RANDOMISED CONTROLLED TRIAL OF A FACILITATED HOME-BASED REHABILITATION INTERVENTION IN PATIENTS WITH HEART FAILURE WITH PRESERVED EJECTION FRACTION AND THEIR CAREGIVERS: THE REACH-HFpEF TRIAL

REACH-HFpEF

Protocol Version:	Version 2.1
Date:	15th December 2021
REC Reference Number:	21/WS/0085
Sponsor's Protocol Number:	GN19CA434
Sponsor:	NHS Greater Glasgow & Clyde
Funder:	NIHR HTA Programme

This protocol has regard for the HRA guidance.

RESEARCH REFERENCE NUMBERS

IRAS Number:	298247
ISRCTN Number / Clinical trials.gov Number:	ISRCTN47894539
SPONSORS Number:	GN19CA434
FUNDERS Number:	NIHR130487

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the trial publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature: Date:

..../...../.....

Name (please print):

.....

Position:

.....

Co-Chief Investigator:

Signature: Date:

..../...../.....

Name: (please print):

.....

Co-Chief Investigator:

Signature: Date:

..../...../.....

Name: (please print):

.....

Statistician:

Signature: Date:

..../...../.....

Name: (please print):

.....

Position:
.....

KEY TRIAL CONTACTS

Chief Investigators	Professor Rod Taylor Chair of Population Health Research MRC/CSO Social and Public Health Sciences Unit & Robertson Centre for Biostatistics University of Glasgow Rod.Taylor@glasgow.ac.uk Professor Chim Lang Medicine and Professor of Cardiology School of Medicine University of Dundee C.C.Lang@dundee.ac.uk
Trial Managers	Mrs Emma Burrell Project Manager Robertson Centre for Biostatistics University of Glasgow Ms Elizabeth Thomson Senior Project Manager Robertson Centre for Biostatistics University of Glasgow Ms Claire Brunton Project Manager Robertson Centre for Biostatistics University of Glasgow REACH-HFpEFproject@glasgowctu.org
Sponsor	Dr Pamela Sandu Research Co-ordinator NHS Greater Glasgow and Clyde Research and Innovation Pamela.Sandu@ggc.scot.nhs.uk
Funder(s)	National Institute for Health Research Health Technology Assessment (HTA) Programme

Clinical Trials Unit	Glasgow Clinical Trials Unit (UKCRC Registration Number 16)
Statistical lead	Professor Alex McConnachie Professor of Clinical Trial Biostatistics Robertson Centre for Biostatistics University of Glasgow Alex.McConnachie@glasgow.ac.uk
Health economics lead	Professor Emma McIntosh Professor of Health Economics Health Economics and Health Technology Assessment (HEHTA) University of Glasgow Emma.McIntosh@glasgow.ac.uk
Process evaluation leads	Dr Julia Frost Senior Lecturer Health Services Research University of Exeter College of Medicine and Health J.Frost@exeter.ac.uk Prof Colin Greaves Professor of Psychology Applied to Health School of Sport, Exercise and Rehabilitation Sciences University of Birmingham c.j.greaves@bham.ac.uk
Patient and Public Involvement Lead	Dr Tracy Ibbotson Research Co-ordinator (General Practice & Primary Care) Institute of Health and Wellbeing University of Glasgow Tracy.Ibbotson@glasgow.ac.uk

i. List of contents

ii. List of abbreviations

Define all unusual or 'technical' terms related to the trial. Add or delete as appropriate to your trial. Maintain alphabetical order for ease of reference.

AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
HF	Heart Failure
HFpEF	HF with preserved ejection fraction
HFrEF	HF with reduced ejection fraction
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
GCTU	Glasgow Clinical Trials Unit
NHS R&D	National Health Service Research & Development
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RCB	Robertson Centre for Biostatistics
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SSI	Site Specific Information
TMF	Trial Master File

TMG	Trial Management Group
TOG	Trial Operational Group
TSC	Trial Steering Committee

iii. Trial summary

Trial Title	Randomised controlled trial of a facilitated home-based rehabilitation intervention in patients with heart failure with preserved ejection fraction and their caregivers	
Internal ref. no. (or short title)	REACH HFpEF	
Trial Design	Multicentre parallel two group randomised (1:1 patient allocation) superiority trial with nested process and health economic evaluations and an internal pilot phase	
Trial Participants	520 patients with HFpEF and their caregivers	
Intervention	REACH-HF home-based rehabilitation intervention plus usual care	
Control	Usual care alone	
Planned Sample Size	520 (across 20 UK sites)	
Treatment duration	12 weeks	
Follow up duration	4 and 12 months post randomisation	
Planned Trial Period	44 months	
	Objectives	Outcome Measures
Primary	To compare the primary outcome of disease-specific health-related quality of life at 12 months follow-up between HFpEF patients in intervention and control groups	Change in Minnesota Living with Heart Failure Questionnaire (MLWHF) score from baseline to 12 months
Secondary	To compare secondary outcomes of patients with HFpEF and caregivers in the intervention and control groups at 4 and 12 months **Patients**	

	a) Exercise capacity	Incremental Shuttle Walk test (performed if COVID-19 restrictions permit participant to attend clinic visit)
	b) Psychological wellbeing	Hospital Depression & Anxiety Scale (HADS)
	c) Level of physical activity	Accelerometry (GENEActiv)
	d) Generic health-related quality of life	EQ-5D-5L and Short-Form-12
	e) Disease specific health-related quality of life	Kansas City Cardiomyopathy Questionnaire
	f) Self-management	Self-care of Heart Failure Index (SCHFI) & Self-efficacy for key-behaviours questionnaire
	g) Frailty	Clinical Frailty Scale
	h) Prognostic biomarker	NT-proBNP
	i) Clinical events	Deaths & hospital admissions (all-cause & heart failure-specific)
	j) Adverse events	Serious adverse events
	Caregivers	
	a) Health-related quality of life	EQ-5D-5L & Family Caregiver Quality of Life Scale questionnaire (FAMQoL)
	b) Psychological wellbeing	Hospital Depression & Anxiety Scale (HADS)
	c) Self-management	Caregiver Contribution to Self-care of HF Index questionnaire (CC-SCHFI)
	d) Burden	Caregiver Burden for HF Questionnaire (CBQ-HF)

iv. Role of trial sponsor and funder

NHS Greater Glasgow and Clyde (GG&C) Health Board will be the trial sponsor.

This trial is funded by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (Ref: NIHR130487). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

The study will be conducted in compliance with the principles of the Declaration of Helsinki, the principles of Good Clinical Practice (GCP) and in accordance with all applicable regulatory requirements.

v. Roles and responsibilities of trial management committees/groups & individuals

The overall delivery of the trial according to the scientific protocol, budget, and time will be the responsibility of the trial Co-Chief Investigators and communicated directly through regular written reports to the funder, NIHR. The management structure of the trial is shown in Figure 1.

Trial Management Group (TMG)

The Trial Management Group (TMG) will consist of an operational group where the procedural and methodological aspects of the trial will be discussed. The TMG will be chaired by the co-Chief Investigators and will include: Trial Manager(s), Trial Administrator, Trial statistician (Professor Alex McConnachie), Trial Health Economist (Professor Emma McIntosh), Trials Process Evaluation co-Leads (Dr Julia Frost & Professor Colin Greaves), Patient and Public Involvement Advisory Group Lead (Dr Tracy Ibbotson), other Co-applicants (Prof John Cleland/Dr Hayes Dalal/Prof Kate Jolly/Prof Christi Deaton/Prof Patrick Doherty/Dr Aynsley Cowie), collaborators (Prof Melvyn Hillsdon, Louise Taylor, Prof Mark Petrie, Prof Iain Squire, Dr Zaheer Yousef, Nick Hartshorne Evans), Sponsor representative (Dr Pamela Sandu) and University of Glasgow representative (Claire Munro or David Innes).

The TMG will normally meet on a quarterly (~12 weeks) basis and receive reports from the Trial Operational and Patient and Public Involvement Groups. Issues arising from the TMG will be referred to the Trial Steering Committee.

Trial Operational Group (TOG)

The Trial Operational Group (TOG) is a subgroup of the TMG consisting of the co-Chief Investigators, Trial Manager(s), and Trial Administrator who are involved in the day-to-day running of the trial. The TOG will normally meet on a 2-weekly basis and invite other TMG members as appropriate. The TOG will receive regular reports from the trial sites with details of progress including summary of screening logs, numbers recruited and completing outcome assessment, and trial protocol deviations.

Trial Steering Committee (TSC)

In accord with NIHR guidance, the role of the TSC is 'to provide overall supervision of the trial on behalf of the Project Sponsor and Project Funder and to ensure that the project is conducted to the rigorous standards set out in the Department of Health's Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice.'

Proposed main roles of the TSC will include:

- Major decisions such as a need to change the protocol for any reason
- Monitoring and supervising the progress of the trial
- Reviewing relevant information from other sources
- Considering recommendations from the DMC
- Informing and advising on all aspects of the trial

The TSC will consist of a group of independent members that include trial methodologist(s) (e.g., statistician or health economist), clinician(s) and at least one individual who is able to contribute a

patient and/or wider public perspective, with an independent Chairperson. Ideally, the TSC meetings should invite observers including a representative from the research network. The Sponsor representative and Trial Statistician will attend TSC meetings. Meetings will normally be attended by members of the TOG (Trial co-Chief Investigators, Trial Manager). The minimum quoracy for the TSC meeting to conduct business will be 67% (two thirds) of the independent appointed members.

The TSC will have its own charter outlining the roles and responsibilities of its members, as well as meeting and reporting formats. TSC meeting minutes will be sent to all members, the sponsor, and the funder and will be retained in the study master file.

Data Monitoring Committee (DMC)

The proposed roles of the DMC are:

- Ensuring the safety, rights, and wellbeing of the trial participants
- Access to the unblinded comparative data (where deemed appropriate)
- Considering the need for any interim analysis
- Advising the TSC regarding the release of data and/or information
- Monitoring serious adverse events data and any other data deemed relevant to make recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue
- Advising the TSC as to whether there is evidence or reason why the trial should be amended or terminated.

DMC membership will consist of 3-4 independent members who are experts in the field, e.g. a clinician with experience in the relevant area and an expert trial statistician.

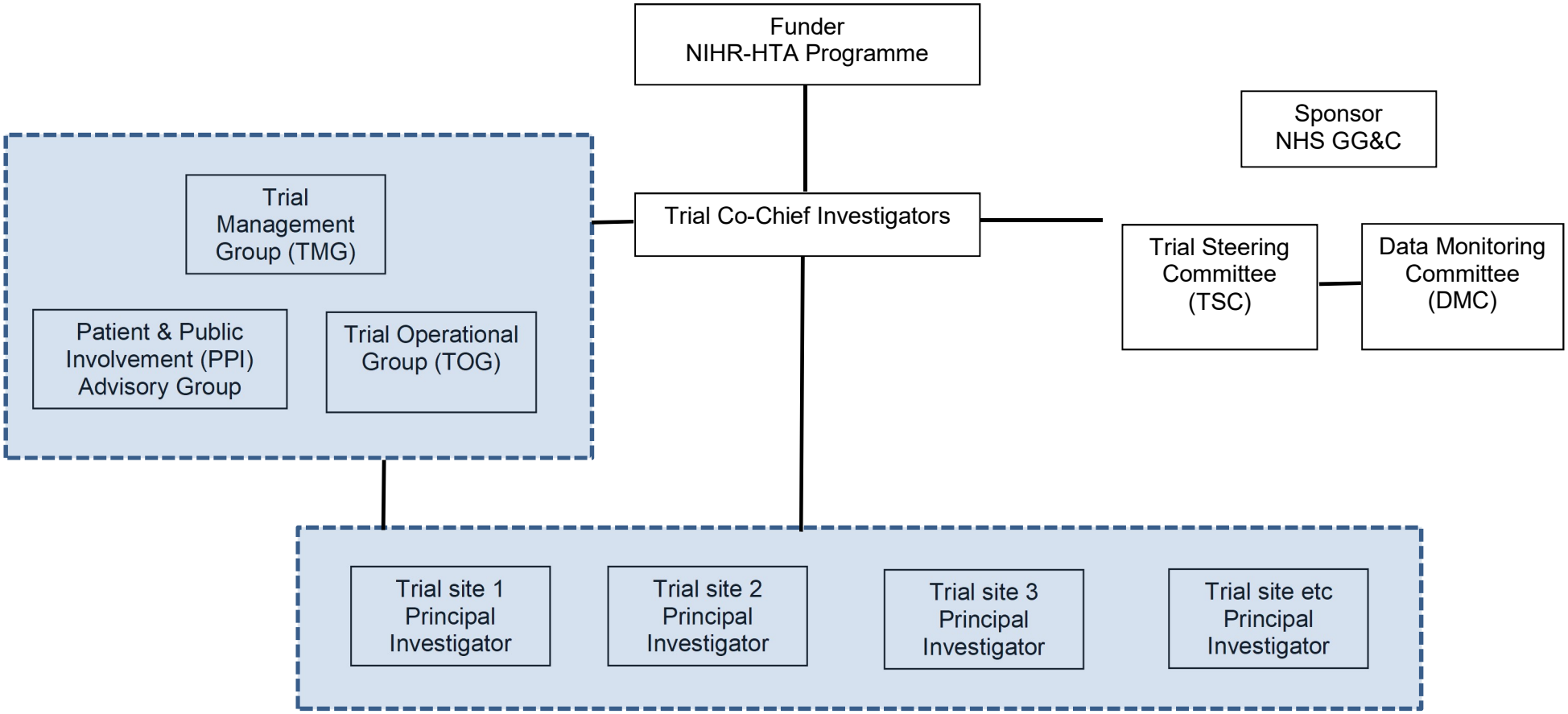
The DMC will have a formal charter outlining the responsibilities of DMC members, GCTU and the sponsor. The trial co-Chief Investigators, Trial Manager, Trial Statistician and Sponsor representative will attend open elements of DMC meetings. DMC meeting minutes will be made available to the funder.

The TSC and DMC will meet separately (in person or online) at regular intervals - at least once per year. DMC meetings will be timed to ensure that reports can be fed into the TSC. Reports will be prepared by the Robertson Centre for Biostatistics (RCB, part of the Glasgow Clinical Trials Unit). Report formats will be agreed at the first TSC and DMC meetings.

Patient and Public Involvement (PPI) Advisory Group

A PPI group will be established for this trial: 4 patients with lived experience of HFpEF and their partners/carers. These patients are usually managed and monitored in general practice [12]. We are working with the cardiovascular PPI group based in the Queen Elizabeth University Hospital, Glasgow, and will develop a method for recruiting local PPI advisors from existing cardiovascular PPI groups.

Figure 1. Trial Management/Organisation summary

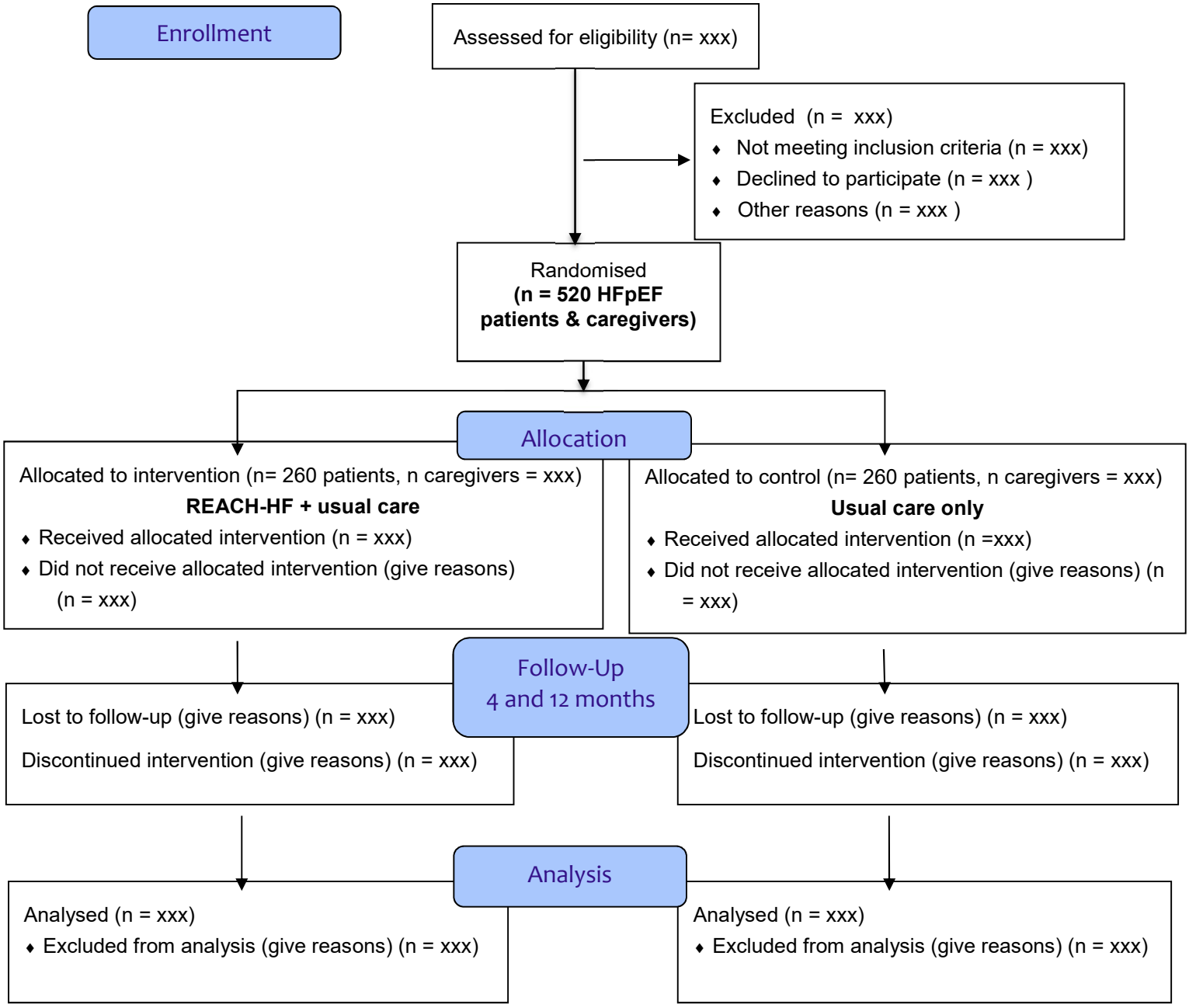


vi. Protocol contributors

The protocol has been written by the Co-Chief Investigators, Professor Rod Taylor and Professor Chim Lang, with extensive input from the Process Evaluation Leads (Dr Julia Frost and Professor Colin Greaves), the Health Economics Lead (Professor Emma McIntosh), the Statistician (Professor Alex McConnachie), the Patient and Public Involvement Lead (Dr Tracy Ibbotson) and the Trial Operational Group. The protocol will be agreed with the TMG.

vii. Key words:	Heart Failure
	Preserved Ejection Fraction
	Cardiac Rehabilitation
	Exercise training
	Randomised controlled trial
	Complex interventions
	Cost-effectiveness
	Process evaluation

ix. Consort flow diagram



1 BACKGROUND

In the United Kingdom (UK), approximately one million people have heart failure (HF) - a condition resulting in relatively inefficient cardiovascular functioning, often presenting with debilitating symptoms of fatigue, shortness of breath (dyspnoea), reduced exercise capacity, and a potentially dangerous accumulation of fluid in bodily tissues [1]. HF has a significant negative impact upon patients' health-related quality of life and often results in unplanned hospital admissions [2,3]. Currently, HF costs the National Health Service (NHS) some £2 billion per year, with ~70% of these costs being as the result of hospitalisations [2,4].

