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Rehabilitation Enablement in Chronic Heart Failure—a facilitated self-care rehabilitation intervention in patients with heart failure with preserved ejection fraction (REACH-HFpEF) and their caregivers: rationale and protocol for a single-centre pilot randomised controlled trial

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ABSTRACT

Introduction: The Rehabilitation EnAblement in CHronic Heart Failure in patients with Heart Failure (HF) with preserved ejection fraction (REACH-HFpEF) pilot trial is part of a research programme designed to develop and evaluate a facilitated, home-based, self-help rehabilitation intervention to improve self-care and quality of life (QoL) in heart failure patients and their caregivers. We will assess the feasibility of a definitive trial of the REACH-HF intervention in patients with HFpEF and their caregivers. The impact of the REACH-HF intervention on echocardiographic outcomes and bloodborne biomarkers will also be assessed.

Methods and analysis: A single-centre parallel two-group randomised controlled trial (RCT) with 1:1 individual allocation to the REACH-HF intervention plus usual care (intervention) or usual care alone (control) in 50 HFpEF patients and their caregivers. The REACH-HF intervention comprises a REACH-HF manual with supplementary tools, delivered by trained facilitators over 12 weeks. A mixed methods approach will be used to assess estimation of recruitment and retention rates; fidelity of REACH-HF manual delivery; identification of barriers to participation and adherence to the intervention and study protocol; feasibility of data collection and outcome burden. We will assess the variance in study outcomes to inform a definitive study sample size and assess methods for the collection of resource use and intervention delivery cost data to develop the cost-effectiveness analyses framework for any future trial. Patient outcomes collected at baseline, 4 and 6 months include QoL, psychological well-being, exercise capacity, physical activity and HF-related hospitalisation. Caregiver outcomes will also be assessed, and a substudy will evaluate impact of the REACH-HF manual on resting global cardiovascular function and bloodborne biomarkers in HFpEF patients.

Ethics and dissemination: The study is approved by the East of Scotland Research Ethics Service (Ref: 15/ES/0036). Findings will be disseminated via journals and presentations to clinicians, commissioners and service users.

Trial registration number: ISRCTN78539530; Pre-results .

Strengths and limitations of this study

- Design of study to inform the feasibility of definitive trial.
- Assessment of facilitated home-based self-management intervention in heart failure.
- Intervention that involves caregivers and evaluation of caregiver outcomes.
- Single centre study limiting external generalisability.
- No definitive evaluation of intervention clinical and cost-effectiveness.

INTRODUCTION

Epidemiological data show that approximately half of those patients with clinical features of heart failure (HF) have preserved ejection fraction population (HFpEF).[1 2]

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Patients with HFpEF are generally older, more often women, have a higher prevalence of hypertension, diabetes and atrial fibrillation and are less likely to have coronary artery disease than those with HF with reduced ejection fraction (HFrEF).[1 3] However, the substantial burden from HFpEF appears to be similar to that from HFrEF, measured by exercise intolerance, poor health-related quality of life (HRQoL), mortality, increased hospital admissions and higher healthcare costs.[4–6]

Although there has been increasing success of pharmacological and device therapy to improve outcomes in HFrEF, prognosis in HFpEF remains unchanged, with no individual large-scale randomised controlled trial (RCT) demonstrating significant treatment benefits.[7] Although no pharmacological therapy has been shown to reduce mortality in HFpEF, pharmacological therapy of HFpEF does demonstrate quantifiable improvements in exercise capacity.[7]

Systematic reviews and meta-analyses have shown promising evidence for the benefit of exercise-based cardiac rehabilitation (CR) in HFpEF.[8 9] The most recent meta-analysis of 6 RCTs in 276 patients found exercise-based CR significantly improved exercise capacity and HRQoL compared to usual care.[9] Notwithstanding that this evidence base consists of small RCTs of short follow-up (typically follow-up of 6-months or less); there were two other important limitations. First, there remain uncertainties in the mechanism of action in exercise-based CR interventions for HFpEF; no significant changes have been observed in the systolic or diastolic function with exercise-based CR in HFpEF patients. Second, the CR programmes undertaken in these RCTs were predominantly supervised and delivered in centre-based settings. There is increasingly recognition for the possibility of alternative delivery models of CR, such as telehealth and home-based programmes in order to overcome suboptimal rates of CR uptake seen with HF.[10] European research indicates that only a minority of eligible HF patients are receiving exercise-based CR.[11]

The Rehabilitation EnAblement in CHronic Heart Failure (REACH-HF) programme of research was designed to develop and evaluate a health professional facilitated home-based self-help rehabilitation intervention to improve self-care and HRQoL in people with HF and their caregivers.[12]

