. Furthermore, a number of trials have been published since, including HF-ACTION, a large National Institute of Health funded trial (2331 HF patients across 82 centres) (17).

Second, the original analysis of the HF-ACTION trial found no interactions between treatment allocation and patient characteristics (age, gender, HF aetiology, NHYA class, ejection fraction, or depression score) for the composite outcome of mortality and hospital admission or health-related quality of life (17). Although the largest exercise trial to date, power to detect small subgroup effects remains limited.

Finally, meta-regression analysis in the 2014 Cochrane review found no association between trial level patient characteristics (age, gender, ejection fraction) and the impact of exercise-based rehabilitation (12). However, such analysis is highly prone to study level confounding (ecological fallacy) and should be interpreted with great caution.

The methodology of individual patient data meta-analysis allows more robust of treatment effects in subgroups and enables time to event data analyses adjusted for baseline covariates. Given the limitations of current evidence and our access to individual data from 20 randomised trials in over 4,000 patients, ExTraMATCH II offers a timely and important opportunity to revisit the question of which HF patient subgroups benefit most from exercise-based rehabilitation.

The information gained from the ExTraMATCH II project will inform future national and international clinical and policy decision-making on the use of exercise-based interventions in HF.

2. Aims and objectives

The Exercise Training Meta-Analysis of Trials for Chronic Heart Failure (ExTraMATCH II) project aims to determine which HF patient subgroups benefit most from exercise-based rehabilitation project using individual patient data meta-analysis.

The project objectives are:

1. To obtain definitive estimates of the impact of exercise-based rehabilitation interventions versus control (no exercise intervention) on all-cause mortality, hospitalisation, exercise capacity, and health-related quality of life in HF patients.
2. To determine the differential (sub-group) effects of exercise-based interventions in HF patients according to their (i) age, (ii) gender, (ii) left ventricular ejection fraction, (iii) HF aetiology, (iv) NYHA class, and (v) exercise capacity.
3. To assess whether the change in patient exercise capacity mediates the impact of the exercise-based interventions on all-cause mortality, hospitalisation, and disease-specific health-related quality of life.

3. Methodology

This project will be undertaken and reported according to current reporting guidelines for individual patient data meta-analyses (21, 26, 27).

Search methods for identification of studies

Trials for inclusion in the ExTraMATCH II project were identified from the original ExTraMATCH study (16) and the 2014 Cochrane review (13). The 2014 Cochrane review searched the following electronic databases up to January 2013: Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, EMBASE, MEDLINE, CINAHL, PsycINFO, and the NHS Centre for Reviews and Dissemination (CRD). Conference Proceedings were searched on Web of Science. Trial registers (Controlled-trials.com and Clinicaltrials.gov) and reference lists of all eligible trials and identified systematic reviews were also checked. No language limitations were imposed. Appendix A details the search strategy.

Eligibility criteria for studies

We included studies if they met the following inclusion and exclusion criteria:

- Study design: Randomised controlled trials with a minimum follow-up of 6 months. We excluded studies with a non-randomised allocation.
- Target population: Adult patients (18 years and older) with diagnosis of systolic HF ('HF with reduced ejection fraction', HFrEF) or diastolic HF ('HF with preserved ejection fraction', HFpEF) based on objective assessment of left ventricular ejection fraction and on clinical findings.
- Setting/context: Patients managed in any setting i.e. hospital, community facility or patient's home.
- Health technologies being assessed:
    - Exercise-based rehabilitation - which should include at least an aerobic exercise training component performed by the lower limbs, lasting a minimum of 3 weeks (16), either alone or as part of a comprehensive cardiac rehabilitation programme that also includes health education and/or a psychological intervention. We excluded interventions without an exercise training component or head-to-head comparisons of two or more exercise interventions.
    - Comparator: A non-exercise group receiving standard medical care or an attention placebo.
- Sample size: We restricted our consideration to studies with a sample size of more than 50, to ensure that the logistical effort in obtaining, cleaning and organising the data is commensurate with the contribution of the data set to the analysis (18).

Appendix B lists the characteristics of the 20 studies from the Cochrane 2014 review and three studies from ExTraMATCH that have been deemed to meet these criteria.