There are two main phenotypes of HF: (1) HF with preserved ejection fraction (HFpEF) and (2) HF with reduced ejection fraction (HFrEF) [3,5]. There are several differences between the two phenotypes in their underlying pathophysiology, associated risk factors and long-standing management strategies. Whereas HFrEF patients are characterised by the presence of depressed left ventricular systolic function ('reduced ejection fraction'), patients with HFpEF are traditionally diagnosed excluding other, more specific cardiac and non-cardiac causes of dyspnoea with normal ejection fraction. HFpEF patients are more likely to be older, female and have multimorbidity, typically with co-existing hypertension, diabetes mellitus, atrial fibrillation, and coronary artery disease [5,6]. In contrast to HFrEF, the prevalence of HFpEF (currently ~50% of all HF) has increased in the past decade and is projected to continue to increase relative to the aging population, with greater cardio-metabolic comorbidities [5].

The health burden of HFpEF on patients, caregivers, the health system and the broader economy, is substantial – with markedly reduced ability to perform activities of daily living, very poor health-related quality of life, high rates of unplanned hospitalisations, high costs and premature mortality [1-6].

In contrast to HFrEF, where evidence-based therapies result in improved life expectancy and health-related quality of life, there is an absence of evidence-based treatment options for HFpEF [3,6]. Drugs or devices shown in trials to be effective for HFrEF, have not successfully altered prognosis in individuals living with HFpEF [7-9]. There has been no large-scale clinical trial that has shown treatment benefits that modify the natural degenerative course of HFpEF or reduce mortality. The 400,000 HFpEF patients in the UK are managed in primary care, without access to the specialist HF treatments and services available to people with HFrEF [10-12]. As a result, HFpEF patients and their caregivers are effectively living with untreated HF, with potentially devastating consequences for patients and their families. Therefore, there is an urgent need for treatments and therapies for HFpEF to be individualised, which may include, for example, tailored programmes of exercise-based cardiac rehabilitation.

2 RATIONALE

2.1 Why this research is important for the public/patients/healthcare services

National Institute for Health and Care Excellence (NICE) guidance states that access to evidence-based therapy that can improve the wellbeing of people with HFpEF and reducing risk of hospitalisation is a national priority for the NHS [4]. Fully powered clinical trials of innovative therapies for HFpEF are therefore urgently needed if such targets are to be met.

A highly promising non-pharmacological therapy for individuals with HFpEF is exercise-based cardiac rehabilitation (CR). The British Association for Cardiovascular Prevention and Rehabilitation (BACPR) recommends that CR programmes should be comprehensive and include exercise, education on risk factor management plus counselling and psychological support [13]. The Cochrane review of randomised controlled trials of exercise-based CR provides strong evidence of the benefits of CR for people with HFrEF that include a reduction in all-cause hospitalisation, HF-specific hospitalisation and a clinically meaningful improvement in patient quality of life [14]. Furthermore, exercise-based CR for HFrEF has been shown to be highly cost effective [15]. The evidence base for the impact of CR on mortality outcomes is equivocal; however, the most recent National Heart Failure Audit demonstrated 12% lower mortality at one year in those individuals offered CR [2].

Faced with the high unmet need for effective interventions in HFpEF, NICE and Scottish Intercollegiate Guidelines Network (SIGN) have extrapolated the strong evidence for rehabilitation in HFrEF to HFpEF [4,16]. Both guidelines have not excluded HFpEF from their recommendation to receive rehabilitation. Whilst it may seem rational to directly apply the positive outcomes of exercise-based CR for HFrEF to HFpEF and simply make the therapy available for all HF patients, evidence from trials of all drugs and devices tested so far in HFpEF show that treatments that work in HFrEF cannot be directly translated to HFpEF [6-9]. Importantly, actual clinical practice reflects the inadequacy of this evidence base.

In December 2019 we undertook an email survey of the British Association for Cardiovascular Prevention and Rehabilitation (BACPR) membership. This survey (~100 respondents) indicates that <5 percent of all HF patients receiving CR in last 12 months had HFpEF. National Institute for Cardiovascular Outcomes Research (NICOR) data provided in January 2020 indicated that 978 (9.8%) had been referred for CR from a total of 9,928 HFpEF patients who had survived to hospital discharge in England and Wales.

The Rehabilitation EnAblement in CHronic Heart Failure (REACH-HF) is a home-based CR intervention that has been developed for people with HF and their caregivers with the aims of improving health related quality of life and functionality and lowering risk of hospitalisations [17]. The details of a pilot trial testing the feasibility of the REACH HF intervention in people with HFpEF are outlined in the 'Existing Evidence' section below [18,19].

An editorial in the *Journal of the American College of Cardiology: Heart Failure* in November 2019 called for a fully powered trial in order to provide the definitive evidence required to inform clinical policy and practice on the role of exercise-based CR for people with HFpEF who currently have no access to evidence-based treatments [20].

2.2 Existing evidence

In contrast to the neutral outcomes of device and drug trials in the HFpEF population, there is promising evidence indicating the potential for exercise-based CR to benefit people with HFpEF [14,19,26]. However, uptake of CR (which is predominantly centre-based) is relatively poor, with less than 5000 individuals offered CR in 2018-2019 attending at least one CR session, and 76% of these

individuals completing the programme (personal communication with Prof Patrick Doherty, Director of the British Heart Foundation National Audit of Cardiac Rehabilitation (NACR), 17th September, 2019). Many people with HF can find it difficult to get to hospital where exercise-based CR is traditionally delivered, because of their illness [21-23]. A dislike of group-based exercise is also a contributing factor to low attendance [21]. Additionally, women, ethnic minorities and those living in rural or deprived areas or with multiple illnesses have been consistently shown to participate less in rehabilitation [23]. Increasing CR uptake is a key policy priority of the NHS Long Term Plan with an ambitious target to increase CR uptake to 85% of all eligible patients with cardiovascular disease by 2028 [24].

Delivering CR for individuals with HFpEF in a more accessible setting, such as the patient's home, offers the opportunity to increase participation. With the support of a National Institute for Health Research programme grant awarded in 2013 (RP-PG-1210-12004), our research group have designed a home-delivered, health professional facilitated, exercise-based CR intervention called Rehabilitation EnAblement in CHronic Heart Failure for people with HF and their caregivers - 'REACH-HF'. The REACH-HF intervention is a comprehensive self-management programme informed by evidence, theory and service user perspectives [17]. It comprises the 'Heart Failure Manual', a Relaxation CD, a choice of exercise (walking programme or a chair-based exercise DVD), a 'Progress Tracker' tool for patients, and a 'Family and Friends Resource' for caregivers. Participating patients and caregivers work through the manual over a 12-week period with facilitation by a trained healthcare professional (e.g. HF-specialist nurse or CR physiotherapist) using both face-to-face support and telephone contact.

We conducted a pilot trial in Tayside, Scotland, in 50 people with HFpEF randomised 1:1 to receive REACH-HF plus usual care or usual care alone [18,19]. Importantly, this study found positive (albeit unpowered) results at 6-months in favour of the REACH-HF intervention, including improvements in disease-specific quality of life (between group mean difference in Minnesota Living with Heart Failure Questionnaire (MLWHFQ) overall score: -11.5, 95% CI: -22.8 to 0.3) [19]. This is particularly promising, given that 5.0 points has been defined as a clinical meaningful difference on the MLWHFQ [25]. This pilot also demonstrated that: (1) we could successfully recruit HFpEF patients into the study; (2) the REACH-HF intervention was well received by patients, caregivers, and healthcare staff and is safe to employ in this population; (3) completion of the REACH-HF intervention by patients was excellent (92%); (4) there were high levels of participant satisfaction with the study design and procedures; and (5) there were low levels of attrition and loss to follow-up at 6-months (<10%). Our economic analysis showed that the intervention was affordable with an average cost of £363 per patient (the current NHS England CR tariff is £477 per patient). The promising effects of REACH-HF were captured by this quote from one of the pilot study participants: "…you should not underestimate the importance of this [REACH-HF programme] as a positive intervention for HFpEF patients and their caregivers" [19].

A comprehensive systematic review (of 8 small, randomised trials in 436 HFpEF patients with 4-24 week follow-up) published in 2019 also shows that exercise-based CR may improve exercise capacity (6-min walk test: mean +33.9 metres, 95% CI: +12.3 to +55.4) and quality of life (MLWHFQ mean: -9.1, 95% CI: -3.1 to 15.0) compared to usual care control [26]. However, given the limited nature of this evidence base (small short-term follow-up pilot trials), the authors of the review conclude that a

large multicentre trial with longer term follow up is needed to confirm the observed effects of exercise-based CR in HFpEF [26]. We now aim to undertake a full scale, fully powered trial to determine the effects of REACH-HF in this population and to inform future policy and NHS practice regarding the role of CR in improving care for HFpEF.

2.3 Evidence why this research is needed now

In summary, a multicentre randomised trial of REACH-HF in people with HFpEF and their caregivers is needed now because:

1. With prior NIHR funding, we have already designed a home-based rehabilitation intervention to promote physical and mental wellbeing and support self-management for people with heart failure and their caregivers - 'REACH-HF' [17]. In a pilot study we showed that people with HFpEF are willing to participate in this type of research, have their outcomes assessed, that they engaged well with the REACH-HF intervention, and that participation in REACH-HF had an indicative strong effect on health-related quality of life in this population [19].
2. There is a high unmet need for effective and cost-effective treatments for HFpEF patients [3,4,6].
3. The NHS Long Term Plan, NICE guidance and international bodies have highlighted the importance of, and urgent need to, increase the uptake of CR in individuals with HF [4,24]. Home-based CR interventions have recently been endorsed in a scientific statement by the American Association of Cardiovascular and Pulmonary Rehabilitation, the American Heart Association and the American College of Cardiology [27]. The REACH-HF home-based programme will offer an alternative option to centre-based CR and improve access to healthcare and support for those with HFpEF and their caregivers. This may potentially reduce health inequalities known to be associated with centre-based CR.
4. There is support from HFpEF patients in the UK for a definitive randomised trial of REACH-HF
5. Despite current SIGN and NICE recommendation, our email survey of BACPR membership indicates currently <5% of all HF patients who receive CR have HFpEF.

2.4 Implementation

A key issue identified in the 2019 NICE guidance for HF [4] and the NHS long-term plan is need [24] for novel models of intervention delivery in order to improve the uptake of cardiac rehabilitation. The home-based mode of delivery in REACH-HF offers the potential to overcome current barriers to CR uptake including patient travel to a rehabilitation centre.

Since the publication of the positive findings of our trial in people with HFrEF in early 2019, we have been working closely with several stakeholders including NHS England, AHSN, the CLARHCs, and BHF to actively take forward the implementation of REACH-HF. In 2019, we opened four Beacon sites (Gloucester/Belfast/London/Wirral) that are now implementing the REACH-HF intervention for HFrEF patients [28,29]. A further four Beacon sites in Scotland (Highland & Islands, Ayrshire & Arran, Lanarkshire, Forth Valley) began recruitment in February 2021 [61]. Since the closure of our NIHR Programme Grant, we established a standing REACH-HF executive group (led by Prof Rod Taylor, Dr Hayes Dalal, Prof Patrick Doherty and Prof Colin Greaves) with the central aim of continuing to drive

implementation of REACH-HF. If shown to be a clinically and cost-effective intervention for people with HFpEF, we would plan to implement the findings through this existing infrastructure.

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

Question: Is REACH-HF plus usual care superior to usual care alone in terms of improving health-related quality of life of patients with HFpEF?

Aim: To assess the clinical effectiveness and cost-effectiveness of REACH-HF plus usual care (intervention) versus usual care alone (control) in HFpEF patients and their caregivers.

3.1 Primary objective

The primary objective is to compare the primary outcome of disease-specific health-related quality of life at 12 months post-randomisation between HFpEF patients in intervention and control groups.

3.2 Secondary objectives

Secondary objectives are:

1. To check adequacy of trial recruitment in initial 6-month internal pilot period
2. To compare the following secondary outcomes between HFpEF patients in the intervention and control groups at 4 and 12 months post-randomisation:
    a. exercise capacity
    b. psychological wellbeing
    c. level of physical activity
    d. generic health-related quality of life
    e. Disease specific health-related quality of life
    f. self-management
    g. frailty
    h. prognostic biomarker
    i. clinical events: death and hospital admission
    j. adverse events
3. To estimate the cost-effectiveness of REACH-HF in HFpEF patients as incremental cost per quality-adjusted life years (QALYs) at 12-months post-randomisation;
4. To qualitatively explore the moderators and mediators of change in the primary outcome of HFpEF patients in the intervention group;
5. To qualitatively explore REACH-HF facilitators' experiences of delivery of the intervention;
6. To compare psychological wellbeing, quality of life, self-care activities and burden between caregivers in the intervention and control groups at 4 and 12 months post-randomisation;
7. To assess the fidelity of delivery of the REACH-HF intervention (to inform further future refinement/implementation in the NHS if the intervention is effective).

3.3 Outcome measures/endpoints

3.3.1 Primary endpoint/outcome

Primary outcome: MLWHFQ score (disease specific health-related related quality of life) at 12 months post-randomisation. This validated questionnaire consists of 21 items to assess the impact of living with HF on the key physical, emotional, social and mental dimensions of quality of life [30]. It provides scores for two dimensions, physical and emotional, and a total score.

3.3.2 Secondary endpoints/ outcomes

Secondary outcomes: Exercise capacity (incremental shuttle walk test) [31]; physical activity levels (accelerometry over a 9-day period, measured using the GENEActiv Original accelerometer) [32]; psychological wellbeing (Hospital Anxiety and Depression Scale (HADS) questionnaire) [33]; quality of life (generic: EuroQol EQ-5D-5L [34], Short-Form-12 (SF-12)) [35]; frailty (Clinical Frailty Scale); Self-care of HF Index (SCHFI) questionnaire [36]; Self-efficacy for key behaviours questionnaire [37]; NT-proBNP levels; and deaths and hospital admissions (with HF-relatedness determined by an independent adjudication panel).

Caregivers: Caregiver Burden for HF Questionnaire (CBQ-HF) [38]; Caregiver Contribution to Self-care of HF Index questionnaire (CC-SCHFI) [39]; Family Caregiver Quality of Life Scale questionnaire (FAMQOL) [40]; EQ-5D-5L [34]; Hospital Anxiety and Depression Scale (HADS) questionnaire [33].

All primary and secondary outcomes will be assessed at baseline (pre-randomisation) and 4 and 12 months post-randomisation. Patients will be asked at 4 and 12 months follow up if they have had any adverse events. The PIs will be asked to comply with the requirement to report Serious Adverse Events (SAEs) within 24 hours of becoming aware of the event to the Pharmacovigilance Office. Serious Adverse Events that occur during the trial will be recorded and reported to the Ethics Committee and the Data Monitoring Committee (see Section 8 – Safety Reporting).