A core element of the REACH-HF intervention is exercise training which will be invested to better understand the mechanisms by which exercise intervention can improve exercise tolerance in HFpEF. In HFrEF patients, exercise intervention has been shown to improve cardiorespiratory fitness though cardiac[13 14] and extra cardiac mechanisms.[15 16] The cardiac mechanisms include reverse left ventricular remodelling[17] and improvement in diastolic function.[18 19] The ability of exercise interventions to improve early diastolic relaxation has also been shown in elderly individuals[20] and in patients after a myocardial infarction with a pre-existent abnormal relaxation pattern. Diastolic dysfunction is an important feature of exercise intolerance in patients with HFpEF.[21] Despite this, little is known about the impact of exercise training on diastolic function in HFpEF. This study will allow the opportunity to assess diastolic function and LV filling in more detail to better understand mechanisms of exercise intervention in HFpEF. As bloodborne biomarkers can offer objective and biologically relevant and mechanistic insights that complement the findings of echocardiographic measurements, we propose to measure biomarkers of distinct mechanisms that contribute to the pathophysiology of HF.

AIM

The overarching aim is to assess the feasibility of a definitive trial of the clinical and cost-effectiveness of the REACH-HF intervention in patients with HFpEF. Specific aims of the study were to estimate recruitment and retention of participants (patients and caregivers); and to evaluate components of the study process: feasibility of outcome data collection processes, and outcome burden and completion/attrition rates for participants (patients and caregivers). Specific objectives of the study were (1) to collect views of participants (patients and caregivers) on acceptability of the study design; (2) to assess the feasibility and experience of the addition of the REACH-HF intervention to usual care for participants (patients and caregivers) and intervention facilitators; (3) to identify barriers to participation and adherence to the intervention and study procedures; (4) to inform a definitive study sample size by assessment of the variance in study outcomes; (5) to assess methods for the collection of data on resource use and costs associated with the delivery of the intervention; (6) to develop the framework for cost-effectiveness analyses for any future full trial and economic evaluation; (7) to assess the fidelity of REACH-HF manual delivery by intervention facilitators and (8) to undertake a mechanistic substudy using echocardiographic and bloodborne biomarkers.

METHODS AND ANALYSIS

This protocol is reported in accord with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 guidance for protocols of clinical trials.[22]

Design

A parallel two-group randomised controlled pilot trial with individual participant allocation to the intervention or control group with a nested mixed methods feasibility evaluation and mechanistic substudy. Participants will be individually randomised to either the intervention group (REACH-HF intervention plus usual care) or the control (usual care alone) group. The design is depicted in figure 1.

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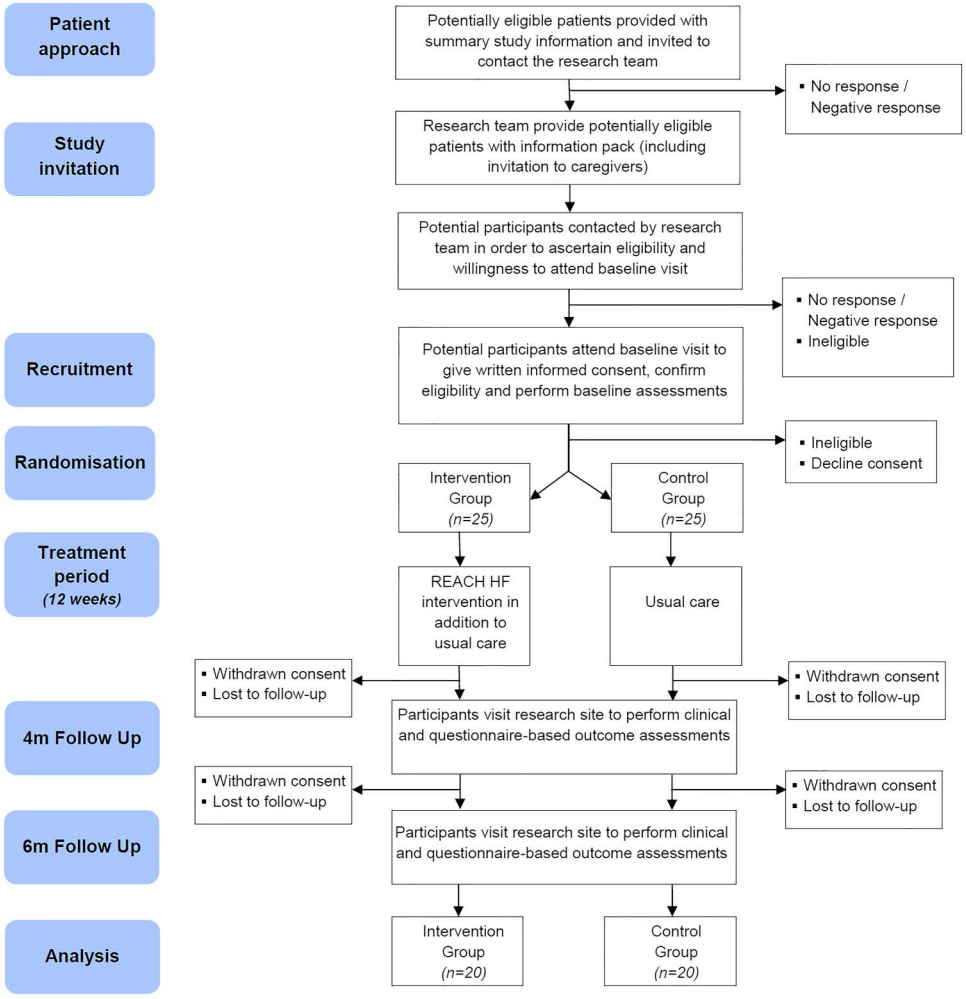

Figure 1 Consort flow chart.