Main outcomes

In accordance with the study research objectives we sought individual patient data for the following outcomes from eligible trials:

- mortality (all-cause, death due to heart failure and sudden cardiac death): incidence and time-to-event;
- hospital admission/re-admission (all-cause, heart failure specific): incidence, duration and time-to-event;
- disease specific health-related quality of life assessed by the Minnesota Living With Heart Failure questionnaire and other validated quality of life outcomes: outcome at baseline (pre-randomisation) and at 6, 12, 24 and >24 months post-randomisation;
- exercise capacity (irrespective of assessment method): outcome at baseline and at 6, 12, 24 and >24 months post-randomisation.

We also require individual key baseline patient demographic and clinical data (including age, gender, ejection fraction, NYHA class, heart failure aetiology (ischemic vs. non-ischemic) and race/ethnicity). Details of exercise training prescription (i.e. session frequency, duration, intensity and overall programme duration) has already been collected as part of the 2014 Cochrane review. However, we have also asked investigators to prove details at an individual patient level of the amount of exercise intervention undertaken.

Collection of data

Investigator requests

We emailed all identified trial investigative teams via the named contact author as detailed in publications to tell them about our individual patient data meta-analysis, and to ask if they are willing to share their original IPD (see Appendix C for contact letter). Over a period of approximately 18 months, we have managed to secure data from 20 trials (in 4043 patients – 2011 receiving exercise rehabilitation & 2032 receiving control) from the pool of 23 trials that were deemed to meet our inclusion criteria (see PRISMA flow diagram). Despite a number of email interactions, one investigator declined to provide their data for this project (Klecha). The data for two trials was ether destroyed (Austin) or lost (Davidson). This represents a loss of data of only 355 patients (8%).

Data format

The procedure for collection and collation of data was coordinated the project team based at the University of Exeter Medical School. Participating study authors were asked to provide anonymised (without identifying data such as patient name or date of birth) primary datasets corresponding to minimum data required to answer the primary research objectives (see Appendix D). Electronic versions of datasets were sought, together with written details of the coding of the variables. We accepted databases in all formats in order to minimise the amount of work for primary study authors; however, where possible we requested a two-dimensional spreadsheet with one subject per row and variables listed by column.

Data transfer and storage

We received anonymised patient data from investigators depending on the security concerns of their host institutions. In most cases data transfer was by email of password protected file with a separate email containing the password. We have saved each raw data set in its original format. We then converted and combined all files into one overall master dataset with standardised variables. All files are stored on a secure password protected computer server managed by the Exeter Clinical Trials Unit. We have agreed as part of establishing the International Steering Group that a copy of the master dataset be held by Duke Clinical Research Institute (DCRI) in the USA (lead site for HF-ACTION trial).

Data checking

We evaluated data from each study and compared these with the available publication(s). We checked each dataset for the range of included variables to make sure all values were reasonable. We assessed missing observations for each variable and checked against the original publication. We checked against results reported in the original publication, including between group balance of baseline characteristics and outcome data at each available follow-up period. We discussed and sought to clarify any discrepancies or missing information between our results and those presented in each original publication with the original study authors. Once data checks were complete and satisfactory, individual study datasets were combined to form a new master dataset with a variable added to indicate the original study. A copy the master data set is securely held by the project team at the Exeter Medical School.

Statistical analysis

Due to the complexity of the statistical analyses, the following section represents the planned principal analyses; some modifications and secondary analyses are likely to emerge during this project. However, a detailed statistical analysis plan will be produced prior to the analysis. Analyses will be conducted in accordance with current recommendations for individual patient data meta-analyses (19-21, 26, 27).

Descriptive analysis

The study-level and patient-level characteristics of included studies will be presented. We will also compare study-level and patient-level characteristics across the included studies and studies that were eligible but did not supply individual patient data (using published sources), to determine if the individual patient data studies available are a representative (unbiased) sample of all available eligible studies (21).

Individual patient data meta-analysis

There are two methods of undertaking individual patient data meta-analysis: (i) using individual patient data to derive aggregate data for each study, followed by meta-analysis of the aggregate data ('two-step individual patient data meta-analysis'); and (ii) analysis of individual patient data using a mixed model and accounting for clustering of patients within studies ('one-step individual patient data meta-analysis'). In this project we will primarily use one-step IPD meta-analysis, which is the most logistically demanding, but does allow for the most sophisticated modelling of covariates and has the best performance in terms of power (19).