Longer follow-up: Although outside the scope of this trial, we will seek consent from participants for longer follow-up (>12 months) of their outcomes (hospitalisation and death) using routine data. A separate funding application will be submitted for longer-term follow-up. Participants will also be asked for optional consent for an additional blood sample (approximately 4-5ml) to be taken at each visit and stored for future, ethically approved, research.

4 TRIAL DESIGN

4.1 Trial Design

Multicentre parallel two group randomised superiority trial with nested process and health economic evaluations and internal pilot phase. Given the complex nature of the intervention, it is not possible to blind participants or those involved in the provision of care beyond the point of randomisation. Researchers collecting outcome data and the statistician undertaking the data analysis will be blinded to treatment allocation to minimise potential bias.

Participants will be randomly allocated in a 1:1 ratio to either intervention (REACH-HF plus usual care) or control (usual care only) groups. Randomisation will be stratified by investigator site and minimised on investigator site, sex and ejection fraction (45-55% vs. >55%). This stratification is guided by the increasing appreciation that patients with HFpEF are phenotypically heterogenous with a possible

differential treatment effect in the study population. There are recent data showing that women and those with a left ventricular ejection fraction <55% may respond differently to treatment [8].

4.2 Health technologies being assessed

4.2.1 REACH-HF Intervention

REACH-HF is a home-based CR programme providing comprehensive self-care support to the patient and their caregiver (http://sites.exeter.ac.uk/reach-hf/). It was co-created with people living with HF and their caregivers, as well as service providers using an established rigorous intervention development framework [17] to incorporate existing evidence, clinical guidance on HF self-care, behaviour change theory and key stakeholder perspectives (patients, caregivers, service providers and experts in the field). A full description of the intervention and its development, adaption and piloting for HFpEF is published elsewhere [17-19].

This comprehensive intervention includes four core elements (see Figure 2):

- REACH-HF Manual for patients with a choice of two structured exercise programs: a chair-based exercise and a progressive walking training program. Patients are advised to exercise ≥3 times per week, starting from their own personal level and gradually building up over 2-3 months in time/distance/walking pace. Detailed exercise prescription programme shown in Appendix 3.
- Patient 'Progress Tracker' – an interactive booklet designed to facilitate learning from experience to record symptoms, physical activity, and other actions related to self-care. Patient's record: (1) how long/far they plan to walk, (2) whether they have done it, (3) how it felt to identify whether they should be moving up or down in efforts next time and (4) their weekly steps per minute (pace).
- 'Family and Friends Resource' – a manual for use by caregivers aimed to increase their understanding of HF and caregiver physical and mental wellbeing.
- Facilitation by healthcare staff (e.g., nurse, physiotherapist, exercise specialist) experienced in cardiac rehabilitation/heart failure management.

The REACH-HF programme was originally designed for patients with HFrEF. However, sections of the manual (including the medication section) has been revised to make it relevant to HFpEF patients, and an additional section on the nature of causes and treatment of HFpEF has been added.

Participating patients and caregivers will work through the self-help manual over a 12-week period with facilitation involving contact by a specially trained intervention facilitator (typically a cardiac rehabilitation nurse, physiotherapist or exercise specialist) who will help to assess patient needs and concerns, build the patient's and caregiver's understanding of how best to manage HFpEF and provide individually-tailored support based on each patient's identified needs and concerns.

Trial funding is provided for two/three healthcare professionals (with experience of cardiac rehabilitation/heart failure) from each site, who will be responsible for delivering the REACH-HF intervention, and will attend a 2-day web-based training course coordinated by the Heart Manual

Department (http://www.theheartmanual.com/About/Pages/default.aspx). This will also involve 2 days of offline reading/preparation.

The REACH-HF collaboration have recently received additional research funding from the British Heart Foundation to digitise the manuals and make them available as web-based resources for patients and caregivers (http://sites.exeter.ac.uk/reach-hf/d-reach-hf-digital-rehabilitation-enablement-in-chronic-heart-failure/). If available, during the conduct of this trial, we will seek to provide REACH-HF intervention patients with the option of paper-based and/or online REACH-HF manuals. As part of process evaluation, we will update the interview with healthcare staff, patients and caregivers to explore the impact of the addition of this delivery format.

Figure 2

4.2.2 Usual care

Both intervention and control patients will receive usual care as per clinical practice guidelines [4,41] recommendations for treatment of patients with HFpEF. This includes the screening of patients with HFpEF for both cardiovascular and non-cardiovascular comorbidities such as hypertension, diabetes mellitus, ischaemic heart disease and atrial fibrillation which, if present, should be treated with safe and effective interventions that exist to improve symptoms, wellbeing and/or prognosis. Further, diuretics are recommended in congested patients with HFpEF in order to alleviate symptoms and .signs. As part of usual care, all patients in the trial will provided with the British Heart Foundation 'Living with heart failure' booklet: https://www.bhf.org.uk/informationsupport/publications/heart-conditions/living-with-heart-failure. At the 4 and 12 month follow-up telephone call we will record any co-therapies including medications and other interventions received as part of usual care.

4.2.3 Difference between current and planned care pathways

Our choice of a usual care only comparator reflects current standard NHS care for HFpEF patients. In this trial, both the intervention and control group patients will receive usual medical management for HF according to national [4,41] and local guidelines, including specialist HF nurse care where available. The vast majority of patients with HFpEF do not have heart failure specialist input and usual care is provided through primary care or non-cardiologists [10].

In the context of this trial, we recognise that the COVID-19 pandemic (and the current policies of social distancing and shielding of high-risk patients) poses some specific challenges: (1) provision of REACH-HF intervention home visits to HFpEF patients and their caregivers by healthcare staff; (2) provision of in-person REACH-HF facilitator training (delivered by a 2-day web-based course); and (3) collection of patient and caregiver outcome data through clinic visits.

However, to mitigate these risks, since March 2020, our REACH-HF research group have been actively exploring how to best repurpose our intervention delivery. (1) We have adapted the REACH-HF protocol to allow delivery of the programme without home visits. Instead, support can be delivered entirely by telephone and/or web-based contact with facilitators. (2) We have switched the REACH-HF facilitator training to a 2-day web-based delivery. By the end of July 2020, we had run 3 x 2-day web-based events and trained 35 trainees (physios, CR nurses, HF nurses & exercise physiologists) from 17 UK and Republic of Ireland centres. (3) Baseline and follow-up questionnaires can be completed by participants online. The option to complete the questionnaires on paper will be available to those participants who are unable to use the online method.

Appendix 2 (Section 14.2) details the COVID-19 resilient model and non COVID-19 model for delivery of the intervention and data collection. Sites will be able to follow the model that is appropriate to their local policies at the time of delivery and given how the COVID-19 pandemic processes. Sites can offer the non COVID-19 model for participants who live >20 miles (>2 hour journey) from the study centre. Both delivery models will be monitored as part of the internal pilot.

As government guidance on the pandemic is continually evolving, the study team will ensure that they remain fully informed of all relevant considerations and measures, and take the utmost care to support the health and wellbeing of all those involved in the REACH-HFpEF study.

4.3 Process evaluation

i) Qualitative process evaluation

To address aims 4 and 5 above, we will undertake semi-structured qualitative interviews (at 4 and 12 months) with 30 intervention participants (20 patients and 10 caregivers) selected to represent diversity in terms of site/facilitator, sex, ethnicity, and presence of a caregiver and baseline MLWHFQ score. We will also interview a purposive sample (n=15) of REACH-HF facilitators, selected to represent diversity in site, background training (e.g. physiotherapy, cardiovascular nursing) and years of experience in CR delivery. The interviews will explore the interviewees' experiences of receiving or

delivering the intervention, ways to improve the intervention and (for facilitators) likely barriers to, and enablers of, 'real-world' NHS delivery.

Our qualitative process evaluation will explore both patients' and caregivers' experiences of participation in the intervention and explicitly examine any potential impact of caregiver presence on patient adherence to the REACH-HF intervention.

ii) Assessment of intervention fidelity

Examining the fidelity (quality) and 'dose' (quantity) of adherence to the HFpEF protocol in practice, and the extent to which the intervention reaches participants with HFpEF will be vital in establishing the extent to which the outcomes evaluation represents a valid test of the intervention theory [42]. Fidelity testing of the quality of intervention delivery will use methods developed in our prior trial. This involves applying a scoring checklist to recordings of all contacts between the patient/caregiver and the facilitator for a purposive sample of participants, including wherever possible those selected for qualitative interviews [43].

Facilitator-patient interactions (face-to-face and phone) for 60 patients will be audio-recorded (approximately 5-6 interactions taking 4-5 hours per patient). Recordings will be assessed using our previously developed and tested fidelity assessment checklist [8], a 12-item checklist focused on identifying key delivery processes, such as the use of a patient-centered communication style, making a plan of action and encouraging self-monitoring of progress (particularly with the exercise programme).

Dose of intervention received will be assessed by asking facilitators to log all contact with patients in the trial, including mode of contact (phone, face-to-face, video call), duration of contact with the patient and duration of contact with the caregiver.

4.4 Economic evaluation

All resources associated with delivering the REACH-HF home-based CR programme, including medical management, will be identified and measured. The specially trained REACH-HF intervention facilitator will keep a log of time spent with each participant. Usual care, including medical management will also be identified and measured using standard trial data capture. Further health and social care resource utilisation (including hospitalisations, GP visits, specialist visits, accident and emergency etc.) for all trial participants will be identified and measured using a standardised self-report questionnaire (successfully used in the pilot study). Estimates of informal carer time and costs will also be measured. Unit costs will then be applied to all measured resources. These health and social care costs will be combined with intervention costs (or usual care) and the total cost per participant estimated. Health related quality of life (patients and carer dyads) will be measured using the EQ-5D-5L and (SF-12) SF-6D, alternatively, to generate QALYs over the 12-month follow-up and a sensitivity analysis using the MLWHFQ mapping algorithm [44,45]. The base-case perspectives will be that of the UK NHS and Personal Social Services, with a broader perspective, addressing partial patient and societal perspectives, considered in sensitivity analyses. The economic evaluation will estimate the incremental cost per QALY associated with the REACH-HF intervention. Depending upon within trial results, a decision analytic model may be used to extrapolate the results over the longer-term.

Given the COVID-19 considerations, we will plan for offering trial participants an alternative to hospital centre visits for their outcome data collection and make available the opportunity to use paper questionnaires and/or internet-based questionnaires (dependent on patient/caregiver preference).

4.5 Study Within a Trial (SWAT)

The REACH-HFpEF Trial will act as the host trial for a SWAT being led by Trinity College Dublin. The objective of the SWAT is to determine if an evidence-based enhanced participant information sheet (PIS) impacts on recruitment and retention of caregivers to a multi-centre host trial. The design of the embedded SWAT will be a cluster randomised trial with allocation of the host trial sites to the enhanced host trial caregiver PIS (SWAT intervention group) or the standard host trial caregiver PIS (SWAT control group). Caregivers will be blinded to the allocation and will be asked to complete a SWAT Carers Survey and a PIS Satisfaction Questionnaire.

The SWAT will follow its own protocol (appendix 5) and will be subject to the same regulatory approvals as the host trial. Analysis of the SWAT will be carried out by the study team at Trinity College Dublin, led by Professor Valerie Smith.

The SWAT will be registered on the ISRCTN registry.

5 TRIAL SETTING

The study will be conducted at 20 sites across England, Northern Ireland, Scotland, and Wales. Patients will be recruited from both primary and secondary care pathways including HF registers and outpatient clinics. 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 research nurse/fellow and/or research assistant at each site, all of whom are trained in Good Clinical Practice and in the requirements of the study protocol. Baseline and follow-up patient and caregiver assessment would have normally been collected by site visits. However, in order to ensure the safety of participants and NHS research staff during the COVID-19 pandemic, these assessments will be switched to mail or web-based (patient and caregiver questionnaires) and telephone (for collection of adverse events and any changes in medical diagnoses and medication).

6 PARTICIPANT ELIGIBILITY CRITERIA

We aim to conduct a pragmatic study and recruit a population that mirrors practice.

6.1 Inclusion criteria

1. Women or men aged ≥18 years;
2. Currently symptomatic HF (NYHA Class II-IV)
3. Prescribed loop diuretics and the need for intermittent loop diuretics for the management of symptoms or signs of congestion
4. Left ventricular ejection fraction (by echocardiography or MRI) ≥45% within 12 months prior to randomisation;
5. At least one of the following risk factors:
    a. Hospital admission in last 12 months for which HF was a major contributor
    b. N-terminal proBNP >300 pg/ml for patients with sinus rhythm
    c. N-terminal proBNP >900 pg/ml for patients in atrial fibrillation
6. Informed consent to participate.

6.2 Exclusion criteria

1. Patients who have undertaken CR within the last 12 months;
2. Patients who have any contraindications to exercise training;
3. Probable alternative diagnoses that in the opinion of the investigator could account for the patient's HF symptoms (i.e. dyspneoa, fatigue), such as significant pulmonary disease (including primary pulmonary hypertension), anaemia, or obesity. Specifically, patients with the following should be excluded:
    a. Severe pulmonary disease including COPD (i.e. requiring home oxygen, chronic nebulizer therapy, or chronic oral steroid therapy or hospitalised for pulmonary decompensation within 12 months)
    b. Haemoglobin <10 g/dll
    c. BMI >40 kg/m²;
4. Patients with prior ejection fraction <45%.
5. Patients who are in a long term care establishment or who are unwilling to travel to research assessments or accommodate home visits.
6. Patients who are unable to understand the study information or unable to complete the outcome questionnaires.
7. Patients judged to be unable to participate in the study for any other reason (e.g. psychiatric disorder, diagnosis of dementia, life-threatening co-morbidity).

Participating caregivers will be aged 18 years or older and providing unpaid support to patients.

7 TRIAL PROCEDURES

A schedule of procedures is included in Appendix 1.

7.1 Recruitment

Patients will be identified from both primary and secondary care. Patients attending outpatient clinics, those who have attended outpatient clinics, outpatient echocardiograms and prospective admissions with signs of symptoms of HF will also be approached.

Except in cases where the PI contacts their own patients directly, the identification of, and initial approach, to potentially eligible patients will be made by professionals responsible for patients' care, rather than the research team members. Patients will be sent an invite letter and a copy of the patient information sheet and consent form. Patients who are interested in participation based on the initial invitation will be asked to contact the research team. Contact details will be available on the invite letter. The patient will be asked for their agreement to their GP being contacted in advance of a baseline visit, in order to obtain medical history information needed to confirm trial eligibility, in cases where medical notes within secondary care are limited. Patient approach letters will undergo Research Ethics Committee review and approval prior to use.

Eligible patients with HFpEF will be identified and recruited from the following primary and secondary care pathways:

1. Patients with HFpEF from a HF and/or HFpEF registry or database
2. Patients with HFpEF with prior hospitalisation for heart failure
3. Patients with HFpEF attending or having attended hospital clinics
4. Patients with HFpEF who have been or are under the HF service care
5. Patients with HFpEF in primary care
6. Patients who had been referred to HF diagnostic pathway or to hospital clinics with suspected of having HFpEF.

Our routine monitoring of recruitment will include assessment of site screening logs to obtain the breakdown of number of participants approached, participants who passed the eligibility criteria, and eligible participants who agree to randomisation.

7.1.1 Internal pilot

A 6-month internal pilot phase will be used to demonstrate acceptability and feasibility of randomisation and so recruitment commensurate with timely completion.

Based on target recruitment rate of 1.5 patients/month/site, in the pilot phase we aim to recruit 180 participants.

	Black	**Red**	**Amber**	**Green**
Fraction of target recruitment by month 12	<55%	55-69%	70-99%	≥100%
Mean site recruitment rate by month 12	<0.8	0.8	1.0	1.5
Number of sites opened*	20	20	20	20
Total number of patients recruited by month 12	<99	99	126	180

* all sites opened at month 7

Threshold actions

Green: On target to achieve sample size. Review recruitment regularly at Trial Management Group (TMG), and Trial Steering Committee (TSC) meetings.

Amber: Improvement needed to achieve target sample size. Present action plan to TSC with clear, achievable strategies to overcome identified recruitment barriers (e.g. replace non-recruiting sites). If satisfactory, TSC reassesses in 3 months, if not, refer to HTA.

Red: Substantial improvement needed. Present action plan to TSC with clear, achievable strategies to overcome identified recruitment barriers (e.g. replace non- and poorly- recruiting sites). If satisfactory, TSC re-assesses in 3 months, if not, refer to HTA.

Black: Very substantial improvement needed. Rescue plan to TSC, which reports to HTA. Consideration and strong likelihood of trial stopping.

7.1.2 Participant identification

To achieve adequate participant enrolment to sample size, each site can recruit through either primary or secondary care pathways, with each site having the opportunity to implement secondary strategies depending on recruitment performance that will be reviewed formally periodically by the Trial Operational Group and Trial Management Group.

Sites will recruit people with HF using their usual means of CR referral to introduce the study. This is likely to include a variety of pathways such as: people with HF referred for CR from acute or primary care; review of patients held on site HF databases; and approaching people with HF at outpatient appointments/home-visits.

Details of the study and study sites will also be listed on the CardioTrials platform (https://cardiotrials.org/). CardioTrials builds awareness of clinical trials and provides an additional avenue for patient recruitment.

