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Exercise Training for Chronic Heart Failure (ExTraMATCH II): Protocol for an Individual Participant Data Meta-Analysis

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And on behalf of ExTraMATCH II Collaborators

*This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Conflicts of interest: none declared

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Abstract

Background
Patients with chronic heart failure (HF) experience a marked reduction in their exercise capacity, health-related quality of life, and life expectancy. Despite substantive evidence supporting exercise training in HF, uncertainties remain in the interpretation and understanding of this evidence base. Clinicians and healthcare providers seek definitive estimates of impact on mortality, hospitalisation and health-related quality of life, and which HF patient subgroups are likely to most benefit. The original Exercise Training Meta-Analysis for Chronic Heart Failure (ExTraMATCH) individual participant data (IPD) meta-analysis conducted in 2004 will be updated by the current collaboration (ExTraMATCH II), to investigate the effects of exercise training in HF.

Methods
Randomised controlled trials have been identified from the updated 2014 Cochrane systematic review and the original ExTraMATCH IPD meta-analysis with exercise training of 3 weeks' duration or more compared with a non-exercise control and a minimum follow-up of 6 months. Particular outcomes of interest are mortality, hospitalisation and health-related quality of life plus key baseline patient 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 approach where the IPD from all studies are modelled simultaneously while accounting for the clustering of participants with studies.

Discussion
The information from ExTraMATCH II will help inform future national and international clinical and policy decision-making on the use of exercise-based interventions in HF and improve the quality, design and reporting of future trials in this field.

Key words: heart failure, meta-analysis, individual participant data, exercise-training, cardiac rehabilitation.
1. Introduction

Patients with chronic heart failure (HF) experience a marked reduction in exercise capacity, which has detrimental effects on their activities of daily living, health-related quality of life, hospital admission rate and survival [1].

Exercise training is known to reduce the debilitating symptoms of chronic HF, such as breathlessness and fatigue, through effects on the cardiovascular and musculoskeletal systems [2-3]. Meta-analyses have shown that exercise interventions can improve short-term (up to 12 months’ follow-up) exercise capacity of those with HF [4-5]. Exercise training is therefore increasingly recognised as an important adjunct in the management of HF and is recommended by the American College of Cardiology Foundation/American Heart Association Task Force, the European Society of Cardiology, and other national guidelines [6-9]. However, some key issues in the interpretation and understanding of the evidence base for exercise training in HF remain.

First is uncertainty of the impact of exercise training in HF on the outcomes of death and hospital admission. In 2004, the Exercise Training Meta-Analysis for Chronic Heart Failure (ExTraMATCH) Collaborative Group published an individual participant data (IPD) meta-analysis [10] that showed a reduction in both all-cause mortality (hazard ratio (HR): 0.65, 95% confidence interval (CI): 0.46 to 0.92) and death or admission to hospital (HR 0.72, 95% CI 0.56 to 0.93) in those who received exercise-based intervention compared with control, using data from nine randomised controlled trials (RCTs). However, a number of RCTs have since been published, including HF-ACTION, a large randomised trial of exercise training including 2331 HF patients across 82 centres in United States, Canada and France [11]. The recently updated Cochrane systematic review and meta-analysis now incorporates aggregate study level data from 33 RCTs in 4740 patients published up to January 2013 [12]. Whilst this 2014 Cochrane review confirms the benefit of exercise training in reduced hospital admissions (relative risk (RR): 0.75; 95% CI, 0.62 to 0.92), the authors reported no significant improvement in mortality in trials with up to 12 months’ follow up (RR: 0.93; 95% CI, 0.69 to 1.27) and a trend towards improved pooled survival in six trials with longer term follow up (RR: 0.88; 95% CI, 0.75 to 1.02).

Second is uncertainty whether exercise training confers differential effects by HF patient subgroup; for example, do patients with less severe disease benefit more (or less) from exercise training than those with more severe disease? The original ExTraMATCH IPD meta-analysis reported no statistically significant subgroup (age, gender, HF aetiology, New York Heart Association (NYHA) class, ejection fraction, or exercise capacity) difference in exercise training effect on overall mortality [10]. The IPD analysis of the HF-ACTION trial also found no interactions between patient characteristics (age, gender, HF aetiology, NYHA class, ejection fraction, or depression score) and either the composite outcome of mortality.
and hospital admission or health-related quality of life [11]. Similarly, the 2014 Cochrane review meta-regression analysis found no association between average trial level patient characteristics (age, gender, ejection fraction) and mortality, hospitalisation or health-related quality of life [12]. However, even with the relatively large sample size of the HF-ACTION trial, the statistical power of these analyses to detect small subgroup effects is likely to be limited. Furthermore, the analysis in the Cochrane review risks study level confounding (ecological fallacy).