Setting

The study will be conducted in a single investigator centre in one Scottish Health Board. In order to achieve adequate participant enrolment to sample size, the site can recruit via a number of secondary care pathways: HF disease/research registers; outpatient cardiology, HF and cardiovascular risk clinics: medicine for the elderly clinics; or CR services. Recruitment performance will be formally reviewed periodically by the central trial management team. Follow-up procedures will usually be conducted on NHS premises. Conduct of the study will be led by a local principal investigator (supported by a coinvestigator), research nurse/fellow and a research assistant (for qualitative elements); all of whom are trained in Good Clinical Practice and in the requirements of the study protocol. The site is responsible for the recruitment and scheduled follow-up visits of participants.

Study population

The study population includes patients and their caregivers. Participating patients will be aged 18 years or older and have a confirmed diagnosis of HFpEF on echocardiography (preferable), radionuclide ventriculography or angiography (ie, left ventricular ejection fraction ≥45% within the last 6 months prior to randomisation). Patients who have undertaken CR within 6 months prior to enrolment will be excluded, as will patients with a contraindication to exercise testing or exercise training (with consideration of adapted European Society of Cardiology guidelines for HF).[23] The full list of patient inclusion and exclusion criteria is listed in box 1.

Participating caregivers will be aged 18 years or older and provide unpaid support to participating patients who could otherwise not manage without such support. Unpaid support includes emotional support, prompting with taking medications, observing for signs and symptoms of HF, getting prescriptions, encouraging participation in social events and physical activity, helping with household tasks or providing physical care.

A patient may still participate if s/he does not have an identified caregiver, or if the patient's caregiver is not willing to participate.

Participants are free to withdraw from the study at any time, without any negative impact to their ongoing care. If a participant chooses to withdraw, their reason for

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withdrawal will be noted where possible. Any data collected on participants prior to withdrawal will be retained for analysis.

Randomisation

Participants will be randomly allocated in a 1:1 ratio to either intervention or control group arms without stratification or minimisation. Randomisation numbers will be computer generated and assigned in strict sequence. At the point of randomisation, participants will be assigned the next randomisation number in the sequence. To maintain concealment and minimise selection bias, randomisation will be performed after the baseline visit by a member of Peninsula Clinical Trials Unit (CTU), independent from investigator teams, using a secure, web-based randomisation system.

Intervention

The REACH-HF intervention is grounded in the support needs and priorities of people living with HF and the services that provide care for them. A systematic, six-step intervention mapping framework guided intervention development,[24] drawing on research evidence, national and international guidelines and stakeholder consultations with patients, caregivers and health professionals to identify 'targets for change'. In line with intervention mapping, regulatory processes underpinning target behaviour patterns and evidence-based change techniques were matched to each behaviour-change target.[25] A key element of the intervention development process was an active patient and public involvement (PPI) group consisting of six people with a range of experiences with HF and three caregivers of people with HF. The intervention development process is described in detail elsewhere.[26] Development of a facilitated self-care and rehabilitation intervention for people with HF and their care givers; Rehabilitation Enablement in Chronic Heart Failure (REACH-HF). Submitted for publication, November 2015).

The REACH-HF intervention is a comprehensive self-care support programme comprising the 'Heart Failure Manual' (REACH-HF manual), with a choice of two exercise programmes for patients, a 'Family and Friends Resource' for caregivers, a 'Progress Tracker' tool for patients and a 3-day training course for intervention facilitators.

Participating patients and caregivers will work through the REACH-HF manual over a 12-week period with facilitation by a specially trained intervention facilitator (cardiac nurse by background), who will help to build the patient's and caregiver's understanding of how to manage HF. The REACH-HF manual includes information and interactive elements covering a wide range of topics relating to living with/adapting to living with HF and includes four core elements:

1. an exercise training programme, tailored according to initial fitness assessments, delivered as a walking programme or a chair-based exercise DVD, or a combination of the two (as selected by the patient);
2. managing stress /breathlessness /anxiety;
3. heart failure symptom monitoring (and associated help-seeking);
4. understanding HF and taking medications.