7.2 Consent

The Principal Investigator (PI) will retain overall responsibility for the conduct of research at their site, which includes the taking of informed consent of participants and caregivers. They must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki. If delegation of consent is undertaken then details should be recorded within the site delegation log.

Written informed consent should be obtained from each study participant and caregiver (where applicable). The PI or designee will explain the exact nature of the study verbally and in writing (with the provision of an information sheet). Study participants/caregivers will be informed that they are free to withdraw their consent for the study or intervention at any time.

As the REACH-HF protocol has been adapted to allow delivery of the programme without home visits, consent to participate in the study may be given over the telephone. Where telephone consent has been arranged, it is the responsibility of the PI or designee to ensure that an information sheet and consent form have been given or sent to the potential participant/caregiver. The PI or delegate must ensure the patient/caregiver is granted sufficient time to consider whether to participate in the study. A telephone appointment will be arranged to discuss the information sheet and consent form in detail. If there is agreement to take part in the study, the patient/caregiver will complete their consent form; at the same time, the PI or designee will complete a separate 'confirmation of consent' form. The patient/caregiver will post the consent form to the study team (or will bring the form to their first visit). The consent and confirmation of consent forms will be scanned together and a pdf file produced for the study records, with a copy being sent back to the patient/caregiver, and a copy being inserted into the patient's notes.

Where the informed consent process can be carried out in-person, the same forms will be used.

Once consent is obtained and contact between the research team and a potential participant has been established, the participant will be issued with baseline questionnaires (by paper or online depending on preference). The local study team will arrange the baseline assessment appointment at clinic, remotely or at the participant's home where necessary.

Given the current context of the COVID-19 pandemic, we will opt to offer the option of a replacement caregiver joining the study, should the initially nominated caregiver have to withdraw (e.g. due to illness). A second caregiver would be provided with a Caregiver PIS and consented in the same way, prior to participation. Baseline data and follow-up questionnaires will not be collected for such participants.

In order to facilitate longer-term follow-up (to assess the long-term impact of the intervention), we will request consent to contact both the participant and their caregiver in the future, for an additional round of data collection, should additional funding be secured.

In addition, NHS staff from each site will be invited to take part in interviews near the end of their involvement in the delivery of REACH-HF. These will include the trained facilitators (typically HF and CR nurses or physiotherapists), as well as other key individuals involved in co-ordinating and commissioning CR (such as senior clinicians and service management). There may be some variation in participant roles due to the differing structures of local HF teams. Potential participants will be approached by the Heart Manual Department at NHS Lothian who will already hold contact details for NHS staff who attend the 2-day web-based training. Staff will be provided with an information sheet and expression of interest form. By signing and returning the expression of interest form, participants agree to be contacted by the study team at University of Exeter. Consent for participation in the interviews will be taken before the interviews take place.

A combination of convenience and purposive sampling will be used, offering the opportunity to participate to all those delivering REACH-HF, and those identified as having a key role in service planning, to ensure capture of diverse perspectives. A participant information sheet will be provided to all potential interviewees. Written consent will be obtained prior to face-to-face interviews. Where interviews are to be conducted by telephone, consent forms will be completed digitally and returned by email.

7.3 The randomisation scheme

Participants will be randomly allocated in a 1:1 ratio to either intervention (REACH-HF plus usual care) or control (usual care only) groups. Randomisation will be stratified by investigator site and minimised on investigator site, sex and ejection fraction (45-55% vs. >55%).

Randomisation will be achieved by accessing a web based randomisation system. The investigator will provide the participant identifier and the system will check the participant's eligibility from information already entered in the eCRF and, if appropriate, the randomisation group will be allocated.

The randomisation list, the program that generated it and the random seed used will be stored in a secure network located within the RCB, accessible only to those responsible for provision of the randomisation system.

7.4 Baseline data

The following baseline data will be collected:

Demographics *(patients and caregivers)*
Completed by site research staff:

- Sex
- Caregiver relationship to patient

Completed by patients and caregivers via online or paper questionnaire:

- Date of birth
- Ethnicity
- Marital/civil partnership status
- Living situation
- Smoking status
- Employment status
- Education status

Medical history *(patients)*
Where the patient is unable to attend a clinic visit, relevant medical history will be taken from the patient's medical notes by the site research staff and entered into the eCRF.

- Heart failure:
  - Date of diagnosis
  - Cause of heart failure
  - LVEF
  - NYHA functional classification
- Charlson Comorbidity Index:
  - Myocardial infarction

  - Congestive heart failure
  - Peripheral vascular disease
  - CVA or TIA
  - Dementia
  - COPD
  - Connective tissue disease
  - Peptic ulcer disease
  - Liver disease
  - Diabetes mellitus
  - Hemiplegia
  - Moderate to severe CKD
  - Solid tumour
  - Leukaemia
  - Lymphoma
  - AIDS
- Other medical history:
  - Hypertension
  - Atrial fibrillation
  - Atrial flutter
  - Arthritis (osteo or rheumatoid)
  - Depression
  - Angina pectoris
  - Chronic back pain
  - Osteoporosis
  - Valvular heart disease
- Treatments:
  - Coronary artery bypass graft
  - Coronary angioplasty
  - Implantable cardiovertor defibrillator
  - Heart transplant
  - Pacemaker

Self-reported medical history *(caregivers)*

Caregiver medical history will be completed by caregivers via online or paper questionnaire.

- Cancer
- Heart disease/disorder
- Stroke/TIA
- MS/epilepsy/paralysis/muscular dystrophy/movement disorders/MND/cerebral palsy
- Artery disease/disorder
- Diabetes
- Mental illness

Baseline medication *(patients)*

Where the patient is unable to attend a clinic visit, relevant medication history will be taken from the patient's medical notes by the site research staff and entered into the eCRF

- Beta blockers
- Angiotensin receptor blockers
- ACE inhibitors
- Mineralocorticoid receptor antagonists
- Loop diuretics
- Thiazide diuretics

- SGLT2 inhibitors
- Ivabradine
- Sacubitril valsartan / Entresto
- Digoxin
- Anti-coagulants
- Other

Measurements (patients and caregivers)
Completed by patients and caregivers via online or paper questionnaires
- Height
- Weight

Physical exam and exercise capacity *(if patient attends clinic)*
- Blood pressure
- Heart rate
- Clinical Frailty Scale (CFS)
- Incremental Shuttle Walk Test (ISWT)

Blood sample *(patients)*
Blood sample can only be taken if the participant is able to attend the clinic.
- NT-proBNP
- Blood sample (approximately 4-5ml) for future, ethically approved research, if optional consent provided.

The following blood results will be collected, if available as part of standard care
- NT-proBNP
- Haemoglobin
- Iron
- Transferrin
- Sodium
- Potassium
- Urea
- Creatinine
- Albumin
- Bilirubin

Physical activity *(patients)*
- Measured over a 9-day period by accelerometry – GeneActive. This will be posted to participants and a pre-paid return envelope provided.

Patient-reported outcomes *(patients)*
Completed by patients via online or paper questionnaires
- Minnesota Living with Heart Failure Questionnaire (MLWHFQ)
- Kansas City Cardiomyopathy Questionnaire (KCCQ) – 23 items
- Short Form 12 (SF-12)
- Self-Care of Heart Failure Index (SCHFI)
- Self-Efficacy for Key Behaviours
- Healthcare Utilisation
- EQ-5D-5L
- Hospital Anxiety and Depression Scale (HADS)

Caregiver-reported outcomes *(caregivers)*
Completed by caregivers via online or paper questionnaires

- Family Caregiver Quality of Life Scale (FAMQOL)
- Caregiver Burden Questionnaire for Heart Failure (CBQ-HF)
- Caregiver Contribution to Self-Care of Heart Failure Index (CC-SCHFI)
- EQ-5D-5L
- Hospital Anxiety and Depression Scale (HADS)
- SWAT Carers Survey
- SWAT PIS Satisfaction questionnaire

7.5 Trial assessments

7.5.1 Treatment Allocation

Randomisation *(patients)*
Intervention or Control (intervention facilitated delivery 12 weeks).

7.5.2 Follow-up (4 months post-randomisation)

Measurements (patients and caregivers)
Completed by patients and caregivers via online or paper questionnaires

- Weight

Physical exam and exercise capacity *(if patient attends clinic)*

- Blood pressure
- Heart rate
- Clinical Frailty Scale (CFS)
- Incremental Shuttle Walk Test (ISWT)

Blood sample *(patients)*
Blood sample can only be taken if the participant is able to attend the clinic.

- NT-proBNP
- Blood sample (approximately 4-5ml) for future analysis, if optional consent provided.

Medical status *(patients)*
Where the patient is unable to attend a clinic visit, changes in medical status will be collected via telephone call between the patient and site research staff and entered into the eCRF.

- To check for AEs/SAEs
- To review concomitant medications and treatments
- To review co-morbidities

Patient-reported outcomes *(patients)*
Completed by patients via online or paper questionnaires

- Minnesota Living with Heart Failure Questionnaire (MLWHFQ)
- Kansas City Cardiomyopathy Questionnaire (KCCQ) – 23 item
- Short Form 12 (SF-12)
- Self-Care of Heart Failure Index (SCHFI)
- Self-Efficacy for Key Behaviours
- Healthcare Utilisation

- EQ-5D-5L
- Hospital Anxiety and Depression Scale (HADS)

Caregiver-reported outcomes *(caregivers)*
Completed by caregivers via online or paper questionnaires
- Family Caregiver Quality of Life Scale (FAMQOL)
- Caregiver Burden Questionnaire for Heart Failure (CBQ-HF)
- Caregiver Contribution to Self-Care of Heart Failure Index (CC-SCHFI)
- EQ-5D-5L
- Hospital Anxiety and Depression Scale (HADS)
- SWAT Carers Survey
- SWAT PIS Satisfaction questionnaire

7.5.3 Follow-up (12 months post-randomisation)

Measurements (patients and caregivers)
Completed by patients and caregivers via online or paper questionnaires
- Weight

Physical exam and exercise capacity *(if patient attends clinic)*
- Blood pressure
- Heart rate
- Clinical Frailty Scale (CFS)
- Incremental Shuttle Walk Test (ISWT)

Blood sample *(patients)*
Blood sample can only be taken if the participant is able to attend the clinic.
- NT-proBNP
- Blood sample (approximately 4-5ml) for future analysis, if optional consent provided.

Medical status *(patients)*
Where the patient is unable to attend a clinic visit, changes in medical status will be collected via telephone call between the patient and site research staff and entered into the eCRF.
- To check for AEs/SAEs
- To review concomitant medications and treatments
- To review co-morbidities

Physical Activity and exercise capacity *(patients)*
- Measured over a 9-day period by accelerometry – GeneActive. This will be posted to participants and a pre-paid return envelope provided.

Patient-reported outcomes *(patients)*
Completed by patients via online or paper questionnaires
- Minnesota Living with Heart Failure Questionnaire (MLWHFQ)
- Kansas City Cardiomyopathy Questionnaire (KCCQ) – 23 item
- Short Form 12 (SF-12)
- Self-Care of Heart Failure Index (SCHFI)
- Self-Efficacy for Key Behaviours
- Healthcare Utilisation
- EQ-5D-5L

- Hospital Anxiety and Depression Scale (HADS)

Caregiver-reported outcomes *(caregivers)*
Completed by caregivers via online or paper questionnaires

- Family Caregiver Quality of Life Scale (FAMQOL)
- Caregiver Burden Questionnaire for Heart Failure (CBQ-HF)
- Caregiver Contribution to Self-Care of Heart Failure Index (CC-SCHFI)
- EQ-5D-5L
- Hospital Anxiety and Depression Scale (HADS)

End of Trial *(patients and caregivers)*

7.6 Long term follow-up assessments

Although not part of this trial, we will seek consent from participants for longer follow-up of their outcomes (hospitalisation and death) using routine data. Participants will also be asked for optional consent for an additional blood sample (approximately 4-5ml) to be taken at each visit and stored at NHS Tayside for future, ethically approved research.

7.7 Qualitative assessments

Our qualitative process evaluation will explore both patients' and caregivers' experiences of participation in the intervention and explicitly examine any potential impact of caregiver presence on patient adherence to the REACH-HF intervention. By interviewing REACH-HF facilitators, we will also explore the experiences of receiving or delivering the intervention, ways to improve the intervention and (for facilitators) likely barriers to, and enablers of, 'real-world' NHS delivery.

i) Qualitative interviews

Across the 20 sites, we will select 15-20 patients (and 10 caregivers of these same patients) for semi-structured interviews. Patients will be selected to represent diversity in terms of site/facilitator, sex, ethnicity, presence of a caregiver and baseline MLWHFQ score.

The research team will interview each of these patients/caregivers, at 4 months after the baseline visit (i.e., immediately after intervention delivery is complete) and 12 months after the baseline visit. This will allow capture of patient and caregiver narratives over time, in relation to both intervention receipt and the longer-term impact /maintenance of self-care following the intervention. We will audio or video record these interviews, which may be conducted in person (if possible) or remotely (if not). Recording will use encrypted recording methods (either via password-protected online meeting software or an encrypted voice-recorder). Written consent will be obtained prior to face-to-face interviews. Where interviews are to be conducted by video/telephone, consent forms will be completed digitally and returned by email.

Topic guides will be co-developed with our PPI advisory group for both the 4- and 12-month interviews. Interviews, where possible with patients alone, are expected to last between 30 - 60 minutes. The researcher will be mindful of the patient's symptoms, such as fatigue or breathlessness, which may be burdensome for the participant. All recorded meetings and the two interviews will be

transcribed verbatim. Thus, for each patient, transcripts of two face-to-face meetings, on average, 5 telephone meetings and two interviews will be available for analyses.

In addition, 15 REACH-HF facilitators will be invited to take part in interviews near the end of their involvement in the delivery of REACH-HF, We will sample REACH-HF facilitators to represent diversity in site, background training (e.g., physiotherapy, cardiovascular nursing) and years of experience in CR delivery. A participant information sheet will be provided to all potential interviewees. Written consent will be obtained prior to face-to-face interviews. Where interviews are to be conducted by telephone, consent forms will be completed digitally and returned by email. A topic guide will be used to structure the interview, premised on the existing literature and gaps in our knowledge about intervention delivery. These interviews, which may be conducted in person (if possible) or remotely (if not).

Potential participants will be approached by the research team and provided with an information sheet and electronic consent form. They will have the opportunity to ask questions, and an appropriate period (at least 24 hours) to decide whether to take part or not. Verbatim meeting and interview transcripts will be categorised and organised using NVIVO for Teams software. A framework analysis will be conducted, and sections of data related to the aims of this research will be assigned a code that summarizes the content either descriptively or interpretively. Codes with common features will be grouped together in emerging themes, before finally being assigned to interpretive overarching themes. Data about self-reported behaviour from the interviews will be compared with actual behaviour evident in the meeting transcripts (see below). A second qualitative researcher from the team will conduct independent analysis of a subset of the data. The researchers' reflexive memo notes will also be used to enhance the transparency and trustworthiness of the analysis.

The analysis will characterise patients' and caregivers observed and self-reported responses to the intervention and link these responses to engagement with intervention and perceived benefit, identifying interpersonal processes that shape effectiveness or ineffectiveness of the intervention. At 4 months, patients' and caregivers' engagement with, response to and use of the REACH HF Manual will be characterised and differences between patients noted. At 12 months, overall use and benefit and maintenance of self-care behaviours and coping skills will be characterised and linked to individual differences in 4-month responses. Analysis will explore both patients' and caregivers' experiences of participation in the intervention and explicitly examine any potential impact of caregiver presence on patient adherence to the REACH-HF intervention.

ii) Assessment of intervention fidelity

Facilitator-patient interactions (face-to-face and phone) for 60 patients will be audio-recorded (approximately 5-6 interactions taking 4-5 hours per patient). Recordings will be assessed using our previously developed and tested fidelity assessment checklist [8], a 12-item checklist focused on identifying key delivery processes, such as the use of a patient-centered communication style, making a plan of action and encouraging self-monitoring of progress (particularly with the exercise programme). This will be used to assess fidelity of delivery of the intended intervention processes across each patient's and caregiver's face-to-face and telephone transcripts. This will clarify how well intervention components were delivered and received and may identify components that were less well delivered. It will also allow researchers to describe variability in fidelity of delivery across patients and facilitators.

Analysis of intervention sessions (see analysis section below) will explore the extent to which facilitators adhere to the HFpEF protocol and tailor the intervention delivery to the needs of the patients and caregivers. Synthesis of the analysis of the intervention sessions and interviews will enable a qualitative evaluation of potential pathways and barriers to improvement, which will pay attention to discrepancies between expected and observed outcomes, to understand how context influences outcomes, and to provide insights to aid implementation.

REACH-HF facilitators will also be asked to complete a brief self-rated fidelity checklist after each session they deliver. This comprises questions about the same 12 main components of the treatment, and allows the facilitators to rate the occurrences of each feature (absence, minimal, some, sufficient, good, very good, excellent). An independent observer-rating is resource-intensive, while self-rated assessment may provide a pragmatic, real-world alternative to monitor delivery quality. The validity of the self-rating method will be checked by examining the relationship with observer-rated intervention fidelity. We will also explore in the qualitative interviews whether use of the checklist facilitates /encourages reflexive practice and, in doing so, quality of implementation.