All analyses will follow the principle of intention-to-treat as closely as possible. Specifically, we will include all randomised patients with outcome data. Time-to-event endpoints will be analysed using appropriate models which accommodate censored data (e.g. Cox proportional hazards models). Continuous outcomes will be analysed using linear models with adjustments for baseline values. Appropriate models 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. Heterogeneity will be assessed using the I^2 statistic from the two-stage meta-analyses and the between studies standard deviation from the one-stage meta-analyses. Due to the clinical heterogeneity between studies (for example, differences in intervention), a random effects approach to the intervention effect will be the preferred over a fixed effect approach for both one- and two-stage models; however, if the between studies standard deviation is very low, fixed effect one-stage models will be used to avoid failure of model convergence.

If original data sets are not available for some studies, we will use methods to combine individual patient data with aggregate data where appropriate. We do not have any of the studies that use a cluster randomised design and thus additional adjustments to account for this will not be necessary.

Subgroup and mediation analysis

Any modification of treatment effects across pre-defined patient subgroups (i.e., age, gender, left ventricular ejection fraction, heart failure aetiology, NYHA class and exercise capacity), exercise programme duration (< 28 vs ≥28 weeks) (16), and trial geographical locality) will be assessed by examining the significance of the subgroup by intervention interaction term within the model. 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 (22-24).

Sensitivity analysis

We will undertake a number of sensitivity analyses to test the robustness of conclusions. These will include: exclusion of studies identified in the Cochrane 2014 review that do not have a low risk of bias (i.e. the risk of bias is at least moderate) and exclusion of trials with an overall exercise duration of less than 12 weeks. In the event of substantive missing data (>10%) in an individual trial data set, a sensitivity analysis will be undertaken imputing data based on different assumptions regarding missingness.

Sources of bias

We will assess sources of bias in this individual patient data meta-analysis in accord with recommended methods (25).

- When individual patient data cannot be obtained, the impact on meta-analysis conclusions should be investigated by including the aggregate data from the studies lacking individual patient data.
- Where the inclusion of studies lacking individual patient data seem to have an important statistical or clinical impact, it may be helpful to compare the

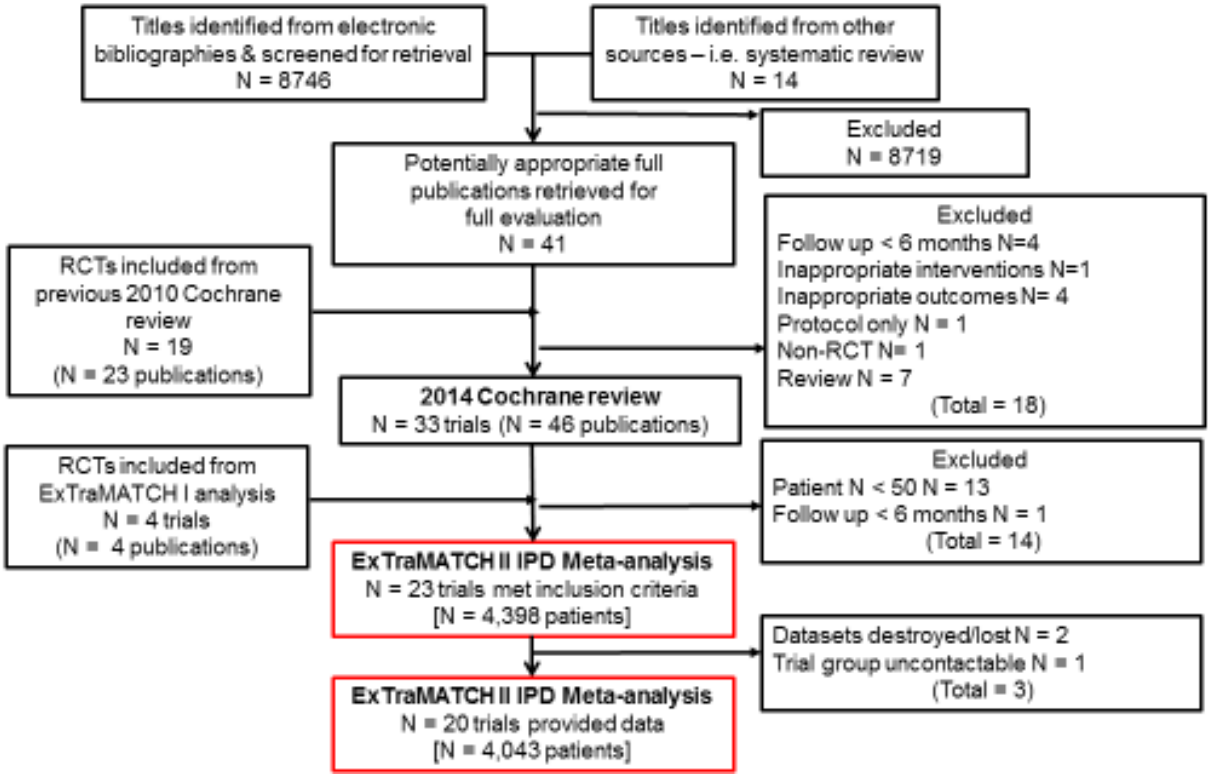
characteristics of the studies with individual patient data and those without to see if there are key differences (e.g. quality, length of follow up, statistical methods).