The REACH-HF manual was originally designed for patients with HFrEF (ejection fraction <45%). There was limited evidence to guide the development of the REACH-HF manual for HFpEF patients; it has been adapted for this pilot study to allow evaluation in patients with HFpEF (ejection fraction ≥45%). The section on medications has been revised to make it relevant to HFpEF patients, and an additional section has been added on the nature of causes and treatment of HFpEF. The majority of the self-care advice in all other sections of the REACH-HF manual is relevant to all patients with HF and corresponds to national HF guidelines.[27 28]

Patients will be advised to use the Progress Tracker, which is designed to encourage patients to monitor their own condition over the period of the intervention and to make associations between improvements in self-care and improvements in symptoms/well-being. It includes sections in which patients can record changes in physical and mental state, intensity of exercise and self-reported walking speed, physical activity, engagement in enjoyable activities, frequency of self-weighing (to monitor fluid build-up) and frequency of use of stress-management techniques. The Family and Friends Resource, a manual for use by caregivers, includes advice on providing support for a person with heart failure, becoming a caregiver, managing the caregiver's own health and well-being and getting help.

Intervention delivery may be discontinued at any time at the request of a participant or by the intervention facilitator if the intervention is no longer deemed appropriate, for example, altered clinical condition.

Adherence by facilitators to the intervention protocols will be measured through fidelity assessment.

Usual care

In accord with findings of our national survey,[29] HF patients typically do not receive CR, despite national recommendations.[28] The choice of a usual care (no CR) comparator in this therefore reflects of the current situation for the vast majority of HF patients in UK. Intervention and control group patients will receive usual medical management for HF according to national and local guidelines. Data related to health service usage and medication use will be captured at each follow-up through participants' completion of healthcare resource use questionnaires and by collection of concomitant medication usage as reported by participants.

Outcome measures

Outcome data will be collected at 4 and 6 months post-randomisation (table 1). The 4-month time point

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Box 1 Trial entry criteria

Inclusion criteria

1. Male or female aged ≥18 years
2. Patients with heart failure, defined by the presence of at least one of the following symptoms at the time of screening:
   - paroxysmal nocturnal dyspnoea
   - or orthopnoea
   - or dyspnoea on mild or moderate exertion

   AND at least one of the following signs prior to study entry:
   - basal crepitations
   - or elevated jugular venous pressure
   - or lower extremity oedema
   - or chest radiograph demonstrating pleural effusion, pulmonary congestion or cardiomegaly.
3. Patients with left ventricular ejection fraction (EF) ≥45% obtained within 6 months prior to randomisation and after any myocardial infarction (MI) or other event that would affect EF (ideally obtained by echocardiography, although radionuclide ventriculography and angiography are acceptable).
4. Provision of informed consent to participate.

Exclusion criteria

1. Patients who have undertaken cardiac rehabilitation (CR) within the last 6 months
2. Patients with severe chronic pulmonary disease defined as requiring home oxygen or hospitalisation for exacerbation within 12 months or significant chronic pulmonary disease in the opinion of the investigator.
3. Patients who have any of the following contraindications to exercise testing or exercise training documented in their medical notes:
   - Early phase after acute coronary syndrome (up to 2 days)
   - Untreated life-threatening cardiac arrhythmias
   - Acute heart failure (during the initial period of haemodynamic instability)
   - Uncontrolled hypertension (systolic blood pressure (SBP) >200 and/or diastolic blood pressure (DBP) >100)
   - Advanced atrioventricular block
   - Acute myocarditis and pericarditis
   - Symptomatic aortic stenosis
   - Severe hypertrophic obstructive cardiomyopathy
   - Acute systemic illness
   - Intracardiac thrombus
   - Progressive worsening of exercise tolerance or dyspnoea at rest over previous 3–5 days
   - Significant ischaemia during low-intensity exercise (<2 metabolic equivalents, <50 W)
   - Uncontrolled diabetes (blood glucose >16 mmol/L or HbA_1C >9% or equivalent unit)
   - Recent embolism
   - Thrombophlebitis
   - Recent-onset atrial fibrillation/atrial flutter (in the last 4 weeks)
4. Patients who are unable to understand the study information or unable to complete study procedures.
5. Patients who are in a long-term care establishment or who are unwilling or unable to travel to research assessments or accommodate home visits.
6. Patients judged to be unable to participate in the study for any other reason, for example, psychiatric disorder, diagnosis of dementia, life-threatening comorbidity.
7. Patients participating in concurrent interventional research which may overburden the patient or confound data collection.

coincides with the planned end of the 3-month intervention delivery period for participants in the intervention arm. This allows a 1-month period after the baseline visit for completion of randomisation and referral processes.

Pilot trial outcome measures

The feasibility of a definitive trial will be determined by collection and analysis of the following pilot study outcome measures.

- Recruitment rate for participants (patients and caregivers) across the various recruitment pathways
- Attrition and loss to follow-up at 4 and 6 months postrandomisation
- Completion and completeness of main trial outcome measures at follow-up
- Fidelity of REACH-HF manual delivery by intervention facilitators (for details of the methods used, see the 'Process Evaluation' section)
- Acceptability of the intervention to HFpEF patients, their caregivers and facilitators (for details, see the 'Process Evaluation' section)
- Acceptability of study participation to participants.