Additionally, facilitators will be asked to complete a Facilitator Contact Log for each participant. This log is a one-page pro forma designed to capture time, expenditure and any other resources required for the implementation of REACH-HF, as well as any adaptations made to the intervention for individual patients. As such it will capture essential data for both the fidelity and economic analyses.

7.8 Withdrawal criteria

Participants may choose to withdraw at any time. Reasons for withdrawal will be recorded providing the participant agrees. Participants will have the option to withdraw from the intervention and/or site visits and continue with completion of the patient reported outcome questionnaires only.

7.9 End of Study Definition

The end of the study will be defined as the final piece of data being collected from the final participant follow up visit.

8 SAFETY REPORTING

8.1 Definitions

Adverse Event (AE)

Any untoward medical occurrence in a subject who has taken part in trial specific including occurrences that is not necessarily caused by or related to that trial specific procedure.

Serious Adverse Event (SAE)

Any adverse event or adverse reaction that:

a) Results in death

b) Is life threatening
c) Requires hospitalisation or prolongation of existing hospitalisation
d) Results in persistent or significant disability or incapacity
e) Consists of a congenital anomaly or birth defect
f) Is otherwise considered medically significant by the investigator
g) Important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above

Related Unexpected Serious Adverse Event (RUSAE)

Any SAE assessed by the local investigator as related to participation in the REACH-HF intervention that is thought to be unexpected; i.e. the event is not listed within the protocol and would not be expected to occur as a result of participating in the intervention or in normal clinical practice.

8.2 Recording and reporting of adverse events

Recording of adverse events

AEs occurring during this timeframe must be recorded, assessed, reported, analysed and managed in accordance with the UK Policy Framework for Health and Social Care Research and the study protocol. All AEs must be assessed for seriousness using the definitions above.

Each participant will receive a telephone call at 4 and 12 months to check for anticipated non-serious adverse events. A member of the research team will record these within the eCRF. These include:

a) Injuries, e.g. skeletomuscular sprains, falls
b) Circulatory/cardiovascular events, e.g. period of syncope

All other non-serious adverse events should be recorded within the patient's medical records

Recording of serious adverse events

Serious adverse events will be collected from the point of randomisation until the end of the study. The PI (or authorised delegate) will question patients about adverse events at the 4 and 12 month visits and is responsible for adjudging relationship to the HF Manual and study procedures.

SAEs reported by the patient will be documented in the study eCRF and in the patient's medical notes. Details will include: nature of the event, start and stop dates, severity, relationship to the REACH-HF intervention and outcome. Where multiple independent SAEs occur within the same timeframe, sites should report each event individually. All events should be followed up until satisfactory resolution.

8.3 Processing of SAEs

The eCRF will assign a unique SAE report number which site staff will be able to view and update via the eCRF as necessary. Should site staff be unable to access the eCRF for any reason at the time of recording, a paper SAE form can be completed - receipt of which will be confirmed to the reporting site

as soon as possible. If complete information is unavailable at the time of reporting, all appropriate information relating to the SAE will be entered to the eCRF as soon as possible.

Events which are both serious and related to the intervention and/or study procedures will be communicated immediately to the CIs who will be required to decide if such an event is unexpected.

8.4 Reporting to Sponsor: Related and Unexpected Serious Adverse Events

Where an RUSAE is identified, it will be reported to the Pharmacovigilance Office within 24 hours of the investigator becoming aware of the event. If necessary, a verbal report can be given by contacting the PV Office on 0141 330 4744. This must be followed up as soon as possible with a copy of the report.

If all of the required information is not available at the time of initial reporting, the investigator must ensure that any missing information is forwarded to the PV Office as soon as this becomes available. The report should indicate that this information is follow-up information for a previously reported event.

The Sponsor will carry out an assessment of expectedness prior to submission of the event to the REC and will liaise with the CI to prepare a report to the REC where applicable.

8.5 Reporting of RUSAEs to the Ethics Committee

The PV Office will report all RUSAEs to the ethics committee within 15 days of the PV office becoming aware of the event, via the 'report of serious adverse event form' for non-CTIMPs published on the Health Research Authority website: http://www.hra.nhs.uk.The form will be completed by the Sponsor and will be signed by the Chief Investigator prior to submission.

8.5.1 Processing events for independent adjudication

GCTU will maintain a record of all SAEs reported via the trial eCRF. All SAEs occurring during the trial will be subject to review by the Data Monitoring Committee.

Summary reports listing all reportable adverse events will be compiled by the GCTU and sent to the CI, Sponsor and the Data Monitoring Committee (DMC) at a frequency agreed by the DMC.

HF-related hospital admissions and HF-related deaths are clinical outcome measures to be collected during this study. Determination of whether or not a reported death or hospitalisation is related to heart failure is the responsibility of the REACH-HFpEF independent events adjudication panel.

GCTU will identify all events of patient death and hospitalisation from the SAEs reported. For each case, death certificates and hospital discharge summaries will be sourced and uploaded, with patient identifiable information fully redacted (i.e. with trial number present but other identifiers removed), to a secure area of the trial database. GCTU will review the documentation and prepare it for adjudication via the same secure area of the REACH-HFpEF database. This process will be detailed in a separate study work instruction.

9 STATISTICS AND DATA ANALYSIS

9.1 Sample size calculation

The trial sample size was calculated and reported in accordance with the DELTA2 guidance [46]. A total of 520 (260 per group) HFpEF patients is required for 90% power at 5% significance to detect a mean difference on the MLWHFQ of 5 points [25], assuming a standard deviation of 20 points [14,26], a within patient correlation of 0.59 between baseline and 6-month follow-up, and an attrition rate of 15%. A 5-point difference in MLWHFQ score represents a minimum clinically important difference. Data from REACH-HFpEF pilot trial [19] indicate that the correlation between baseline and 6 months will be at least 0.59 (estimated correlation 0.73, 90% CI: 0.59 to 0.83).

It has been agreed with the funder, that the first DMEC meeting will draw to the committee's attention the HTA feedback (therapist clustering and within person correlation coefficient on and agree a process to monitor these assumptions as the trial progresses (including any practical implications around unblinded data access).

9.2 Planned recruitment rate

9.2.1 Recruitment, internal pilot, and progression criteria

To achieve the target sample size within 18 months, we expect 20 sites to recruit an average of 2 participants per month. Retrospective audits from the HFpEF databases in two of our proposed centres (Dundee and Leicester) have shown that our proposed recruitment of 35 patients per site (i.e. 2 patients/month over 18 months) to be a very realistic and achievable target.

Our routine monitoring of recruitment will include assessment of site screening logs to obtain the breakdown of numbers of participants approached, participants who passed the eligibility criteria and eligible participants who agreed to randomisation.

9.2.2 Internal pilot

As outlined in section 9.1.1, a 6-month internal pilot phase from month 7 to the end of month 12 will be used to demonstrate acceptability and feasibility of randomisation and so recruitment commensurate with timely completion.

9.3 Statistical analysis plan

9.3.1 Statistical analysis

Data analyses will be carried out according to an a priori statistical analysis plan agreed with the TMG and TSC.

Participation from screening to completion of the final follow-up assessment will be reported. Baseline patient characteristics and outcome scores will be summarised descriptively.

The main analysis for both primary and secondary outcomes will take an intention to treat approach (according to randomised allocation) based on complete data. For continuous outcome measures, mixed-effects regression will be used with a random effect of recruiting site and adjusting for baseline outcome score and minimisation variables. Additional clustering of outcomes due to therapist effects will be accounted for in sensitivity analyses.

A number of secondary analyses will be undertaken. Patterns and reasons of missing outcome data will be assessed, and sensitivity analyses will use appropriate imputation models to assess the impact of missing data. Potential subgroup treatment effects will be explored by adding treatment-by-subgroup interaction terms to analysis models. Potential subgroups assessed will include sex, study site and participant baseline NT-proBNP levels, ejection fraction, and important markers of inequity, such as age, socio-economic status, and having a carer. Since the trial is powered to detect overall differences between the groups rather than interactions of this kind, these subgroup analyses will be regarded as exploratory. Before the start of recruitment, the TMG (with TSC approval) will be asked to define the minimum adherence to the REACH-HF intervention required to indicate compliance. Complier average causal effects analyses will be used to estimate the causal intervention effect in relation to each outcome.

Adherence will be defined using criteria adapted for the delivery processes proposed for the current study. These criteria will be developed with the Trial Management Group, building on the criteria used in the prior REACH-HF trial (Dalal et al., 2018. EJPC). Associations between physiological, cognitive and demographic factors and intervention adherence will be explored.

Estimated between-group differences will be presented using both absolute and relative measures, with associated 95% confidence intervals, where appropriate. No correction of P-values for multiplicity of testing will be undertaken. However, the analysis for the primary outcome will be performed before all other analyses and the P-values of all subsequent analyses interpreted in the context of multiple testing. No interim analyses are planned. Safety/adverse events outcomes will be reported descriptively by group.

9.3.2 Procedures for monitoring and/or minimising bias

Selection bias	We will assign trial allocations using a minimisation algorithm balancing on variables including the trial centre, sex and ejection fraction, incorporating a probabilistic element making prediction virtually impossible. A secure web system hosted by GCTU will conceal allocation.
Detection bias	Given the nature of the intervention, it is not possible to blind participants or those involved in the provision of care. HF-relatedness of mortality and hospitalisation will be assessed by independent clinical adjudicators blinded to participant allocation (see section 8.5.1). Researchers undertaking collection of outcome data and the statistician undertaking the data analysis will not deliver trial interventions and will

	be blinded to treatment allocation in order to minimise potential bias. We will ask participants not to discuss their group allocation during follow-up visits. We will record any accidental blind breaks and ask outcome researchers to guess group allocation at the end of each follow-up visit.
Selective reporting bias	We will demonstrably avoid this by registering the trial before recruitment starts and publishing the trial protocol well before recruitment closes. We will clearly describe outcomes and planned analyses, upload the statistical analysis plan to the trial registry entry before analysis commences, and we will report all data collected.
Contamination bias	It is highly unlikely that participants randomised to the control arm could have access to the REACH-HF intervention materials during the trials and no instances of this were reported in our pilot trial [19].
Intervention bias	We will assess co-interventions by participants in both groups at follow-up to check for any potential between group imbalances.
Interpretation bias	The results will be presented to the TMG and interpretation of the results agreed before the groups are unblinded.
Generalisability	We will seek to recruit sites that reflect the high prevalence of HF (see additional uploads: NIHR business intelligence team maps of HF prevalence and HF research in E&W – Scotland not available but no prevalence is high).

9.4 Economic evaluation

Following on from the results of the economic evaluation pilot study [19] a within trial cost-utility analysis will be conducted. Pilot findings revealed potential resource impacts across primary, secondary and social care as well as impacts on informal carer time and costs. These findings also revealed differential resource distributions between these sectors hence, bespoke data capture instruments will be developed to ensure a broad resource use capture across these health, social care and personal sectors. There is evidence of insensitivity of the EQ-5D-5L in patients with mild HF [47-50]. A recent study comparing the EQ-5D-5L and short-form six-dimension (SF-6D) in elderly participants with HF recommends use of SF-6D in those with milder disease and economic outcomes (utility) [59]. Therefore, we propose to use both the SF-6D (from SF-12) and the EQ-5D-5L. As recommended by NICE, economic evaluation guidance regarding the base-case perspectives will be that of the UK NHS and Personal Social Services. Further, broader perspectives, addressing patient/carer and societal perspectives will be considered in sensitivity analyses along with a sensitivity using the MLWHFQ mapping algorithm [44,45]. The economic evaluation will estimate the incremental cost per QALY associated with the REACH-HF intervention and reported in line with recommended reporting guidelines for economic evaluations [51]. Missing resource and outcome data will be handled using multiple imputation [52]. If within trial results reveal differences in quality of life, a decision analytic model will be used to extrapolate the cost-effectiveness results over the longer-term.

9.5 Process evaluation

Case-based mixed methods analysis, managed in Nvivo Pro, will enable exploration of intervention fidelity for each 'case'. This will allow for multiple case-connections and comparisons between and across subgroups with a high degree of specificity [53,54].

Overall, the process evaluation will use mixed methods at multiple case levels (patient, facilitator, centre) to test the programme theory in the HFpEF population, identifying which components and configurations are best suited to meet their needs [55,56]. The process evaluation will inform refinements of the programme theory, to optimise implementation and ensure that the essential ingredients of future interventions are better identified, interrogated and tested [57]. As our analysis progresses, we will explore best-fit of data on barriers to and enablers of implementation with an implementation strategy, such as Normalisation Process Theory [58]. This will maximise the clinical application of our research findings and enhance the capacity of staff working with HFpEF patients to implement the intervention.

Intervention fidelity data will be presented descriptively (mean scores with standard deviations or 95% CIs) and broken down by site and by facilitator (as well as the calculation of overall fidelity scores) for each checklist item.

10 DATA MANAGEMENT

10.1 Data Collection tools

Data collection will occur in accordance with the principles of Good Clinical Practice (GCP). Each member of the research team is required to be trained in GCP.

An eCRF, developed by the RCB, will capture all data required to meet this protocol's requirements. Access to the eCRF will be restricted, via a trial-specific web portal, and only authorised personnel will be able to make entries to patient data via the web portal. The PI or their designee(s) will be responsible for all entries into the eCRF and will confirm that the data are accurate, complete, and verifiable. Data will be stored in a MS SQL Server database at the RCB, University of Glasgow.

Two options for questionnaire data collection will be offered to participants: questionnaires can be completed on a paper CRF which will then be entered into the eCRF, or they can be completed electronically. Where completed electronically, data will be entered directly into a participant-facing version of the eCRF. As the eCRF will be adapted for self-completion, consent will be sought to use the participant contact details provided for re-contact to verify responses as needed.

Direct access to the RCB web portal will be granted, on request, to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

10.2 Data Validation

Where it is practical, quantitative data will be validated at the point of entry into the eCRF. Any additional data discrepancies will be flagged to the investigator and any data changes will be recorded to maintain a complete audit trail (reason for change, date change made and who made the change).

10.3 Data handling and record keeping

Trial-specific work instructions will be developed in accordance with GCTU procedures. Regular data management/cleaning will be undertaken in order to assess data quality. Quality assurance checks will be undertaken to monitor the level of missing data and the timeliness of data entry and check for illogical or inconsistent data. The research team will monitor data collection procedures, ensuring that study data entry procedures are followed.

10.4 Data security

The RCB systems are fully validated in accordance with industry and regulatory standards, and incorporate controlled access security. High volume servers are firewall protected and preventative system maintenance policies are in place to ensure no loss of service or data. Web servers are secured by digital certificates. Data integrity is assured by strictly controlled procedures, including secure data transfer procedures. Data are backed up on-site nightly and off-site to a commercial data vault weekly. The RCB has an ISO 9001 quality management system and ISO 27001 for Information Security, and is regularly inspected against the standards by the British Standards Institution.

Personal data (contact details including name, postal address and email address) will be collected for use if any of the self-completed questionnaire responses are unclear and need verified. Should participants consent to long-term follow-up of their outcomes using routine data, NHS/CHI numbers will be collected to facilitate the process in future. All personal data will be encrypted and stored on a separate secure server.

10.5 Archiving

Study documentation will be archived by the Sponsor at the end of the trial for a minimum period of 10 years.

Archiving of Site Files will also be for a minimum of 10 years from completion of the trial, and this action will be delegated to the sites in the Clinical Trial Site Agreement that will be put in place between Sponsor and Sites. Sites will be notified by the Sponsor when Site Files can be archived. Destruction of Site Files can only take place with the approval of the Sponsor.

Data sharing will be facilitated in line with sponsor policy. Consent to share non-identifiable data with other researchers will be sought from study participants (people with HF, caregivers, health professional interviewees) prior to participation.

Some study data (anonymised questionnaire data, pseudonymised interview transcripts) will be suitable for sharing for research and teaching. Other study data (fidelity data, implementation log) will be site-specific and not suitable for sharing. Pseudonymised interview data (transcripts) will be archived via the UK Data Service's (UKDS) Reshare data repository or similar, which will generate a Digital Object Identifier (DOI) for the dataset. An entry for this dataset/DOI will be created in the

University of Glasgow Enlighten: Research Data repository. At the end of the study, the study web page will give information on data sharing, including a contact email address. The study dataset will be discoverable through the UKDS repository (or similar). All publications using the data will include data sharing information and the dataset DOI.

Data access will require the approval of the chief investigator in each instance, and will require adherence to a strict licence that includes a confidentiality agreement (in line with the UKDS terms and conditions). Interview data will have personal information removed or replaced, other identifying details (for example place names, names of organisations) will be substituted with more general terms, and specific dates replaced with months or years. We will attempt to do this as much as possible without compromising the usefulness of the dataset. The chief investigator will retain control over who will access interview transcripts. Archived data will be embargoed until the publication of all study papers and reports. Until then, the study team will have exclusive use of the data.

11 ETHICAL AND REGULATORY CONSIDERATIONS

11.1 Research Ethics Committee (REC) review and reports

The TMG will ensure that the trial adheres to relevant regulations and guidance in the UK Framework for Health and Social Care research, as well as the principles of Good Clinical Practice (GCP) and the Declaration of Helsinki. The protocol, study materials (e.g. consent form, participant information sheet) and any proposed advertising material will first be submitted to an NHS Research Ethics Committee, the Health Research Authority and then local NHS sites for approval in a timely fashion after project commencement.