The third uncertainty is the amount of exercise training required to deliver optimal outcomes in HF patients. The trials included in the 2014 Cochrane review varied widely in their exercise prescription, overall exercise duration of exercise training ranging from 24-52 weeks with a study average of 2-7 sessions of exercise per week of 15-120 minutes per session and intensity of 40% maximal heart rate to 85% maximal oxygen uptake. Nevertheless, meta-regression showed that the average exercise dose per study (calculated as number of weeks x average number of sessions)/(week x average duration of session in hours)) was not associated with mortality, hospitalisation or health-related quality of life. Similarly, the ExTraMATCH IPD meta-analysis review found no interaction between mortality outcome and study exercise duration (< 28 weeks versus ≥ 28 weeks). However, as with patient subgroups, these analyses are limited by statistical power and Cochrane analysis subject to ecological fallacy.

In the context of these uncertainties, IPD meta-analysis offers a number of important advantages [13, 14]. IPD allows the application of standardised and appropriate data analysis methods across studies and thereby improves statistical power and precision. In the case of exercise training trials, time-to-event analyses can be applied to mortality and hospitalisation outcomes, and analysis of covariance to exercise capacity and health-related quality of life data, thus allowing the consistent calculation of HRs and adjusted mean differences between exercise and control groups. Furthermore, IPD meta-analysis allows subgroup effects to be examined via interaction terms utilising within-trial data. These subgroup analyses can be consistently applied and tested across all exercise training trials for each pre-defined patient characteristic. In summary, IPD meta-analysis has greater statistical power, and is more likely to provide definitive estimation of overall and subgroup effects of an exercise-based intervention for HF than has been possible by previous aggregate data meta-analyses or analyses of single trials.

ExTraMATCH II is an international collaboration with the goal of undertaking IPD meta-analysis of RCTs that investigate impact of exercise training in HF based on a systematic review of contemporary RCT evidence. The information gained from the ExTraMATCH II project will help inform future national and international clinical and policy decision-making on the use of exercise-based interventions in HF.
The primary objectives of the EXTraMATCH II IPD meta-analysis are to:

1. Provide definitive estimates of the impact of exercise-based interventions in HF versus control on all-cause mortality, hospitalisation and health-related quality of life.
2. Analyse the influence of pre-randomisation patient characteristics on the impact of exercise-based interventions in HF, including age, gender, ejection fraction, heart failure aetiology, NYHA class and exercise capacity.
3. Perform an exploratory analysis to assess whether the change in exercise capacity mediates the impact of the exercise-based interventions on all-cause mortality, hospitalisation and disease-specific health-related quality of life.
4. Perform an exploratory analysis to assess the importance of both the amount of exercise prescribed and the setting in which exercise is undertaken (centre versus home) on the impact of exercise-based interventions in HF.
5. Describe in detail the effect of exercise-based interventions versus control on hospitalisation outcomes including recurrent hospitalisation, total number of hospitalisations, and duration of stay.
2. Methods

2.1 Search methods for identification of studies
Trials for inclusion in the ExTraMATCH II project were identified from the original ExTraMATCH study [10] and the recently updated 2014 Cochrane review [12]. 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. The search strategy used in the Cochrane 2014 review is listed in Appendix A.

2.2 Eligibility criteria for studies
We included 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:** 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’, HFP EF) based on objective assessment of left ventricular ejection fraction and on clinical findings.
- **Context:** Patients managed in any setting i.e. hospital, community facility or home.
- **Intervention:** Receiving an exercise-based intervention, which should include at least an aerobic exercise training component performed by the lower limbs, lasting a minimum of 3 weeks [10], either alone or as part of a comprehensive cardiac rehabilitation programme defined as also including components of health education and psychological treatment. 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 [14].

Table 1 lists the characteristics of the 20 studies from the Cochrane 2014 review and three studies from ExTraMATCH that meet these criteria.
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 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; and
- exercise capacity (irrespective of assessment method): outcome at baseline and at 6, 12, 24 and >24 months post-randomisation.

Data will be sought for all patients at all time points and grouped for purposes of analysis: short term (6-12 months), medium term (13-24 months) and long term (> 24 months).