Main trial outcome measures

The following outcomes proposed for a future definitive trial will be collected in this pilot trial:

- Primary outcome measure for HF patients

  Patients' disease-specific HRQoL measured using the Minnesota Living with Heart Failure questionnaire (MLHFQ).[30]
- Secondary outcome measures for HF patients will include:
  - Composite outcome of death or hospital admission related to HF or not related to HF.
  - N-terminal Brain Natriuretic Peptide (NT-pro-BNP) levels.[31]
  - Exercise capacity (incremental shuttle walking test ISWT).[32]
  - Physical activity level (GeneActive accelerometry over a 7-day period).[33]
  - Psychological well-being using Hospital Anxiety and Depression Scale (HADS) questionnaire.[34]
  - Generic HRQoL using the EQ-5D-5L questionnaire.[35]
  - Disease-specific HRQoL using the Health Related Quality of Life (HeartQoL) questionnaire.[36]
  - Self-care of HF Index questionnaire (SCHFI).[37]
  - Self-efficacy for key behaviours questionnaire (developed by the research team).
  - Healthcare usage (primary and secondary care contacts, social care contacts and relevant medication usage, reported by patient participants).
  - Safety outcomes.

Patients who are unable or not willing to undertake the exercise capacity assessment will not be excluded;

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Table 1 Tabulated summary of study schedule

			Postrandomisation	
	Baseline		+4 months	+6 months
TIME POINT	t_0	Randomisation	t_1	t_2
ENROLMENT:				
Eligibility screen	X			
Informed consent	X			
Demographics	X			
Medical History	X			
Randomisation*		X		
INTERVENTIONS:				
Intervention group:				
Usual care	◆	———	———	——— ◆
REACH-HF manual facilitation†		◆ ·····	····· ◆	
Control group:				
Usual care	◆	———	———	——— ◆
ASSESSMENTS:				
MLHFQ Questionnaire	X		X	X
SCHFI Questionnaire	X		X	X
HADS Questionnaire	X		X	X
Heart-QOL Questionnaire	X		X	X
EQ-5D-5L Questionnaire	X		X	X
Self-efficacy for key behaviours questionnaire	X		X	
Trial process questionnaire				X
CC-SCHFI Questionnaire (caregivers)	X		X	X
CBQ-HF Questionnaire (caregivers)	X		X	X
FAMQOL Questionnaire (caregivers)	X		X	X
HADS Questionnaire (caregivers)	X		X	X
EQ-5D-5L Questionnaire (caregivers)	X		X	X
Trial process questionnaire (caregivers)				X
Resource Use Data Collection	X		X	X
Echocardiography	X			X
Blood sample for NT-pro-BNP	X			X
Blood sample for bloodborne biomarkers	X			X
Incremental Shuttle Walk Test	X		X	X
Accelerometry	X		X	X
SAFETY MONITORING:				
Adverse event reporting	◆	———	———	——— ◆

*Randomisation will be performed by the Peninsula Clinical Trials Unit (CTU), typically within 10 days of the baseline clinic, following receipt of baseline data and blood sample result.
†REACH-HF manual facilitation will start ~1 month postrandomisation.
CBQ-HF, The Caregiver Burden Questionnaire for HF; CC-SCHFI, Caregiver Contribution to Self-care of HF Index questionnaire; FAMQOL, Family Caregiver QoL questionnaire; HADS, Hospital Anxiety and Depression Scale questionnaire; HF, heart failure; MLHFQ, Minnesota Living with HF questionnaire; pro-BNP, pro-brain natriuretic peptide; QoL, quality of life; SCHFI, Self-care of HF Index questionnaire.

these patients will start on the lower levels of the chair-based exercise or walking programme.

For caregivers a series of measures will be captured which include:

- Caregiver Burden Questionnaire—HF (CBQ-HF).[38]
- Caregiver Contribution to Self-care of HF Index questionnaire (CC-SCHFI).[37]
- Family Caregiver Quality of Life Scale questionnaire (FAMQOL).[39]
- Generic HRQoL using the EQ-5D-5L questionnaire.[35]
- Psychological well-being using HADS questionnaire.[34]

Given the nature of the REACH-HF intervention, it is not possible to blind participants or those involved in the provision of care. Researchers undertaking collection of outcome data and the statistician undertaking the data analysis will be blinded to treatment allocation in order to minimise potential bias. As part of the 4-month and 6-month data collection, the researchers undertaking collection of outcome data will confirm whether or not any inadvertent unblinding occurred during the clinic visit.

Sample size

We aim to recruit 50 patient participants (25 intervention: 25 control). This number will allow us to achieve the feasibility aims and objectives of this study, that is, an estimate of attrition (mean 20%, 95% CI of 23%), estimates of the SD of the primary and secondary outcome

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measures and sufficient numbers of patients to undertake qualitative interviews to assess feasibility and acceptability of study design and intervention. It is estimated that a total of 216 patients would be needed for a definitive trial to detect a clinically meaningful between group difference in the primary outcome of MLHFQ (for details of this sample size calculation, see ref. [12]). No sample size calculation has been applied to the caregiver participants. A previous RCT in CR indicates a ratio of caregivers to patients of 0.6–0.7:1.0,[40] therefore it is expected that between 30 and 35 caregivers will be recruited in this pilot.