Substantial amendments that require review by REC will not be implemented until the REC grants favourable opinion for the study (it is noted that amendments may also need to be reviewed and accepted by NHS R&D departments before they can be implemented in practice at sites).

All correspondence with the REC will be retained in the Trial Master File/Investigator Site File.

An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended (this is the Chief Investigator's responsibility).

The Chief Investigator will notify the REC of the end of the study.

11.2 Peer review

This study was reviewed and approved by the National Institute for Health Research Health Technology Assessment Programme.

11.3 Public and Patient Involvement

There was extensive involvement of patients and carers in the development of the REACH-HF intervention. A public and patient involvement (PPI) group of 9 patients and carers led by a lay chair co-created the REACH-HF intervention [17].

Patients and carers were also involved in a process evaluation conducted in parallel to the REACH-HF trial [19,43]. The process evaluation assessed intervention fidelity and patient's and carer's experience of trial participation. A total of 19 patients were sampled from the intervention group. The researcher conducted interviews at 4 and 12 months after the baseline visit. Research questions and topic guides were developed with the PPI group. The process evaluation was key to identifying effective elements of the intervention and improving those that were not.

The proposed study will continue to engage fully with patients and carers. We are in the process of establishing a new PPI group for this trial: 4 patients with lived experience of HFpEF and their partners/carers. These patients are usually managed and monitored in general practice [12]. We are working with the cardiovascular PPI group based in the Queen Elizabeth University Hospital, Glasgow and the Pumping Marvellous Foundation (a UK HF charity) to develop a method for recruiting a diverse range of PPI advisors from existing cardiovascular patient groups.

Over the 42 months of this project, the PPI group will meet 4 times with activities that include a review of all patient-facing documents, advice on patient recruitment strategy, feedback on training for service providers and shaping the dissemination plans. An experienced member of the research team, Dr Tracy Ibbotson (TI) is funded to take the lead responsibility for PPI activity and to support PPI training needs and the patient voice on the trial management group. Two members of the PPI group will be invited to attend the TMG where appropriate and to maximise PPI involvement in the project. Additionally, the minutes of the PPI meetings will be tabled and presented by TI at the TMG.

In response to the HTA's feedback on representativeness, we will recruit to the PPI group for REACH-HFpEF trial through a survey of over 10,000 contacts of Pumping Marvellous across the country. We will specify that potential contacts should have experience of HFpEF and seek members who can also bring perspectives from BAME and socially deprived communities. The outcomes of the PPI process will be recorded in a PPI activity and impact log. Membership/recruitment will be continuously reviewed in order to reflect potential changes in members health. This will be done at meetings, updates between meeting (including newsletters) and an email discussion forum where members can post relevant items about the topic.

Training and support: To identify any gaps in skills and training PPI contributors may require, we will develop and deliver an induction programme to clarify the PPI role and expectations, and to build trust and rapport with the group members. This induction programme can be delivered as a webinar or in a face-to-face format, depending on the preferences of the PPI contributors and any COVID-19 restrictions which may be in place. Training in other research methods will be provided if requested by members of the PPI group and a PPI-led buddy system will be available to members without previous PPI experience. TI is the lead for the PPI team at the College of Medical, Veterinary & Life Sciences at the University of Glasgow. The PPI team will be able to offer additional support such as quarterly PPI newsletters and a PPI-led mentorship programme for new PPI contributors. We will ensure that the

members of the PPI group will receive feedback from the meetings in a format that is suitable for their needs and preferences.

PPI involvement has been fully costed using INVOLVE guidelines.

11.4 Protocol compliance

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used e.g. it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the trial protocol. Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator, Sponsor and GCTU immediately. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

11.5 Notification of Serious Breaches to GCP and/or the protocol

A "serious breach" is a breach which is likely to affect to a significant degree –

1. the safety or physical or mental integrity of the subjects of the trial; or
2. the scientific value of the trial

If any of the above occurs then the CI and Sponsor will be notified. The sponsor will notify the appropriate authorities in writing of any serious breach in accordance with their standard operating procedures.

11.6 Data protection and patient confidentiality

All investigators and trial site staff must comply with the requirements of the Data Protection Act 2018 and the General Data Protection Regulation with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

- Personal information will be collected via the eCRF in order to facilitate the process for patient reported outcome questionnaires. These data items will be encrypted and only those individuals who require to see these data, i.e. the person issuing the questionnaires and site research staff, will be able to view them. All electronic data will be held securely in accordance with ISO 27001 at the RCB. All Centre staff are required to sign confidentiality agreements and to follow Standard Operating Procedures in accordance with Good Clinical Practice and ISO certification.
- The trial data managers, statisticians, health economists or any other staff who will perform data related tasks will only be able to access depersonalised data where the participant's identifying information is replaced by a unique study identifier.
- Only those that have been trained and approved will be able to enter or view any data via the web portal. Each site can only see their own patients' data. Patient consent forms will be stored at the study site in a secure location accessible only to study teams.

11.7 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

A log of financial or other competing interests for the CI, PIs and committee members will be held centrally by the Trial Manager throughout the trial. The Trial Manager will request this information at the site initiation visit and at regular intervals during study conduct, and it will be made available to the Sponsor.

11.8 Indemnity

The trial sponsor is a member of the Clinical Negligence and Other Risks Indemnity Scheme (CNORIS), which covers the Sponsor's legal liability in relation to clinical trials; this includes clinical negligence. All NHS sites are covered by this or a similar shared risk scheme and therefore for clinical negligence. Harm from protocol design is covered by the University of Glasgow's clinical trial insurance.

Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the CI, who will pass the claim to the Sponsor's Insurers or University's insurers, via the Sponsor's office.

There are no specific arrangements for compensation made in respect of any SAE occurring though participation in the trial.

11.9 Amendments

Any change in the study protocol will require an amendment. Any proposed protocol amendments will be initiated by the CIs following discussion with the Sponsor and TSC and any required amendment forms will be submitted to the ethics committee and Sponsor. The Sponsor will determine whether an amendment is non-substantial or substantial. All amended versions of the protocol will be signed by the CIs and Sponsor representative. Following a substantial amendment, favourable opinion/approval must be sought from the original reviewing REC and Research and Development (R&D) office prior to implementation. The Chief Investigator will be responsible for informing the TMG of all protocol amendments.

11.10 Post trial care

At the end of the trial, participants will continue with their usual care.

12 DISSEMINIATION POLICY

12.1 Dissemination policy

The study database will be owned by the University of Glasgow and maintained on behalf of the Study investigators, represented by the Trial Steering Committee as it is constituted during and after the trial.

Given their high unmet need for effective and cost-effective therapies, if positive, the findings of this trial will potentially impact the outcomes and current services available for HFpEF patients and their caregivers. Results will inform future national and international guidelines and provide guidance to

health professionals and healthcare commissioners on the need for rehabilitation and how to deliver it efficiently and effectively.

Anticipated outputs of this study will include: presentations at national and international conferences; open access publications in high impact peer reviewed journals including end of trial NIHR monograph; stakeholder dissemination workshop (with patients, clinicians, commissioners, academics and key groups such as British Heart Foundation, British Association for Cardiovascular Prevention and Rehabilitation (BACPR), and Pumping Marvellous); copyright REACH-HF programme that include patient & caregiver manuals (we already have an IP arrangement from our previous NIHR Programme Grant that we would seek to roll over to this trial if this application is successful); trial data that will inform future national (NICE, SIGN) and international (e.g. European Society of Cardiology, American Heart Association) clinical guidance for the management of people with HFpEF.

A TMG subgroup publications committee and policy will be established and will develop a trial dissemination and implementation strategy. Feedback will be given to trial participants (with PPI input) and a digital dissemination strategy (e.g. involving REACH-HF website (http://sites.exeter.ac.uk/reach-hf/), Twitter, Facebook) put in place to liaise with participants and the public.

13 REFERENCES

1. Braunwald E. The war against heart failure: the Lancet lecture. *Lancet* 2015;385:812–24.

2. National Cardiac Audit Programme. *National Heart Failure Audit: 2019 summary report* (2017/18 data). London: NICOR; 2019.

3. Ponikowski P, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronicheart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the ESC. Developed with the special contribution of HFA of the ESC. *Eur Heart J.* 2016;37:2129-200.

4. National Institute for Health and Care Excellence. Chronic heart failure in adults: diagnosis and management. NICE Guideline NG106. London: NICE; 2018.5.

5. Lam CS, Donal E, Kraigher-Krainer E, Vasan RS. Epidemiology and clinical course of heart failurewith preserved ejection fraction. *Eur J Heart Fail.* 2011;13:18-28.

6. Zakeri R, Cowie MR. Heart failure with preserved ejection fraction: controversies, challenges andfuture directions. *Heart.* 2018 Jan 5

7. Pitt B et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med.* 2014;370:1383-92.

8. Solomon SD et al; PARAGON-HF Investigators and Committees. Angiotensin-Neprilysin Inhibitionin Heart Failure with Preserved Ejection Fraction. *N Engl J Med.* 2019;381:1609-1620.

9. Komajda M et al. Effect of ivabradine in patients with heart failure with preserved ejection fraction: the EDIFY randomized placebo-controlled trial. Eur J Heart Fail 2017;19:1495–503.

10. *Review of Specialist Heart Failure Nurse Services*, Scotland 2018. https://www.chss.org.uk/documents/2014/10/review-of-specialist-heart-failure-services-in-scotland.pdf

11. Chew-Graham C et al. *How can we optimise the management of people with Heart Failure with Preserved Ejection Fraction (HFpEF)? a qualitative study.* SAPC ASM 2019. Exeter.

12. Deakin C, Benson J. Time for correct diagnosis and categorisation of heart failure in primary care. *Br J Gen Pract.* 2016; 66: 554-555.

13. Cowie A et al. Standards and core components for cardiovascular disease prevention and rehabilitation. Heart. 2019;105:510-515

14. Taylor RS et al. Exercise-based rehabilitation for heart failure: Cochrane systematic review, meta-analysis, and trial sequential analysis. *J Am Coll Cardiol.* 2019;73:1430-1443

15. Reed SD et al. Economic evaluation of the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) randomized controlled trial: an exercise training study of patients with chronic heart failure. *Circ Cardiovasc Qual Outcomes.* 2010;3:374-81.

16. Scottish Intercollegiate Guidelines Network (SIGN). *Management of chronic heart failure.* 147 Edinburgh: March 2016. https://www.sign.ac.uk/assets/sign147.pdf

17. Greaves CJ et al. Optimising self-care support for people with heart failure and their

caregivers: development of the Rehabilitation Enablement in Chronic Heart Failure (REACH-HF) intervention using intervention mapping. *Pilot & Feasibility Studies.* 2016;2:37.

18. Eyre V et al. Rehabilitation Enablement in Chronic Heart Failure - a facilitated self-care NIHR130487 (19/59) rehabilitation intervention in patients with heart failure with preserved ejection fraction (REACHHFpEF) and their caregivers: rationale and protocol for a single-centre pilot randomised controlled trial. *BMJ Open.* 2016;6(10):e012853.

19. Lang C et al. A randomised controlled trial of a facilitated home-based rehabilitation intervention in patients with heart failure with preserved ejection fraction and their caregivers: the REACH-HFpEF Pilot Study. *BMJ Open.* 2018;8(4):e019649.

20. Fleg JL. Exercise rehabilitation for heart failure: The neglected stepchild. *JACC Heart Fail.* 2019;7:706-708.

21. Dalal HM et al. Why do so few patients with heart failure participate in cardiac rehabilitation? A cross-sectional survey from England, Wales and Northern Ireland. *BMJ Open.* 2012;2(2).

22. Golwala H, et al. Temporal trends and factors associated with cardiac rehabilitation referral among patients hospitalized with heart failure: Findings from Get With The Guidelines-Heart Failure Registry. *J Am Coll Cardiol.* 2015;66:917-26.

23. Beswick AD et al. Provision, uptake and cost of cardiac rehabilitation programmes: improving services to under-represented groups. *Health Technol Assess.* 2004;8(41):iii-iv, ix-x, 1-152

24. NHS England. *NHS long term plan*. London: NHS England; 2019. https://www.longtermplan.nhs.uk/online-version/chapter-3-further-progress-on-carequality-andoutcomes/better-care-for-major-health-conditions/cardiovascular-disease/

25. American Thoracic Society. *Minnesota Living with Heart Failure Questionnaire. 2004.* New York: American Thoracic Society; 2004. http://qol.thoracic.org/sections/instruments/ko/pages/MLWHFq.html

26. Fukuta H, et al. Effects of exercise training on cardiac function, exercise capacity, and quality of life in heart failure with preserved ejection fraction: a meta-analysis of randomized controlled trials. *Heart Fail Rev.* 2019;24:535-547.

27. Thomas RJ, et al. Home-based cardiac rehabilitation: a scientific statement from the American Association of Cardiovascular and Pulmonary Rehabilitation, the American Heart Association, and the American College of Cardiology. *J Am Coll Cardiol.* 2019;74:133-53.

28. Purcell C, Daw P, Kerr C, Cleland J, Cowie A, Dalal HM, Ibbotson T, Murphy C, Taylor R. Protocol for an implementation study of an evidence-based home cardiac rehabilitation programme for people with heart failure and their caregivers in Scotland (SCOT:REACH-HF). BMJ Open. 2020;10:e040771.

29. Daw P, van Beurden SB, Greaves C, Veldhuijzen van Zanten JJCS, Harrison A, Dalal H, McDonagh STJ, Doherty PJ, Taylor RS. Getting evidence into clinical practice: protocol for evaluation of the implementation of a home-based cardiac rehabilitation programme for patients with heart failure. BMJ Open. 2020 Jun 21;10(6):e036137.

30. American Thoracic Society. Minnesota Living with Heart Failure Questionnaire. New York: American Thoracic Society, 2004. http://qol.thoracic.org/sections/instruments/ko/pages/mlwhfq.html

31. Pulz C, Diniz RV, Alves AN, et al. Incremental shuttle and six-minute walking tests in the assessment of functional capacity in chronic heart failure. Can J Cardiol 2008; 24: 131–135.

32. Van den Berg-Emons HJ, Bussmann JB, Balk AH, et al. Validity of ambulatory accelerometry to quantify physical activity in heart failure. Scand J Rehabil Med 2000; 32: 187–192.

33. Snaith RP. The Hospital Anxiety And Depression Scale. Health and Quality of Life Outcomes. 2003 Aug, 1:29.

34. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, Bonsel G, Badia X. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011 Dec;20(10):1727-36.

35. Gandek B, Ware JE, Aaronson NK, et al. Cross-validation of item selection and scoring for the SF-12 health survey in nine countries: results from the IQOLA project. J Clin Epidemiol. 1998; 51: 1171–8.

36. Riegel B, Barbaranelli C, Carlson B, Sethares KA, Daus M, Moser DK, Miller J, Osokpo OH, Lee S, Brown S, Vellone E. Psychometric Testing of the Revised Self-Care of Heart Failure Index. J Cardiovasc Nurs. 2019 Mar/Apr;34(2):183-192.

37. Dalal HM, Taylor RS, Jolly K, Davis RC, Doherty P, Miles J, van Lingen R, Warren FC, Green C, Wingham J, Greaves C, Sadler S, Hillsdon M, Abraham C, Britten N, Frost J, Singh S, Hayward C, Eyre V, Paul K, Lang CC, Smith K. The effects and costs of home-based rehabilitation for heart failure with reduced ejection fraction: The REACH-HF multicentre randomized controlled trial. Eur J Prev Cardiol. 2019 Feb; 26 (3): 262-272.

38. Humphrey, L., K. Kulich, C. Deschaseaux, S. Blackburn, L. Maguire and A. Strömberg (2013) The Caregiver Burden Questionnaire for Heart Failure (CBQ-HF): face and content validity. Health and Quality of Life Outcomes 11(1): 84.

39. Vellone E, Barbaranelli C, Pucciarelli G, Zeffiro V, Alvaro R, Riegel B. Validity and Reliability of the Caregiver Contribution to Self-Care of Heart Failure Index Version 2. J Cardiovasc Nurs. 2020 May/Jun;35(3):280-290.

40. Nauser, J. A., T. Bakas and J. L. Welch (2011) A New instrument to measure quality of life of heart failure family caregivers. Journal of Cardiovasc Nursing 26(1): 53-64

41. Piotr, P., Voors, A.A., Anker, S.D., Bueno, H., Cleland, J.G.F., Coats, A.J.S., Falk, V., Gonzalez-Juanatey, J.R., Harjola, V.P., Jankowska, E.A., Jessup, M., Linde, C., Nihoyannopoulos, P., Parissis, J.T., Pieske, B., Riley, J.P., Rosano, G.M.C., Ruilope, L.M., Ruschitzka, F., Rutten, F.H., van der Meer, P., and ESC Scientific Document Group (2016). 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). European Heart Journal 37(27): 2129-2200.

42. Steckler A, LInman L. *Process evaluation for public health interventions and research.* San Fransisco: Jossey-Bass. 2002.

43. Frost J, et al. Home-based rehabilitation for heart failure with reduced ejection fraction: mixed methods process evaluation of the REACH-HF multicentre randomised controlled trial. *BMJ Open.* 2019;9(8):e026039.