We will also seek 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, where available, we will seek from investigators details at an individual patient level of the amount of exercise intervention undertaken.

2.4 Collection of data

2.4.1 Investigator contact

We will initially email all identified trial investigative teams via the named contact 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 (see Appendix B for contact letter). As part of the Cochrane review we have previously been in contact with a number of investigators for the purpose of obtaining further data or clarification. In all cases we have received positive responses from contact authors.

Members of the ExTraMATCH Executive Management 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 Executive 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.

2.4.1 Data format
The procedure for collection and collation of data will be coordinated by the project secretariat based at the University of Exeter Medical School. Participating study authors will be asked to provide anonymised primary datasets corresponding to minimum data required to answer the primary research objectives (draft data fields are shown in Appendix C). 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.

2.4.2 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 secretariat or via the University of Exeter password-protected drop box facility. Once received, data will be stored in a secure computer server managed by the Exeter Medical School Clinical Trials Support Unit. 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.

2.4.3 Data checking

We will evaluate data from each study and compare these with the available publication(s). We will check each dataset for the range of included variables to make sure all values are reasonable. We will assess missing observations for each variable and check against the original publication. We will 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. We will 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 both the project secretariat at the Exeter Medical School and Duke Clinical Research Institute (DCRI) in the US (coordinating centre for the HF-ACTION trial). Data from individual datasets will remain the property of the ExTraMATCH II 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; 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 accord with current recommendations for IPD meta-analyses [13-15].

2.5.1. 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 IPD, to determine if the IPD studies available are a representative (unbiased) sample of all available eligible studies [15].

2.5.2. IPD meta-analysis
There are two methods of undertaking IPD meta-analysis: (i) using IPD to derive aggregate data for each study, followed by meta-analysis of the aggregate data (‘two-step IPD meta-analysis’); and (ii) analysis of individual patient data using a mixed model and accounting for clustering of patients within studies (‘one-step IPD meta-analysis’). In this project we will 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 [13].

All analyses will follow 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-analysis and in the unlikely event it is very low or zero we will run a sensitivity analysis using standard general linear models (fixed-effect).

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

2.5.2 Subgroup and mediation analysis
Any modification of treatment effects across pre-defined patient subgroups (i.e., age, gender, socio-economic group, ethnicity, ejection fraction, heart failure aetiology, NYHA class and exercise capacity), exercise programme duration (< 28 vs ≥28 weeks) [10], 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 [17-19].

2.5.3 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 and exclusion of trials with an overall exercise duration of less than 12 weeks.

2.5.4 Publication bias
We will assess publication bias in this IPD meta-analysis in accord with recommended methods [15].

- When IPD cannot be obtained, the impact on meta-analysis conclusions should 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, it may be helpful to 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).
- Assess funnel plot asymmetry (with and without studies using IPD).

2.5.5 General
Analyses will be undertaken using Stata v12. Study data will not be used for any other purpose without the permission of collaborators.

2.6 Project management and ethics
The ‘ExTraMATCH II Executive Management Group’ refers to the core team of researchers who will oversee the strategic direction of the protocol; the ‘ExTraMATCH II Collaborators’ refers to all those linked to the project and includes 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 ExTraMATCH II Executive Management Group
The roles of the ExTraMATCH II 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;
- 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; and
- lead future applications for research funding.

2.6.2 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 will be given opportunities to participate in decision-making regarding the study design and analyses. We intend members of the collaborative will have opportunities to network and identify future ExTraMATCH II 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 University of Exeter Medical School, 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

We will follow recommendations for authorship in IPD analyses and multicentre studies [20, 21]. Where possible, we will follow the policy of members of the Executive Management Group and the Collaborative Group being listed as authors and names of other participating collaborators listed in the acknowledgements. 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 ExTraMATCH II manuscript drafts will be circulated to the Collaborative Group for comment, revision and approval.
3. Discussion
The ExTraMATCH II project will establish a collaborative group and conduct an IPD meta-analysis of randomised controlled trials of exercise-based interventions in HF. This project provides a unique opportunity to investigate a number of uncertainties in the literature regarding exercise training for those with HF. In particular, we will provide clinicians and healthcare policy makers with definitive estimates of the impact of exercise-based interventions in HF on all-cause mortality, hospitalisation and health-related quality of life. A particular strength of the IPD approach is the application to investigating treatment modifiers. We will be able to provide guidance on differential responses to exercise therapy across different HF patient subgroups. It is also our intention that the ExTraMATCH II collaboration will help improve quality, design and reporting of future trials in this field.