- Publication bias will be assessed by funnel plot asymmetry (with and without studies using individual patient data)

General

Analyses will be undertaken using Stata v14.1. Study data will not be used for any other purpose without the permission of collaborators.

PRISMA FLOW DIAGRAM SUMMARISING SELECTION OF STUDIES FOR EXTraMATCH II IPD META-ANALYSIS



4. Dissemination and projected outputs

Our results will be disseminated as openly and as widely as possible to clinical, managerial, patient, and policy groups to ensure our results are implemented widely.

- The Press Office of the University of Exeter will inform the public via press releases.
- The research team will work with our established Patient and Public Involvement (PPI) network to develop dissemination materials for patients and carers. This will be enhanced by our established links with the British Heart Foundation.
- We will also use traditional scientific channels for dissemination. We have costed the application to include funds to support presentation of the results at either the Annual meeting of the American Heart Association or European Society of Cardiology as well as two open access publications in the mainstream literature. In addition to publication of the HTA monograph, we will seek publication in a high impact general medical journal such as *The Lancet*, *JAMA* or *BMJ* and a high impact cardiology journal e.g. *J Am Coll Cardiol*, *Am Heart J*, *Eur Heart J*. Results will also be presented at national meetings including annual meetings of the British Association of Cardiac Rehabilitation and British Cardiovascular Society.
- Non-traditional media will also be utilised. For example, for a recent BMJ editorial in the on cardiac rehabilitation (http://www.bmj.com/content/351/bmj.h5000.long) we included an online author pod-cast and also from a patient with lived experience of HF and rehabilitation (since publication in Sept 2015, these podcasts have been played online 5400 and 4100 times respectively).

5. Project management

Prof Taylor will provide overall management for the project alongside the full time research fellow who will undertake and coordinate day-to-day research activities. This will include input into all aspects of the project: methodological input, supervision and overseeing the work, quality assurance, ensuring milestones are met. It will also include ensuring regular communication with the project Advisory Group, the collaborators, the International Steering Committee, and NIHR.

The progress of the project will be assessed against detailed project milestones.

Weekly meetings will take place between the Chief Investigator and research fellow, with two monthly input from the other Exeter and external co-applicants either face-to-face or by telephone/video-conferencing.

6. Approval by ethics committees

The ethics of obtaining data have been carefully considered and we have sought advice from HSCIC. The original trials each obtained ethical/IRB committee approval and obtained individual patient consent. Given the fully anonymised nature of all the trial datasets that

have in our possession (i.e. no inclusion of data, such as patient name or dob, that would allow individual patients to be identified), HSCIC have confirmed that there is no further legal/ethical or contractual requirements for use of this data for the purpose of this project.

We have already obtained copies of individual patient data sets and are storing these data in accordance with the Exeter CTU Standard Operating Procedure 'Data Security (Inc. Protection, Confidentiality & Transfer)' (NIHRexe/195/GEN, V1, 28/04/2015).

7. Patient and Public Involvement

As part of our ongoing NIHR Programme Grant (Rehabilitation Enablement in Chronic Heart Failure - REACH-HF, PGfAR RP-PG-0611-12004) we established a PPI Group in 2009 that consists of eight active members (5 with lived experience of heart failure and 3 patient carer givers). The PPI Group have become familiar over the last 24-months with our ongoing portfolio of Cochrane systematic reviews in cardiac rehabilitation.

We presented this proposed individual patient data meta-analysis to the PPI group meeting in Truro on 1st Nov 2015 and sought views on our proposed research questions. Kevin Paul (the Chair of the PPI Group) is a co-applicant for our ongoing NIHR study and also a member of the REACH-HF Programme Steering Committee. Kevin is a core colleague and valued member of our team. He has agreed to join the Project Advisory Group for this project and to act as conduit with our established PPI Group. Kevin commented on the plain English summary of this application.