44. Goldsmith KA et al. Mapping of the EQ-5D index from clinical outcome measures and demographic variables in patients with coronary heart disease. *Health Qual Life Outcomes.* 2010;8:54.

45. Edlin R et al. *Mapping the Minnesota Living with Heart Failure Questionnaire to the EQ-5D index.* Sheffield: University of Sheffield, 2002.

46. Cook JA, Julious SA, Sones W et al. Practical help for specifying the target difference in sample size calculations for RCTs: the DELTA2 five-stage study, including a workshop. Health Technol Assess. 2019;23(60):1-88. doi: 10.3310/hta23600.

47. Kularatna S et al. Comparison of contemporaneous responses for EQ-5D-3L and Minnesota Living with Heart Failure; a case for disease specific multiattribute utility instrument in cardiovascular conditions. Int J Cardiol. 2017;227:172-76.

48. Kularatna S et al. Comparison of the EQ-5D-3L and the SF-6D (SF-12) contemporaneous utility scores in patients with cardiovascular disease. *Qual Life Res.* 2017;26:3399-408.

49. Ambrosy AP et al. Aerobic exercise training and general health status in ambulatory heart failure patients with a reduced ejection fraction—findings from the Heart Failure and A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) trial. *Am Heart J.* 2017;186:130-38.

50. Flint K. Cardiac rehabilitation in heart failure with reduced ejection fraction: A "take it or leave it" intervention. *Am Heart J.* 2017; 186:12729.

51. Husereau D et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *BMJ* 2013;346 :f1049.

52. Glick H, Doshi J, Sonnad S, Polsky D. *Economic evaluation in clinical trials*. Oxford: Oxford University Press, 2007.

53. Bazeley P. *Integrating analyses in mixed methods research.* 2018 Sage: London.

54. Bartholomew LK et al. Planning health promotion programs. An intervention mapping approach. 3rd ed. San Francisco: John Wiley & Sons 2011.

55. Richards DA et al. Integrating quantitative and qualitative data and findings when undertaking randomised controlled trials. *BMJ Open.* 2019;9(11):e032081.

56. Moore GF et al. Process evaluation of complex interventions: Medical Research Council guidance. *BMJ* 2015;19;350:h1258.

57. Craig P et al. *Developing and Evaluating Complex interventions: draf*t guidance (circulated for comments 2019).

58. May C et al. Process evaluation for complex interventions in primary care: understanding trials using normalization process theory. *BMC Family Practice*. 2007:8;42.1-9.

59. Kularatna S, et al. Comparison of the EQ-5D-3L and the SF-6D (SF-12) contemporaneous utility scores in patients with cardiovascular disease. Qual Life Res 2017;26:3399–408

60. Purcell C, Daw P, Kerr C, Cleland J, Cowie A, Dalal HM, Ibbotson T, Murphy C, Taylor R. Protocol for an implementation study of an evidence-based home cardiac rehabilitation programme for people with heart failure and their caregivers in Scotland (SCOT:REACH-HF). BMJ Open. 2020;10:e040771.

61. https://bmjopen.bmj.com/content/10/12/e040771

14 APPENDICES

14.1 Appendix 1 – Schedule of Procedures

Patients				
	Baseline (pre-randomisation)	**Treatment allocation**	**Follow up 4 months post-randomisation**	**Follow up 12 months post-randomisation**
Inclusion/exclusion criteria checked	X			
Patient consent obtained	X			
Medical history	X			
Demographics	X			
Physical exam*	X			
Randomisation †	X	X		
Intervention or control		X (intervention facilitated delivery 12 weeks)		
Primary & secondary outcomes 1. Minnesota Living with Heart Failure questionnaire (MLWHFQ)	X		X	X

2. Mortality (HF-relatedness determined by an independent adjudication panel)	X		X	X
3. Hospitalisation (HF-relatedness determined by an independent adjudication panel)	X		X	X
4. Blood samples *(including an additional sample (approximately 4-5ml) for future, ethically approved research, if consented)*	X		X	X
5. Physical activity (over a 9-day period by accelerometry - GeneActive)	X			X
6. Kansas City Cardiomyopathy Questionnaire (KCCQ)	X		X	X
7. Short-Form 12 questionnaire (SF-12)	X		X	X
8. EQ-5D-5L questionnaire	X		X	X
9. Self-Care in Heart Failure Index (SCHFI)	X		X	X
10. Hospital Anxiety and Depression Scale (HADS)	X		X	X
11. Clinical Frailty Scale (CFS)	X		X	X
12. Incremental shuttle walk test (ISWT)*	X		X	X
13. Self-efficacy for key behaviours questionnaire	X		X	X
14. Healthcare utilization questionnaire	X		X	X
15. Adverse events			X	X

End of trial				X

Assessment window ± 2 weeks; † allocation will be performed via IWRS within 2 weeks of baseline and following receipt of baseline data and blood sample result.

*Performed if COVID-19 restrictions permit participant to attend clinic visit.

Caregivers				
	Baseline (pre-randomisation)	**Treatment allocation**	**Follow up 4 months post-randomisation**	**Follow up 12 months post-randomisation**
Caregiver consent obtained	X			
Demographics	X			
Intervention or control (allocation as patient dyad)		X (intervention facilitated delivery 12 weeks)		
Primary & secondary outcomes 1. Family Caregiver Quality of Life Scale questionnaire (FamQol) 2. Caregiver Burden Questionnaire HF (CBQ-HF) 3. Caregiver Contribution to Self-care of HF Index questionnaire (CC-SCHFI)	 X X X		 X X X	 X X X

Caregivers				
	Baseline (pre-randomisation)	**Treatment allocation**	**Follow up 4 months post-randomisation**	**Follow up 12 months post-randomisation**
4. Hospital Anxiety and Depression Scale (HADS) 5. EQ-5D-5L questionnaire 6. SWAT Carers Survey 7. SWAT PIS Satisfaction Questionnaire	X X X		X X X X	X X
End of trial				X

Assessment window ± 2 weeks

14.2 Appendix 2 – Intervention Delivery and Data Collection Models

	COVID-19 RESILIENT MODEL	**NON COVID-19 MODEL**
REACH-HF intervention delivery	All delivery 'remote' through telephone/online support. If home visit not possible, would encourage facilitator to set up contact as web-call.	First and last facilitator meeting with patient (and caregiver) in person at home Remainder of contacts (~each 2-3 weeks) by phone/online
Data collection (at baseline, 4 and 12 months follow up)		

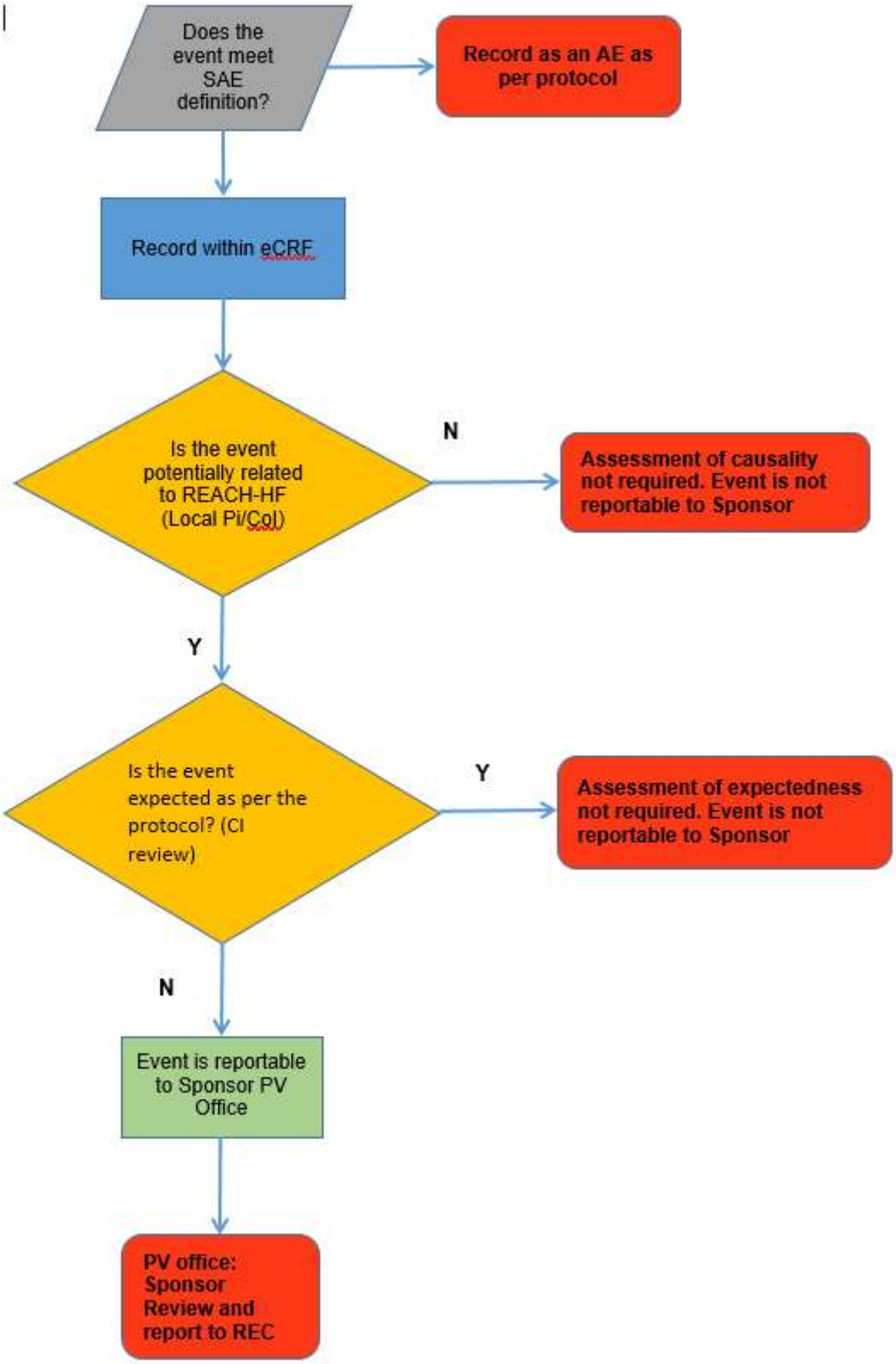
	COVID-19 RESILIENT MODEL	NON COVID-19 MODEL
Patient and caregiver reported questionnaires	Offer patients/caregivers completion by paper or online (coordinated by GCTU) at baseline, 4 and 12-month follow up	Offer patients/caregivers completion by paper or online (coordinated by GCTU) at baseline, 4 and 12-month follow up
Blood sample (NT-proBNP secondary outcome)	Arrange for patient bloods to be taken at baseline, 4 and 12-month follow up	Take at clinic visit
Patient incremental shuttle walk	Outcome not collectable (research team investigating if 'research acceptable' remote alternative exercise test)	Undertake at clinic visit
Patient demographics, medical history, medications	Sites collect at baseline through notes and enter to eCRF	Sites collect at baseline through notes and enter to eCRF
Patient hospitalisations	Site collect all hospital discharge reports and forward to GCTU for independent adjudication	Site collect all hospital discharge reports and forward to GCTU for independent adjudication
Patient adverse events, changes in medical status, medication	Collected by site through patient telephone call and enter to eCRF	Collected at site visit and enter to eCRF

14.3 Appendix 3 - REACH-HF Training Programmes - Summary of Exercise Prescription

	Chair based exercise programme (CBE)	Walking Programme (WP)
Duration (support by facilitators)	10-12 weeks	10-12 weeks
Frequency Days/week	2-3 days/week	Progress to 3-4 days/week
Session duration Minutes/session	Range 13-40 mins Level 1 ~ 13 mins includes warm up (WU) and cool down (CD) only * Level 2 ~ 21 mins (6 mins WU & CD) Level 3 ~ 21 mins (6 mins WU & CD) Level 4 ~ 25 mins (6 mins WU & CD) Level 5~ 28 mins (7 mins WU & CD) Level 6 ~ 30 mins (7 mins WU & CD) Level 7 ~ 38 mins (7 mins WU & CD)	Progress to 20-30 mins (with additional 3-5 mins warm up/cool down) Level 1: 5-10 minutes Level 2: 10-15 minutes Level 3: ≥20 minutes
Intensity	'Moderate' The initial exercise training intensity is in the range of 40% to 70% of a patient's capacity. This is ideally based on incremental shuttle walk test (ISWT) or 6-minute walk test (6MWT) calculated metabolic equivalents (METs) prior to commencing the core exercise training component. Each of the seven CBE levels has a known METs value which aligns with roughly 70% of the mean METs score derived from the ISWT and 6MWT. The CBE programme has built in (on screen) pacing and	'Moderate' The initial exercise training intensity is in the range of 40% to 70% of a patient's capacity. This is ideally based on ISWT or 6MWT calculated METs prior to commencing the core exercise training component. Each prescribed walking level is based on walk test distances or speeds with goals tailored to patient preferences.

	quality assurance of movement (video narrative).	
	The allocated CBE level or WP pace or distance is validated by facilitators through (1) subjective checks using patient sensations ("make you breathe heavier, feel warmer and have a slightly faster heartbeat, but you should still be able to talk") and (2) Use of the REACH-HF manual tracker (0 to 10) effort scale where zero ~ no significant effort in carrying out the task to 10 representing excessive effort that is very difficult to maintain. Patients with facilitators are encouraged to understand and gain experience of the effort scale and try to avoid too many occasions where patients go above a rating scale 7 on the effort scale. If the effort required during a period of sustained exercise (e.g. 3 or more mins) is rated as 8 or above then the next exercise period (intensity level) should be adjusted down to a lower level.	
**Although the CBE has a defined warm up period of 6 to 7 mins per session all exercises in the main part of each CBE level are also steadily progressive allowing the muscles, joints and physiological responses to adapt with each minute of the exercise.*		

14.4 Safety Reporting Flowchart



14.5 Appendix 4 – SWAT Protocol (version 1.0, dated 13th September 2021)

Title: Evidence-based enhanced participant information sheet for recruiting caregivers to the REACH-HFpEF multicentre randomised trial: **Protocol** for a Study Within a Trial (SWAT)

SWAT Team:

Valerie Smith: Professor in Midwifery, School of Nursing & Midwifery, Trinity College Dublin and Research Associate, Health Research Board-Trials Methodology Research Network, Ireland

Rod S Taylor: Professor of Population Health Research, MRC/CSO Social and Public Health Sciences Unit & Robertson Centre for Biostatistics, Institute of Health and Well Being, University of Glasgow. REACH-HFpEF (host trial) co-chief investigator.

Hannah Delaney: Post-doctoral Research Fellow, School of Nursing & Midwifery, Trinity College Dublin and Health Research Board-Trials Methodology Research Network, Ireland

Tracy Ibbotson: Research coordinator, West Node of the Scottish Primary Care Research Network since 2011 and Patient and Public Involvement (PPI) lead, General Practice & Primary Care, University of Glasgow.

Emma Burrell: Project Manager, Robertson Centre for Biostatistics, Institute of Health and Well Being, University of Glasgow. REACH-HFpEF (host trial) Lead Trial Manager.

Background

Challenges with poor recruitment and retention to randomised trials can lead to delays in trial completion, non-completion of trials, or reduced statistical power. Trial researchers, in attempts to optimise recruitment may prospectively, or as a responsive action to slow recruitment, embed efforts aimed at improving recruitment; for example, purposeful site visits by the principal investigator, incentives, increased or altered training for recruiters, and enhanced communication strategies.[1-4]

A trial participant information sheet (PIS), depending on the depth, length, and the user's perspective of the content (relevance, readability, complexity, etc.) has the potential to impact on recruitment negatively or positively.[5,6] This has been recognised, and Study Within A Trial (SWAT) projects have been/are being conducted to evaluate the effect of PIS design on recruitment to trials (Table 1). A SWAT is defined as "*a self-contained research study that has been embedded within a host trial with the aim of evaluating or exploring alternative ways of delivering or organising a particular trial process*".[7 (p.1)] Current evidence, however, appears limited. In a recently updated Cochrane review on methods for enhancing recruitment to trials,[8] three studies only comparing optimised PIS and standard PIS on recruitment to trials were included. The results overall showed no difference in recruitment rates between groups, although individual study results were conflicting. A Cochrane review, published in 2021, that focused on strategies to improve retention in trials also found no difference between optimised and standard PIS on retention rates; two studies only were included in this comparison and the evidence was of very low certainty (GRADE).[9] Notably the studies included in these reviews all involved host trial 'primary' participants; that is, those with the condition of interest, rather than caregivers who often also participate in clinical trials, either separately or alongside primary trial participants.