Trial data collection

Trial data are collected from trial participants (patients and caregivers) during three clinic visits (at baseline, 4 and 6 months). In order to encourage participant retention and completeness of data, participants may claim travel expenses associated with clinic visits and are provided with postage-paid envelopes to return questionnaires by post. Participants who are unwilling or unable to travel to research assessments or accommodate home visits are excluded at the point of consent.

At the baseline clinic visit, after written informed consent has been obtained by the principal investigator or authorised delegate, the following information will be collected:

- medical history (including comorbidities (number and severity scored with Charlson comorbidity index), New York Heart Association class, HF aetiology, concomitant HF medication and presence of implantable HF devices);
- healthcare resource usage over the prior 6 months;
- sociodemographic information (ie, date of birth, ethnicity, weight, employment status, education level, smoking status).

Participating patients will be asked to:

- complete a booklet comprising the primary and secondary outcome questionnaires;
- perform an incremental shuttle walking test;
- undergo echocardiography examination at rest;
- provide two blood samples (~4 mL blood sample for measurement of NT pro-BNP level and ~4 mL for the analysis of bloodborne biomarkers);
- wear a wrist-worn accelerometer for 8 days.

Participating caregivers will also be asked to provide sociodemographic information (ie, age (date of birth), ethnicity, weight, employment status, education level, smoking status) and to complete a booklet comprising the caregiver outcome questionnaires.

At the 4-month and 6-month clinic visits investigators will record details of any changes to patients' HF medication or implantable cardiac devices, details of any hospitalisations and healthcare resource usage since the previous visit. Investigators will also check that participating patients have not developed contraindications to exercise testing before conducting the incremental shuttle walking tests. The echocardiography examinations at rest will be conducted at baseline and 6 months, unless an appropriate echocardiography examination has been conducted within 2 weeks prior to the clinic visit, and the patient agrees to the data being used for the study. Echocardiographic measurements will include diastolic and systolic parameters. Blood samples collected for determination of NT pro-BNP levels) will be dispatched to a central laboratory (Royal Cornwall Hospital NHS Trust). Blood samples collected for the analysis of bloodborne biomarkers will be analysed at the recruiting site. Biomarkers of distinct mechanisms that contribute to the pathophysiology of HF will be measured (growth differentiation factor 15 (GDF15); ventricular remodelling (soluble ST2); myonecrosis (highly sensitive troponin T (hsTnT)) and wall stress (NT-pro-BNP)).[41] Accelerometer devices will be worn for 8 days then returned by participants using postage-paid to the CTU for data extraction. Participant safety will be monitored through recording, reporting and review of all serious adverse events collected from baseline until final follow-up visit.

Data collected at clinic visits will be recorded on study-specific case report forms (CRFs) by the research team at each site. Completed CRFs will be checked and signed at the research sites by a member of the research team before being sent to the CTU. Original CRF pages and completed questionnaire booklets will be posted to the CTU at agreed time points for double-data entry in to the study database. Accelerometer data will be imported directly into the study database. All forms and data will be tracked using a web-based trial management system. Double-entered data will be compared for discrepancies according to a data management plan held in CTU. Discrepant data will be verified using the original paper data sheets.

Separate participant contact details will be retained for the purpose of managing intervention delivery and follow-up interviews. Investigators will ensure that the participants' anonymity is maintained on all other documents. Within the CTU, anonymised and identifiable study data will be stored separately, to prevent the identification of participants from research records, in locked filing cabinets within a locked office. Data will be collected and stored in accordance with the Data Protection Act 1998. Electronic records will be stored by the CTU in a secure and Secure Sockets Layer (SSL) encrypted web-based database maintained by the University of Plymouth with daily back up. Direct access to the trial data will be restricted to members of the research team and the CTU, with access granted to the sponsor on request and overseen by the CTU data manager and trial manager.

Process evaluation

Alongside the main patient and carer follow-up, a process evaluation will be completed using a nested mixed methods design to assess the following elements of the intervention.

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Intervention fidelity

A 13-item intervention fidelity checklist developed and piloted as part of the REACH-HF programme will be used to assess fidelity of delivery of the intended intervention processes.[12] The checklist is based on a Dreyfus Scale which has been used to assess clinical competence in the delivery of psychological therapies,[42] as well as in other self-care behaviour interventions.[43] All contacts (telephone and face to face) between intervention facilitators and six purposively sampled patient will be audio recorded by intervention facilitators and then reviewed and coded (using the fidelity checklist) by two independent researchers. This will clarify how well intervention components are delivered and received and will also allow researchers to describe variability in fidelity of delivery across patients and facilitators.

Acceptability of the intervention to HFpEF patients, their caregivers and facilitators

A series of semistructured individual interviews will be conducted with ~15 patients and their caregivers (where available) at the end of the intervention delivery period (~4 months from baseline visit). Using an interview schedule, the researcher will explore participants' experiences of the REACH-HF intervention and the acceptability of study participation. Purposive sampling will be used to ensure maximal variation in relation to clinical and demographic characteristics, caregiver involvement and engagement with the intervention.