Based on the INVOLVE guidelines, we have included the cost of his time to attend Project Advisory Group meetings plus his travel. As a minimum, he will be asked to contribute to and give his views on: (i) the protocol (e.g. whether we have prioritised the appropriate outcomes); (ii) lay summaries of the project that we will make available on the project website; (iii) the implications for clinical practice and future research; and (iv) the planned dissemination strategy. Our PPI Group and Chair will continue to be supported for the duration of this project by Dr Jenny Wingham, an experienced research nurse, whose time is funded through the REACH-HF and NIHR support funding.

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Appendix A – Example database search strategy from 2014 Cochrane review

MEDLINE(R) Ovid 1946 to January Week 4 2013

1. exp Myocardial Ischemia/
2. (myocard$4 adj5 (ischaemi$2 or ischemi$2)).ti,ab.
3. ((ischaemi$2 or ischemi$2) adj5 heart).ti,ab.
4. exp Coronary Artery Bypass/
5. coronary.ti,ab.
6. exp Coronary Disease/
7. exp Myocardial Revascularization/
8. Myocardial Infarction/
9. (myocard$5 adj5 infarct$5).ti,ab.
10. (heart adj5 infarct$5).ti,ab.
11. exp Angina Pectoris/
12. angina.ti,ab.
13. exp Heart Failure/
14. (heart adj5 failure).ti,ab.
15. (HFNEF or HFPEF or HFREF or "HF NEF" or "HF PEF" or "HF REF").ti,ab.
16. or/1-15
17. exp Heart Diseases/
18. (heart adj5 disease$2).ti,ab.
19. myocard$5.ti,ab.
20. cardiac$2.ti,ab.
21. CABG.ti,ab.
22. PTCA.ti,ab.
23. (stent$4 and (heart or cardiac$4)).ti,ab.
24. Heart Bypass, Left/ or exp Heart Bypass, Right/
25. or/17-24
26. *Rehabilitation Centers/
27. exp Exercise Therapy/
28. *Rehabilitation/
29. exp Sports/
30. Physical Exertion/ or exertion.ti,ab.
31. exp Exercise/
32. rehabilitat$5.ti,ab.
33. (physical$4 adj5 (fit or fitness or train$5 or therap$5 or activit$5)).ti,ab.
34. (train$5 adj5 (strength$3 or aerobic or exercise$4)).ti,ab.
35. ((exercise$4 or fitness) adj5 (treatment or intervent$4 or programs$2 or therapy)).ti,ab.
36. Patient Education as Topic/
37. (patient$2 adj5 educat$4).ti,ab.
38. ((lifestyle or life-style) adj5 (intervent$5 or program$2 or treatment$2)).ti,ab.
39. *Self Care/
40. (self adj5 (manage$5 or care or motivate$5)).ti,ab.
41. *Ambulatory Care/
42. exp Psychotherapy/
43. psychotherap$2.ti,ab.
44. (psycholog$5 adj5 intervent$5).ti,ab.
45. relax$6.ti,ab.
46. exp Relaxation Therapy/ or exp Mind-Body Therapies/
47. exp Counseling/
48. (counselling or counseling).ti,ab.
49. exp Cognitive Therapy/
50. exp Behavior Therapy/
51. ((behavior$4 or behaviour$4) adj5 (modify or modificat$4 or therap$2 or change)).ti,ab.
52. *Stress, Psychological/
53. (stress adj5 management).ti,ab.
54. (cognitive adj5 therap$2).ti,ab.
55. meditat$4.ti,ab.
56. *Meditation/
57. exp Anxiety/
58. (manage$5 adj5 (anxiety or depress$5)).ti,ab.
59. CBT.ti,ab.
60. hypnotherap$5.ti,ab.
61. (goal adj5 setting).ti,ab.
62. (goal$2 adj5 setting).ti,ab.
63. (psycho-educat$5 or psychoeducat$5).ti,ab.
64. (motivat$5 adj5 (intervention or interv$3)).ti,ab.
65. Psychopathology/
66. psychopathol$4.ti,ab.
67. psychosocial$4.ti,ab.
68. distress$4.ti,ab.
69. exp Health Education/
70. (health adj5 education).ti,ab.
71. (heart adj5 manual).ti,ab.
72. Autogenic Training/