Table 1: Exemplar SWATs evaluating alternative PIS

SWAT 32: Effects of a re-designed Participant Information Sheet
Objective: To establish if the number of patients recruited and retained in a clinical trial is improved by the use of participant information sheets (PIS) with different input to their design. – Intervention 1: Original PIS, based on the NHS ethics template, plus a covering letter. – Intervention 2: Enhanced, user tested PIS, plus a user tested covering letter. – Intervention 3: 'Template' PIS developed using an enhanced PIS from another trial in a similar population, plus the original covering letter. *Registered Protocol*: https://www.qub.ac.uk/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/FileStore/Filetoupload,679553,en.pdf *Published Report*: Cockayne S, Fairhurst C, Adamson J, et al. An optimised patient information sheet did not significantly increase recruitment or retention in a falls prevention study: an embedded randomised trial. Trials 2017; 18:144. https://doi.org/10.1186/s13063-017-1797-7
SWAT 101: Design of the patient information leaflet: dOes ParTicipant InforMatIon ShEet Design affect the recruitment rate into an interventional trial (OPTIMISED)?
Objective: To explore whether improving the readability of a participant information leaflet (PIL) has an effect on the recruitment rate into an interventional trial. To assess the impact or "value" of the PIL in the patient's decision making. - Intervention 1: Patient Information Leaflet A (PIL A) - "Optimised" information sheet, developed based on similar improved information sheets - Intervention 2: Patient information leaflet B (PIL B) - "Conventional" information sheet based on Health Research Authority (HRA) example. *Registered Protocol:* - https://www.qub.ac.uk/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/FileStore/Filetoupload,926067,en.pdf
SWAT 102: Addition of a pictorial aid to the patient information leaflet to improve recruitment in a randomised trial
Objective: To determine whether the addition of a pictorial aid to the patient information leaflet (PIL) will improve recruitment in the POSNOC trial. - Intervention 1: A clearly illustrated pictorial aid at the end of the PIL to depict the randomisation process and crucial information about the two treatment arms in the POSNOC trial. - Intervention 2: Standard PIL.

Registered Protocol:

- https://www.qub.ac.uk/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/FileStore/Filetoupload,927252,en.pdf

In a previous SWAT (SWAT-55), key motivators and challenges that influenced informal carers' when making decisions about participating in a randomised trial were identified and ranked in descending order.[10] Based on the perspectives of caregivers, 28 motivators and 17 challenges were presented (Appendix 1). Using these motivators and challenges to conceptually develop an enhanced PIS, we propose to evaluate the effectiveness of the enhanced PIS compared to a standard PIS as a SWAT in the REACH-HFpEF multicentre trial [Trial registration ID: ISRCTN47894539].

Host trial

The REACH-HFpEF trial, hereafter referred to as the 'host trial', is a multicentre trial involving 20 sites across England and Scotland. The trial aims to assess the clinical effectiveness and cost-effectiveness of the home-based cardiac rehabilitation programme 'REACH-HF' plus usual care versus usual care alone in patients with heart failure with preserved ejection fraction (HFpEF). The effect of the intervention on patients' carers/support persons (*'caregivers'*) will also be formally evaluated as part of the trial. Participating caregivers will be aged 18 years or older and providing unpaid support to patients. The host trial sample size is 520 patients (260 per group), and their caregivers. Although entry to the trial is not dependent on both patient and caregiver entering as a dyad; that is, patients can enter the trial without identifying a caregiver, the aim is to recruit and deliver the intervention to both patient and caregiver simultaneously. As part of trial recruitment, potential trial participants and their identified caregivers will be provided with a separate/distinct written PIS about the study.

Objective of the SWAT

To determine if an evidence-based enhanced participant information sheet (PIS) impacts on recruitment and retention of caregivers to a multicentre randomised host trial.

Hypothesis: caregivers who receive an enhanced PIS will be more likely to agree to participate and more likely be retained in the REACH-HFpEF trial compared to caregivers receiving the usual PIS.

The SWAT protocol has been submitted for prospective registration in the SWAT Repository hosted by Queen's University Belfast (go.qub.ac.uk/SWAT-SWAR), [link pending]. The SWAT will also be registered with the ISRCTN trial registry [ISRCTN15757498]. Ethical approval for the SWAT will be sought from the involved University's Research Ethics Committee.

Methods

SWAT design

The primary randomisation of the host trial involves allocation of patients to REACH-HFpEF plus usual care ('REACH-HFpEF intervention group') or usual care alone ('REACH-HFpEF control group') (1:1 individual patient level randomisation, stratified by centre). Caregivers of patients recruited to REACH-

HFpEF will be allocated to the treatment group (intervention or control) in accord with their care recipient's allocation.

The design of the embedded SWAT will be a cluster randomised trial with allocation of the host trial sites to the enhanced caregiver host trial PIS (SWAT intervention group) or to the standard caregiver host trial PIS (SWAT control group). Random allocation of sites will be carried out by the Robertson Centre for Biostatistics (RCB), University of Glasgow using a cluster randomisation process. A blocked randomisation list (with mixed block sizes of 4 and 6) will be computer-generated in advance of the trial. When each study site obtains approval to begin recruitment, the research team will email the RCB, who will select the next allocation from the randomisation list, and notify the research team. Neither the study site nor the research team will know the next available allocation prior to randomisation. The cluster design has the advantages of administrative convenience (same PIS used across participants within a site) and optimising protocol compliance by preventing unintentional or erroneous distribution of the non-allocated rather than the allocated PIS to a potential caregiver participant that an individual allocation design would likely present and minimising intervention contamination between groups.

Interventions and comparators

- SWAT Intervention: Enhanced caregiver PIS

Using the motivators and challenges prioritised by SWAT-55 participants,[9] the content of the standard host trial PIS will be enhanced to include and place emphasis on aspects that relate to the identified motivators and challenges. The enhanced PIS was designed by conceptually mapping the ranked motivators and challenges to the content of the standard host trial caregiver PIS. To avoid the risk of potential contamination, the enhanced PIS cannot be publicly made available until the SWAT is complete. Box 1, however, provides an illustrative exemplar of how the standard PIS will be enhanced using an identified challenge as an example.

- SWAT control: Usual PIS based on the host trial standard caregiver PIS.

Box 1: Approach to PIS enhancement

SWAT-55 identified challenge

'*Life as a carer makes it difficult to plan ahead'* was the highest ranked challenge, by caregivers, when deciding to participate in a trial.

PIS enhancement

The standard PIS text should be conceptually enhanced to place emphasis on and provide clarity for potential caregiver participants as to the flexibility/flexible arrangements around the processes which caregivers will be involved in as part of participating in the trial.

Outcome measures

The primary outcome measures will be:

i. Proportion of caregivers in SWAT who are approached and agree to participate in the host trial
ii. Proportion of caregivers allocated in each SWAT intervention and control group who provide host trial outcomes at 4- and 12-months follow-up

The secondary outcome measures will be:

iii. Caregiver's level of satisfaction with the PIS (measured on a Likert scale of 1 not at all satisfied to 5 extremely satisfied) in both SWAT groups measured at baseline following randomisation to the trial, and at 4-months following entry to the trial.
iv. Caregivers' priority motivators and barriers for participating in the host trial; we will use a modified version of the SWAT-55 survey to assess these. We will also assess whether priority motivators and barriers change over time from baseline at trial entry and at 4-months following entry to the trial as a measure of overall change, within group change, and between group differences.

Sample Size and Statistical Analysis

In the previous REACH-HFrEF trial, a total of 97 carers for 216 patients (i.e., ~50%) were recruited.[11,12] Assuming a 15% increase in the proportion of carers recruited in the SWAT intervention group, we will require to recruit a total of 268 caregivers (134 per group) at 90% power and 5% alpha. Given the design of the trial, clustering of caregivers by site and potential increased variance, we may require a larger sample size to detect a 15% difference between SWAT groups.

We will report odds ratios and mean differences with 95% confidence intervals for the comparison between SWAT intervention and SWAT control group for dichotomous and continuous, respectively. We will also report the intra-cluster correlation coefficient of all primary and secondary outcomes.

Discussion

Optimising recruitment and retention to trials continues to present an ongoing challenge for trial recruiters. Existing evidence suggests that as many as 50% of trials fail to meet their recruitment target or, in doing so, require an extension to the originally planned recruitment duration.[13-15] Furthermore, many trials terminate early, with low recruitment identified as the dominant reason in almost one third of trials.[16] To successfully evaluate healthcare interventions, meeting sample size estimates and recruitment targets is essential. Evaluating trial processes, through embedded research such as the SWAT described here, provides a means for assessing aspects of trial design which can then inform future trial designs.

Caregivers, as a discrete population can be hard to reach for many reasons, not least because of the demands of their caring role, and the time commitments associated with this.[17,18] Yet, for these very reasons, designing and evaluating interventions that have the potential to support caregivers, psychologically, socially, physically, or otherwise, is important.[10] The host trial takes cognisant of this by involving both patients and their caregivers in the REACH-HFpEF trial, yet the success of the intervention for caregivers will depend on optimum caregiver involvement. The embedded SWAT will evaluate the potential benefit for enhancing a caregiver PIS based on motivating and challenging factors, deemed important by caregivers themselves when making decisions about taking part in a trial. SWAT-XX will add further to the body of evidence on trial processes for recruiting and retaining

trial participants. Importantly, through measuring caregiver satisfaction with the PIS (both SWAT groups) and through the further assessment of the motivators and challenges identified in SWAT-55,[10] factors important to this discrete group of caregivers of people with heart failure will be identified and highlighted. The results of this SWAT will be informative for future trials involving caregivers, and ultimately, may help increase trial feasibility and success and reduce research waste into the future.

Implementation of the SWAT and implications for the host REACH-HFpEF trial

We do not anticipate problems with implementing SWAT, nor should SWAT have any negative implications for the host trial. Our cluster trial design will overcome any potential issues related to inaccurate PIS allocation or erroneous distribution of the allocated PIS to SWAT intervention and control group personnel. There will be a small additional burden due to the collection of additional outcome measures (satisfaction and priority motivators and barriers) for caregivers. Given that we are recruiting caregivers and collecting their outcomes as part of the host trial, we would also expect SWAT to be effectively cost neutral. Ethical approval for SWAT will be sought as an amendment following approval of the host trial. A data sharing arrangement will be put in place so the Glasgow CTU (overseeing the data management of the host trial) can allow data to be securely transferred to the SWAT research group at Trinity college Dublin.

Conclusion

This SWAT, embedded in the REACH-HFpEF host trial, will evaluate the effectiveness of an enhanced PIS versus a standard PIS, based on caregiver identified motivators and challenges when deciding to take part in a trial, on host trial caregiver recruitment and retention. The findings will add to the body of evidence on trial processes which can be considered by future trialist involving caregivers when designing a trial PIS. The findings will also contribute data to systematic reviews on the effectiveness of using enhanced PIS's[8,9] to provide, overall, higher level evidence on this topic.

References

1. Smith V, Clarke M, Begley C, Devane D. SWAT-1: The effectiveness of a 'site visit' intervention on recruitment rates in a multi-centre randomised trial. Trials, 2015; 16:211. https://doi.org/10.1186/s13063-015-0732-z
2. Du W, Mood D, Gadgeel S, Siman MS. An educational video to increase clinical trials enrolment among lung cancer patients. J Thorac Oncol, 2008; 3:23-9.
3. Free C, Hoile E, Robertson S, Knight R. Three controlled trials of interventions to increase recruitment to a randomised controlled trial of mobile phone based smoking cessation support. Clin Trials 2010; 7:265-73.
4. Monaghan H, Richens A, Colman S, *et al*. A randomised trial of the effects of an additional communication strategy on recruitment into a large-scale multi-centre trial. Contemp Clin Trials, 2007; 28:1-5.

5. Man MS, on behalf of the Healthlines Study Group, Rick J, Bower P, on behalf of the MRC-START Group. Improving recruitment to a study of telehealth management for long-term conditions in primary care: two embedded, randomised controlled trials of optimised patient information materials. Trials 2015; 16:309 https://10.1186/s13063-015-0820-0
6. Parker A, Knapp P, Treweek S. *et al.* The effect of optimised patient information materials on recruitment in a lung cancer screening trial: an embedded randomised recruitment trial. Trials, 2018; 19**:**503 https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-018-2896-9
7. Treweek, S., Bevan, S., Bower, P. *et al.* Trial Forge Guidance 1: what is a Study Within A Trial (SWAT)? *Trials* **19,** 139 (2018). https://doi.org/10.1186/s13063-018-2535-5
8. Treweek S, Pitkethly M, Cook J, *et al.* Strategies to improve recruitment to randomised trials. Cochrane Database of Systematic Reviews 2018, Issue 2. Art. No.: MR000013.
9. Gillies K, Kearney A, Keenan C, *et al.* Strategies to improve retention in randomised trials. Cochrane Database of Systematic Reviews 2021, Issue 3. Art. No.: MR000032.
10. Smith V, Corry M, Devane D, *et al*. Prioritising key motivators and challenges influencing informal carers' decisions for participating in randomised trials: An embedded Study Within A before and after Trial (SWAT 55) [version 1; peer review: 1 approved, 1 approved with reservations] HRB Open Res, 2020; 3:71 https://doi.org/10.12688/hrbopenres.13125.1

Appendix 1: SWAT-55 Motivators and Challenges[10]

Rank	Motivator	Mean (SD)
1	The research will help create awareness about carers	4.40 (1.30)
2	The study is held at a time that suits me	4.39 (1.23)
3	The study is held at a place that is easy to find and easy to travel to	4.26 (1.29)
4	I can take part in the study online	4.19 (1.34)
5	The study is held at a place I feel comfortable in	4.16 (1.27)
6	Taking part will help researchers get valuable information about carers and their needs	4.15 (1.41)
7	The researchers understand the different issues carers face when caring for a younger person or an older person	4.13 (1.38)
8	I am very interested in the topic being studied	4.13 (1.41)
9	By taking part, carers might get more access to doctors or useful information	4.10 (1.32)
10	It is simple and easy to understand what is being studied and why	4.06 (1.30)
11	Doing research is important	4.06 (1.39)
12	I am interested in research on carers	4.06 (1.46)
13	The language used is easy to understand	4.03 (1.30)
14	The study treats carers for a younger person and carers for an older person as unique groups with different needs	4.03 (1.38)
15	New research might help carers in their day-to-day lives	4.00 (1.46)
16	Taking part will make my voice heard	3.97 (1.38)
17	I trust the institution running the study	3.97 (1.40)
18	I can choose how I take part in the study (for example, online or face-to-face)	3.90 (1.40)
19	I trust the person running the study	3.84 (1.19)
20	By taking part, I might gain access to doctors or useful information	3.80 (1.45)
21	Being asked to take part in the study makes me feel valued	3.74 (1.24)
22	Taking part in the study would benefit me socially (for example, reduce isolation or provide company)	3.55 (1.48)
23	I was invited to take part by a carer support group	3.48 (1.06)
24	I know the institution running the study	3.35 (1.02)
25	I can take part by talking with someone face-to-face	3.26 (0.97)
26	I found out about the study through a friend or family member	3.00 (0.97)
27	I found out about the study through a leaflet	2.97 (0.75)
28	I know the person running the study	2.84 (0.97)

Rank	Challenges	Mean (SD)
1	Life as a carer makes it difficult to plan ahead	4.13 (1.25)
2	The person I care for cannot be left alone (I do not have anyone else to take care of them)	4.09 (1.28)
3	Life as a carer makes it difficult to find time to take part in a research trial	4.04 (0.83)
4	I cannot travel to the place the study is held in	3.78 (1.28)
5	The study is held in a place I might not feel comfortable in	3.65 (1.27)
6	The language used in the study is hard to understand	3.64 (1.18)
7	I do not trust the institution running the study	3.52 (1.28)
8	I do not trust the person running the study	3.48 (1.28)
9	Taking part in a study would interfere with my daily life	3.39 (1.23)
10	The research does not directly affect carers	3.39 (1.31)
11	I do not know the institution running the study	3.09 (1.08)
12	I am not interested in the topic being researched	3.09 (1.35)
13	I do not believe the research will help carers	3.09 (1.51)
14	The topic being studied makes me uncomfortable or upset	2.96 (1.19)
15	I can only take part in the study online	2.96 (1.30)
16	The study requires me to talk to someone face-to-face	2.95 (1.13)
17	I do not know the person running the study	2.74 (1.18)

14.6 Appendix 5 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
01	2.0		Rod Taylor Emma Burrell Claire Brunton	Key trial contacts • change of Sponsor representative contact details, p4. Trial summary • Addition of secondary outcome for disease specific health-related quality of life (Kansas City Cardiomyopathy Questionnaire), p8. Longer follow-up • Addition of optional consent for additional blood samples to be taken for future, ethically approved research, p21, p39. • Addition of collection of NHS/CHI numbers to facilitate record linkage for participants who consent to long term follow-up, p48. Trial Design • Removal of baseline NT-proBNP value as randomisation variable, p22, p31. • Addition of section 4.5 to include SWAT analysis, p26 (SWAT protocol added as appendix 4). Eligibility • Amendment to relax exclusion criteria as suggested by TSC. Change will allow the trial to be externally generalisable, p27. Participant Identification • Addition of sentence to state details of the study and study sites will be listed on the CardioTrials platform, p30. Consent • Clarification that facilitator contact will first be made by the Heart Manual Department who already hold facilitator contact details.

				Facilitators will be provided with an expression of interest form to contact the process evaluation team if they wish to participate in the evaluation. Data Collection • Baseline, 4 and 12 month data collection variables updated following eCRF development, p31-39. Withdrawal Criteria • Updated to clarify that participants can withdraw from the intervention and sites visits but continue to complete patient reported outcome questionnaires if they want to, p41. Other minor clarifications/corrections throughout.
02	2.1		Emma Burrell	Blood samples for future research, amount of blood changed from 5ml to approximately 4-5ml for clarity.