The facilitators who have delivered the intervention will be interviewed individually by either the intervention development team or the Dundee-based researcher after the majority of participants have completed the intervention. A topic guide has been developed for this study, informed by the REACH-HF feasibility study.[44]

In addition, all participants (patients and caregivers) will be invited to complete a 'Trial Process' questionnaire at the end of their participation in which their views and comments on various aspects of the study will be captured.

A facilitator contact sheet will be completed for each patient contact to record basic attendance at each contact and contact time. The contact sheet will also ask the intervention facilitator to make notes immediately after the patient contact about what was covered, what went well in the session; what worked less well; what s/he could have performed differently and what we could improve about the intervention materials or the delivery process. The importance of completing these sheets was emphasised in the facilitator training session.

Economic evaluation

In this pilot study, we will estimate the additional resource use and related costs, associated with the delivery of the intervention, and assess the methods used to collect participant level data on healthcare services used and other related resource use. Data on these areas of resource use will be collected within trial, using reported input by intervention facilitators, and self-report (interviewer administered) participant resource use questionnaires (eg, primary and community healthcare, hospital-based healthcare). In any future economic evaluation, alongside a full trial, the primary perspective of the evaluation is expected to be that of factors related to collecting clinical and resource-use data within the trial will be evaluated. The primary perspective will be that of the UK NHS and personal social services (consistent with the reference case approach used in the UK by NICE),[45] with a broader perspective, addressing partial patient and societal resource use, explored in sensitivity analyses. That will therefore be the guiding perspective for data collection in the current pilot study perspective. Informed by CRFs, methods for estimating the resource use and costs associated with delivery of the intervention will be developed and tested. Alongside the data collection on resource use, consideration will be given to outcomes, including the anticipated primary economic end point of the EQ-5D-5L[35] and to the development of the framework for future within trial and longer term cost-effectiveness analyses.

Data analysis

All analyses, quantitative and qualitative, will be conducted according to best practise and reported in accordance with Consolidated Standards of Reporting Trials (CONSORT) guidelines for reporting of clinical trials and appropriate guidelines for reporting process evaluations and qualitative research.[46–48]

Pilot study outcomes

Given the feasibility objectives of this pilot study, the focus of data analysis will be descriptive. The participant flow will be summarised using the CONSORT flow diagram, reporting detailed recruitment and attrition rates (treatment and study drop-outs) with 95% CIs. All protocol deviations along with reasons and number of missing items on questionnaires will be reported.

Intervention fidelity checklist scores will be summarised using simple descriptive statistics (means and SDs) and collated as an overall total score, individual item scores and (total and item) scores for each facilitator. Examples of good practice will be flagged, transcribed and extracted as audio clips or transcripts (with the facilitator's permission) to inform future training. Checklist items will be scored for each recording.

Participant interview data will be analysed using descriptive, thematic analysis to identify salient themes from the interview transcripts. The data will be analysed with the aim of addressing the study aim and the study objectives, that is, to seek the views of patients, caregivers and facilitators on the acceptability of intervention manual and/or the intervention delivery processes and to collect the views of patients and caregivers on the study design.

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Primary, secondary and economic outcomes

Baseline sociodemographic and health-related variables will be reported descriptively by treatment arm. For all the primary and secondary outcome variables, we will report descriptive statistics only (total number of observations available, with mean and SD, or median and IQR, as appropriate), at baseline, 4-month follow-up and 6-month follow-up. All analyses will be conducted by a statistician who is blinded to treatment allocation and will be performed on an intention-to-treat, complete case basis. Given the pilot nature of the study, we will report levels of missing of data (and reasons for loss) but we will not undertake any imputation analyses.

While we do not seek to formally estimate cost-effectiveness in this pilot study, estimates of intervention cost will inform exploratory modelling and estimates of the resources and costs needed to run a future trial. In any future definitive RCT, cost-effectiveness analysis is expected to involve within trial analysis and evidence synthesis with decision-analytic modelling, to assess the longer term consequences of the intervention (eg, changes in outcomes, events avoided, life-years and quality-adjusted life-years gained). It is expected that this modelling will use/adapt existing economic models on outcomes for HF, and the subsequent cost-effectiveness of interventions. This pilot study will be used to consider how best to construct such analyses and to develop an economic evaluation plan for any future definitive RCT.

Data monitoring and quality assurance

The site principal investigators (CCL, KS) or authorised delegate(s) will check completed CRFs for missing data or obvious errors before the forms are sent to the CTU. Data will be monitored centrally for quality and completeness by the CTU, and every effort will be made to recover data from incomplete forms where possible.