73. autogenic$5.ti,ab.
74. or/26-39
75. or/40-73
76. 16 or 25
77. 74 or 75
78. 76 and 77
79. randomized controlled trial/
80. randomized controlled trial.pt.
81. controlled clinical trial.pt.
82. controlled clinical trial/
83. Random Allocation/
84. Double-Blind Method/
85. single-blind method/
86. (random$ or placebo$).ti,ab.
87. ((singl$3 or doubl$3 or tripl$3 or trebl$3) adj5 (blind$3 or mask$3)).ti,ab.
88. exp Research Design/
89. Clinical Trial.pt.
90. exp clinical trial/
91. (clinic$3 adj trial$2).ti,ab.
92. or/79-91
93. 78 and 92
94. (Animals not Humans).sh.
95. 93 not 94
96. limit 95 to yr="2008 -Current"

APPENDIX B. Identified randomised controlled trials meeting inclusion criteria

First author (year)	Total patients (N)[1]	Trial setting	NYHA class	Mean ejection fraction (%)	Mean age (yrs)	Male (%)	Exercise type[2]	Overall exercise duration (minutes)	Exercise frequency (sessions/ week)	Mean session duration (minutes)	Exercise setting[3]	Longest follow- up (months)
Cochrane 2014 review (13)												
Austin (2005/8)	200	Single centre	II/III	NR	72	43	Mix	120	2.5	24	Both	60
Bellardinelli (1999)	99	Single centre	II/IV	28	55	89	Aerobic	40	2.5	56	Centre	26
Bellardinelli (2012)	123	Single centre	II/III	37	59	78	Aerobic	40	2.5	56	Centre	120
Davidson (2010)	105	Single centre	I/II/III/IV	.NR	72.3	67	Mix	40	1	12	Centre	12
Dracup (2007)	173	Single centre	II/IV	26	54	72	Mix	28	4	52	Home	12
DANREHAB (2008)	91	Single centre	I/II/III	NR	66	90	Mix	90	3	12	Both	12
Gary (2010)	65	Single centre	II/III	NR	65.8	42	Aerobic	37.5	3	12	Home	6
Giannuzzi (2003)	90	Multi centre	II/III	25	60.5	.	Aerobic	30	4	24	Both	6
Hambrecht (2000)	73	Single centre	I/II/III	29	54	100	Aerobic	15	6.5	24	Both	6
HF-ACTION (2009)	2331	Multi centre	II/III/IV	25	59	72	Aerobic	30	2.5	120	Both	48
Jolly (2009)	169	Multi centre	I/II/IV	NR	66	75	Mix	25	5	48	Home	12
Klecha (2007)	50	Single centre	II/III	28	61	100	Aerobic	20	3	24	Centre	6
McKelvie (2002)	181	Multi centre	I/II/III	NR	65.5	81	Mix	30	2	36	Both	12
Mueller (2007)	50	Single centre	NR	NR	55	100	Aerobic	120	5	4	Centre	74
Nilsson (2008)	80	Single centre	II/III	31	70	79	Aerobic	50	2	16	Centre	12
Passino (2006)	95	Single centre	I/II/III	34	60.5	87	Aerobic	30	3	36	Home	9
Willenheimer (2000)	54	Single centre	NR	36.5	64	71.5	Aerobic	30	2.5	16	Centre	10
Witham (2005)	82	Single centre	II/III	NR	80.5	55	Mix	20	2.5	24	Both	6
Witham (2012)	107	Single centre	II/III	NR	81	100	Mix	60	2	24	Both	6
Yeh (2011)	100	Multi centre	I/II/III	29	67.5	64	Aerobic	30	2.5	12	Both	6

ExTraMATCH I (2004) (16)												
Dubach (1997)/ Meyers (2002)	51	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	8.5
Zannelli (1997)	155	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	10
Wielenga (1999)	80	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	47.3

[1]Total number of patients randomised; [2] 'Mix' includes aerobic and resistance training; [3]Whether exercise setting is home or centre or both; NR: not reported in either Cochrane (2014) or ExTraMATCH I (2004) reports.
NHYA: New York Heart Association

APPENDIX C. Collaboration invitation letter to trial investigators

Dear Trial Investigator [personalise]

Exercise Training for Chronic Heart Failure (ExTraMATCH II): individual patient data meta-analysis

In 2004, the ExTraMATCH collaboration (led by Dr Massimo Piepoli) published the first individual patient data meta-analysis of randomised controlled trials of exercise training in chronic heart failure (copy of PDF attached). In the last decade a number of important trials of exercise training in heart failure have been published. The ExTraMATCH II international collaborative has been formed to bring together this new trial data to produce an updated individual patient data meta-analysis. We are contacting all the lead investigators of trials of exercise training in heart failure to seek their participation.