ExTraMATCH II Management Executive Group
All authors are members of the ExtraMatch II Management Executive Group

ExTraMATCH II Collaborator Group (as of December 2013)
Emeline M. Van Craenenbroeck, Department of Cardiology, Antwerp University Hospital, Belgium,
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Miles Witham, University of Dundee, Dundee, UK
Ann Dorthe Zwisler, CopenHeart, Copenhagen, Denmark
References


Table 1. Identified randomised controlled trials meeting inclusion criteria

<table>
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<th>Mean ejection fraction (%)</th>
<th>Mean age (years)</th>
<th>Male (%)</th>
<th>Exercise type</th>
<th>Overall exercise duration (minutes)</th>
<th>Exercise frequency (sessions/week)</th>
<th>Mean session duration (minutes)</th>
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<td>43</td>
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<td>II/III</td>
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<td>3</td>
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<td>3</td>
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<td>Setting 4</td>
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<td>Setting 7</td>
<td>Setting 8</td>
<td>Setting 9</td>
<td>Setting 10</td>
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<td>-----------------</td>
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<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>NR</td>
<td>8.5</td>
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<td>Zannelli (1997)</td>
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<td>NR</td>
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<td>NR</td>
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</tbody>
</table>

*Total number of patients randomised; ‘Mix’ includes aerobic and resistance training; 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 A – Search strategy from 2014 Cochrane review [12]

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. 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 Executive Management 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 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 HFrEF 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 C: Draft ExTraMATCH II core data fields

<table>
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<tr>
<th>Variable</th>
<th>Description</th>
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<td>Centre name</td>
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<td>Randomised exercise patients (N)</td>
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<td><strong>Patient level data – descriptive</strong></td>
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<td>2 Control</td>
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<td>3 Asian</td>
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<tr>
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<td>4 Other</td>
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<td>2 Idiopathic dilated cardiomyopathy</td>
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<td>2 NYHA Class II</td>
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<tr>
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<td>3 NYHA Class III</td>
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<tr>
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<td>4 NYHA Class IV</td>
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<td>Ejection fraction at entry/baseline (%)</td>
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**Patient level data - Outcomes**

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<th>Method of exercise capacity assessment</th>
<th>1 6-minute walk test</th>
<th>2 Bicycle ergometer test</th>
<th>3 Treadmill test</th>
<th>4 Other [state]</th>
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<table>
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<tr>
<th>Exercise capacity score at entry (units)</th>
<th>Follow-up time (months)</th>
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<td>Follow-up time (months)</td>
</tr>
<tr>
<td>Follow-up 2 exercise capacity score</td>
<td>Follow up time (months)</td>
</tr>
<tr>
<td>Follow-up 3 exercise capacity score</td>
<td>Follow up time([months)</td>
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<td>Health related quality of life</td>
<td>Minnesota Living With Heart Failure</td>
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<table>
<thead>
<tr>
<th>HRQoL at entry</th>
<th>Total &amp; subscores</th>
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</thead>
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<td>Follow-up 1 HRQoL score</td>
<td>Total &amp; subscores</td>
</tr>
<tr>
<td>Follow-up 2 HRQoL score</td>
<td>Total &amp; subscores</td>
</tr>
<tr>
<td>Follow-up 3 HRQoL score</td>
<td>Total &amp; subscores</td>
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</table>

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<th>Cause of death</th>
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<th>Sudden death</th>
<th>Heart failure</th>
<th>Other cardiac</th>
<th>Stroke</th>
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<td>[1–4, cardiac; 1–6, cardiovascular]</td>
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</table>

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**: --- weeks (ranges if appropriate)
- **Session duration**: ---- minutes (range if appropriate)
- **Frequency of sessions**: --- sessions/week (range if appropriate)
- **Intensity**: ----% 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: 1 Yes
<table>
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<th>training</th>
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<tr>
<td>2</td>
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<td>3</td>
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<td>Are details available at patient level on exercise dose received?</td>
<td>1</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>No</td>
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</table>

*Whatever the measure exercise capacity*
Highlights

- We undertake an updated individual participant data meta-analysis conducted to investigate the effects of exercise training in heart failure.
- Randomised controlled trials have been identified from the updated 2014 Cochrane systematic review and the original individual participant data meta-analysis.
- This study seeks to produce definitive estimates of the impact of exercise-based interventions on all-cause mortality, hospitalisation and health-related quality of life.
- This study seeks to determine the influence of patient and intervention characteristics on these outcomes.