The CTU data manager will oversee data tracking and data entry and initiate processes to resolve data queries where necessary. The CTU trial manager(s) (CH and VE) will devise a monitoring plan specific to the study which will include central monitoring strategies and study site visits as appropriate. The participating site will be required to permit the CTU trial manager or deputy, or representative of the sponsor, to undertake study-related monitoring to ensure compliance with the approved study protocol and applicable standard operating procedures (SOPs), providing direct access to source data and documents as requested. All study procedures will be conducted in compliance with the protocol and according to the principles of the International Conference on Harmonisation Good Clinical Practice (ICH GCP). Procedures specifically conducted by the CTU team (eg, data management, study management and study monitoring) will be conducted in compliance with CTU SOPs.

Trial management and independent committees

Team members directly involved with the day-to-day running of the trial at site will meet regularly to discuss trial progress, teleconferencing with external members of the REACH-HF management team on a monthly basis with email and telephone exchange as necessary between. The Programme Management Group including health economics, statistics, process evaluation and patient and public representation will meet on a quarterly basis to review status of the overall programme, including trial progress.

The REACH-HF Programme Steering Committee (Chair: Professor Martin Cowie and four other independent members including a patient and public involvement representative) have formally agreed to adopt the role of Trial Steering Committee and will oversee the conduct of the trial with safety and ethics review by a fully independent Data Monitoring Committee (Chair: Dr Ann-Dorthe Zwisler and two other independent members). Evidence for treatment differences in the main efficacy outcome measures will not be monitored through review of accumulating outcome data, and no interim data analyses will be conducted.

The Trial Steering Committee and Data Monitoring Committee meet one to two times per year. Detailed descriptions of the remit and function of the oversight committees are documented in specific charters held in the Trial Master File by CTU.

The Independent Adjudication Committee (Professor Ian Squire (Chair), De Sern Lim and Dr Francisco Levya) will independently assess all hospitalisations and deaths of patient participants during the study for their relatedness to HF in accordance with the study-specific procedure.

ETHICS AND DISSEMINATION

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ICH GCP and in accordance with the Research Governance Framework for Health and Social Care, Second edition (2005). The study is sponsored by Royal Cornwall Hospitals NHS Trust (Research Development and Innovation Department, Royal Cornwall Hospital, Treliske, Truro, Cornwall, TR1 3LJ). Written informed consent will be obtained from all participants prior to study enrolment. Participants enrolled into the study are covered by indemnity for negligent harm arising from the management, design and conduct of the research through standard NHS Indemnity arrangements. The study is approved by the East of Scotland Research Ethics Service (ref 15/ES/0036). Any subsequent amendments will be made using the Integrated Research Applications System in order to maintain ethical approval and NHS permissions. Amended documents will be provided to the investigator site by CTU. In the event of changes to study design requiring

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significant amendment to the content of the participant information sheet, participants will be required to provide renewed informed consent.

The ISRCTN number was granted on 7 July 2015 following significant correspondence between the Trials Unit, the permissions team in Scotland and the South West Peninsula CRN team, with regard to the ISRCTN registration. The first participant was randomised on 2 July 2015 in good faith by the trial team following green light from the sponsor. It took 1 month to ascertain that the UKCRN was unable to support an ISRCTN registration and that the sponsor would need to apply and pay independently, as the study was not going to be network adopted. The 5-day period between randomisation and ISRCTN registration accounts for 1 patient out of a planned 50 patient sample size. No changes to any trial procedures or protocol were made during or as a result of this recruitment period and the trial protocol was already registered with the Trust, sponsor and ethics committee.

Findings will be published in peer-reviewed journals and presented at local, national and international meetings and conferences to publicise and explain the research to clinicians, commissioners and service users. A final report will be submitted to the National Institute for Health Research which will be available on request to any interested others.

CONCLUSIONS

This pilot trial aims to assess the feasibility of a definitive trial of the clinical effectiveness and cost-effectiveness of the REACH-HF intervention (a manualised home-based rehabilitation intervention designed to improve self-care and HRQoL) in patients with HFpEF and their caregivers.

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Contributors The REACH-HFpEF pilot trial was designed by CCL, KS, HMD, RST, JW, KJ, RD, PD, JA, RVL, SS, CA, NB, CG, CJG, KP and SB. KJ, RST, RD and HMD developed the original idea for REACH-HFpEF. CCL, KS, HMD, RST, KJ and RD developed the protocol for the mechanistic substudy elements. VE undertook the first draft of the manuscript that was then edited by CH, RST and HMD. All authors provided critical evaluation and revision of the manuscript and have given final approval of the manuscript accepting responsibility for all aspects.

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Competing interests All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: RST is the lead for the ongoing portfolio of Cochrane reviews of cardiac rehabilitation. RST and HMD are named topic specific experts for the NICE clinical guidelines update in heart failure. HD is an ordinary member of the British Association for Cardiovascular Prevention and Rehabilitation (BACPR) council.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Individual participant data will be made available as soon as reasonably possible after the end of the research project on a controlled access basis. Data requesters may make an application to the corresponding author for access to the data, with supporting documentation describing proposal for use. Any access granted will be subject to a Data Use Agreement.

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