As a contributor of data [reference] to the previous ExTraMATCH collaboration we are hoping that you will again agree to make available your trial individual patient dataset for the purpose of this new project.
OR
Your trial [reference] was identified in our recently updated 2014 Cochrane review of exercise-based interventions for heart failure (in press). We would like to invite you to join ExTraMATCH II as a collaborator and make available the individual patient dataset from your trial for the purpose of this project.

We request that you **read the attached frequently asked question document and reply back to us as indicated**.

We very much look forward to hearing from you, and hope you will wish to be involved in this important international collaboration in the field of exercise-based rehabilitation for heart failure.

Yours sincerely

Professor Rod Taylor, University of Exeter Medical School, Exeter, United Kingdom
And on behalf of the ExTraMATCH II International Steering Group

Dr Massimo Piepoli, Cardiology Unit, Guglielmo da Saliceto Hospital, Piacenza, Italy
Dr Neil Smart, School of Science and Technology, University of New England, Armidale, NSW, Australia
Dr Oriana Ciani, University of Exeter Medical School, Exeter, UK
Dr Hayes Dalal, Primary Care Research Group, University of Exeter Medical School, Truro, UK
Dr Fiona Warren, Primary Care Research Group, University of Exeter Medical School, Exeter, UK
Professor Christopher O'Connor, Division of Cardiology and Clinical Pharmacology, Duke Heart Center, North Carolina, USA
Dr David Whellen, Duke Clinical Research Institute, North Carolina, USA
Dr Stephen Ellis, Duke Clinical Research Institute, North Carolina, USA

ExTraMATCH II – Invitation letter to trial investigator

Frequently asked questions

How does an individual patient data meta-analysis differ from a standard meta-analysis?

Traditional meta-analysis methods involve combining and analysing trial level (or 'aggregate') results typically obtained from publications from that trial. An alternative and increasingly popular approach is meta-analysis of individual patient data (IPD), in which the raw individual level data for each study are obtained and used for analysis.

IPD meta-analyses offer a number of advantages over traditional meta-analyses, including:

- statistical analysis can be standardised across studies (for example, the analysis method, how continuous variables are analysed, the time points assessed etc.) and more advanced methods (e.g. time to event) can be applied where necessary;
- superior power to assess the treatment effects in specific subgroups of participants (e.g. NYHA I and II patients vs NYHA III and IV patient), and differential treatment effects (e.g. centre-based training vs. home-based programmes); and
- missing data can be observed and accounted for at the individual level.

What data am I being asked to share?

The initial phase of the ExTraMATCH II project is seeking individual patient data for the following outcomes from your trial:

- patient baseline data (socio-demographic characteristics, clinical characteristics e.g. heart failure aetiology, ejection fraction)
- mortality (all-cause death, death due to heart failure, and sudden cardiac death): rates and time-to-event;
- hospital admission/re-admission (all-cause, heart failure specific): rates and time-to-event;
- disease specific health-related quality of life assessed by the Minnesota Living With Heart Failure questionnaire and other validated quality of life outcomes: outcome at baseline and at 6, 12, 24 and >24 months' follow-up;
- exercise capacity (irrespective of assessment method): outcome at baseline and at 6, 12, 24 and >24 months' follow up.

Do I need ethics (IRB) permission to make my data available?

No. Participants have consented to participate in their original trial. Given that the analyses proposed by the ExTraMATCH II project are simply an extension of the core analysis of the constituent trials, we do not anticipate that additional ethical permission will be required.

Will my data be securely held?

Yes. We will ensure that datasets shared as part of the project include no patient-identifiable information (such as names and addresses), and that all data storage complies with the regulations governing research at University of Exeter Medical School.
All data will be received and stored in a secure database at the Clinical Trials Support Network, University of Exeter Medical School, Exeter, United Kingdom. A copy of the dataset will be held by both the coordinating centre at University of Exeter Medical School, and Duke Clinical Research Institute (DCRI) in the USA (coordinating centre for HF ACTION trial).

How should I organise the transfer of my data?

We will work with you and each individual trial site to determine the best way to transfer your patient level data.

What will be done with the data?

Individual trial datasets will be combined into one overall dataset with standardised variables, working with individual trial authors to ensure standardisation of variables and to check that our initial analyses of individual datasets are consistent with the published results from the trial. Once the combined dataset has been developed, the first phase of ExTraMATCH II data analysis will be to address the following three primary objectives:

- to obtain reliable and precise estimates of the impact of exercise-based interventions in HF on the following outcomes: time to death and admission to hospital (overall and heart failure specific), exercise capacity and disease-specific health-related quality of life;
- to compare the effects of exercise-based interventions in HFpEF and HFrEF subgroups and other patient clinical and demographic characteristics (e.g. disease severity, gender and age), and to compare intervention effects according to whether it is delivered in a centre- or home-based setting
- to assess whether the change in exercise capacity mediates the effect of the intervention on disease-specific health-related quality of life and clinical outcomes and the extent to which exercise capacity acts as an acceptable surrogate outcome for mortality and hospitalisation.

Who owns the data?

Data from individual datasets will remain the property of the ExTraMATCH collaborators who have provided IPD. You remain the custodian for your own data and retain the right to withdraw your data from the ExTraMATCH II collaboration at any time.

How will I be acknowledged on presentations and publications based on the ExTraMATCH II data?

All publications from the combined data will include the ExTraMATCH II research team and all collaborators. Where collaborators involve multiple individual authors, nominations for authorship will be made to the management committee. Requirements for authorship are those of the International Committee of Medical Journal Editors (http://www.icmje.org). Before publication of any ExTraMATCH II manuscripts, drafts will be circulated for comment, revision and approval. Publications using these data will be authored on behalf of the ExTraMATCH II Collaboration, either with specific named authors, or on behalf of the Collaboration as a whole; names of other participating Collaborators will be listed in the Acknowledgements.

APPENDIX D. ExTraMATCH II core data fields

Variable	Description
Study level data	
Centre ID	Centre name
Randomised control patients (N)	
Randomised exercise patients (N)	
Patient level data – descriptive	
Patient ID	
Date of randomisation	dd/mm/yyyy
Allocated treatment	1 Exercise 2 Control
Date of birth	dd/mm/yyyy
Gender	1 Male 2 Female 9 Data unavailable
Race	1. White/Caucasian 2 African/African-American 3 Asian 4 Other 9 Data unavailable
Aetiology of heart failure	1 Ischaemic heart disease 2 Idiopathic dilated cardiomyopathy 3 Other/Unknown 9 Data unavailable
Year of heart failure diagnosis	yyyy
New York Heart Association class at entry/baseline	1 NYHA Class I 2 NYHA Class II 3 NYHA Class III 4 NYHA Class IV 9 Unknown/Unavailable
Ejection fraction at entry/baseline (%)	.
Patient level data - Outcomes	
Method of exercise capacity assessment	1 6-minute walk test 2 Bicycle ergometer test 3 Treadmill test 4 Other [state]
Exercise capacity[1] score at entry (units)	
Follow-up 1 exercise capacity score	Follow-up time (months)
Follow-up 2 exercise capacity score	Follow up time (months)
Follow-up 3 exercise capacity score	Follow up time([months)
Health related quality of life	1 Minnesota Living With Heart Failure 2 Other measure (state)

HRQoL at entry	Total & subscores
Follow-up 1 HRQoL score	Total & subscores Follow up time (months)
Follow-up 2 HRQoL score	Total & subscores Follow up time (months)
Follow-up 3 HRQoL score	Total & subscores Follow up time (months)
Date of death	dd/mm/yyyy
Cause of death	1 Acute myocardial infarction 2 Sudden death 3 Heart failure 4 Other cardiac 5 Stroke 6 Other vascular/thrombo-embolic 7 Non-cardiovascular 8 Unknown [1–4, cardiac; 1–6, cardiovascular]
Date of first all-cause hospital admission	dd/mm/yyyy 1 de novo hospitalisation 2 rehospitalisation
Date of first HF hospital admission	dd/mm/yy 1 de novo hospitalisation 2 rehospitalisation
Number of all-cause hospitalisations	
Number of all HF hospitalisations	
Drop-out	
Date of study discontinuation	dd/mm/yyyy
Reason for study discontinuation	
Exercise training (only applies to exercise group patients)	
Study level data	
Prescribed exercise training Overall duration Session duration Frequency of sessions Intensity	 --- weeks (ranges if appropriate) ---- minutes (range if appropriate) --- sessions/week (range if appropriate) ----% units (range if appropriate)
Setting	1 Centre only 2 Home only 3 Both centre and home (define proportion of sessions at each location) 4 Other (state)
Patient level data	
Attended first exercise training	1 Yes 2 No 3 Not reported
Are details available at patient level on exercise dose received?	1 Yes 2 No

[1]Whatever the measure exercise capacity