Optimising Management of Patients with Heart Failure with Preserved Ejection Fraction in Primary Care

STUDY PROTOCOL

1.0 Contents Page

1.1 Study Summary

Trial Title	**Optimising Management of Patients with Heart Failure with Preserved Ejection Fraction in Primary Care (Optimise-HFpEF)**	
Short Title	Optimise-HFpEF	
Trial Design	Multi-method programme of research culminating in the development of an optimised programme of management for patients with heart failure with preserved ejection fraction (HFpEF). This protocol details one work package: a longitudinal cohort study of patients with HFpEF.	
Trial Participants	Patients with HFpEF	
Planned Sample Size	270 patients with confirmed HFpEF in the cohort study recruited from 10 - 15 primary care practices and 1-2 specialist services each in Cambridge, Oxford and London (total 20-30 practices). Specialist secondary care settings with cardiology research expertise, will contribute ~20 patients.	
Follow-up Duration	Patients in the cohort will be followed for one year (recruitment planned Completion of analysis March – May 2020.	
Planned Trial Period	Original sites (Cambridge and Oxford) will recruit for 27 months covering the period January 2018 to May 2020. Additional secondary care sites will recruit from April 2019 for a period of 1 year.	
Objectives	We hypothesise that outcomes of patients with heart failure with HFpEF can be improved through an optimised management programme which would be based in primary care, in collaboration with specialist services. To develop this programme our study will seek better understanding of the needs and experiences of patients with HFpEF, their management in primary care and important outcomes. We will integrate findings from research with the expertise of clinicians and patients to develop the programme of optimised management. Our objective for this work package is to: • Identify patients with HFpEF in primary care and assess comorbidities, lifestyle factors, frailty, self-management, symptoms, quality of life, cognitive function, types of care received, management of risk factors and comorbidities, and one year morbidity and mortality.	
Funder	National Institute for Health Research/National School for Primary Care Research (NHIR SPCR). Grant Ref no: 384	
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1.2 Abbreviations

EHFScB	European Heart Failure Self-care Behaviours questionnaire
HADS	Hospital Anxiety and Depression Scale
HCP	Health Care Providers
HES	Hospital Episodic Statistics
HFSN	Heart Failure Specialist Nurse
HF	Heart Failure
HFpEF	Heart Failure with preserved Ejection Fraction
HFrEF	Heart Failure with reduced ejection fraction
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVSD	Left Ventricular Systolic Dysfunction
MOCA	Montreal Cognitive Assessment
NIHR SPCR	National Institute for Health Research School for Primary Care Research
NYHA	New York Heart Association
RCGP	Royal College of General Practitioners
SSQHF	Symptom Status Questionnaire – HF

1.3 List of Tables

2.0 Plain English Summary

Heart failure (HF) is a condition in which the heart does not work well to pump blood around the body. About half of all people with HF have a type in which the heart is very stiff. This type is more common in older people with a history of high blood pressure, obesity and diabetes, but it is hard to diagnose and poorly understood. No specific drugs have been found to help it, except for diuretics or 'water pills'. For now, recommendations for managing this type of HF focus on controlling blood pressure, blood sugar, and being active. Most patients are looked after in general practice sometimes in collaboration with specialists. In this study we want to identify and follow a group of patients with this type of HF for a year to better understand their HF, their other conditions, needs for support, experience of treatment, and if they have problems requiring hospital care. We will collect information at the start, then 6 and 12 months later. We will use the information from the data collected and from a review of other studies, to develop the best (optimised) way of managing patients with collaboration between general practice and specialist services. We will invite patients and health care professionals to work with us to agree ways of managing patients that are practical and acceptable to patients and healthcare providers. The final agreed optimised management programme will be tested in future studies to see whether it improves patients' care and health outcomes.

2.1 Abstract

Heart failure (HF) accounts for 2% of NHS expenditure, and 5% of emergency hospitalisations. Patients with HF with preserved ejection fraction (HFpEF) are older, have more comorbidities, have similarly poor or worse outcomes compared to patients with reduced ejection fraction (HFrEF), and currently lack an evidence base for treatment. We hypothesise that outcomes of patients with HFpEF can be improved through optimised management and self-management of comorbidities, fluid status and lifestyle delivered in primary care in collaboration with specialists. The primary aim is to develop a programme of optimised management by improving our understanding of needs and experiences of patients with HFpEF, clinical decision-making and management in primary care, and integrating research findings with patient and clinical expertise. The main objective for this work package is to identify patients with HFpEF in primary care and assess comorbidities and other factors, management, morbidity and mortality at one year. The methodology employed will be a longitudinal cohort study of 270 patients with HFpEF in primary care followed for 12 months.

2.2 Background and Rationale

Around 900,000 people in the UK have heart failure (HF) (1), which accounts for 2% of NHS expenditure, and causes or complicates 5% of emergency hospitalisations (2). A heterogeneous clinical syndrome characterised by fatigue and dyspnoea, around half of patients with HF have a preserved ejection fraction (HFpEF) rather than a reduced ejection fraction (HFrEF) also known as left ventricular systolic dysfunction (LVSD) (3, 4). Patients with HFpEF are usually older, female and more likely to have multiple comorbid conditions such as obesity, hypertension and diabetes (4, 5). Patients with HFpEF face substantial challenges related to under diagnosis, poor outcomes and sub-optimal management (6-8). In contrast to LVSD, there is only a limited evidence base on which to base treatment. Perhaps as a result of this, programmes of care have lagged behind (7). Accordingly, it has been termed a stealth syndrome and a clinical crisis (8, 9). Yet HFpEF has remained neglected as a focus for study. This is the void that this project will address.

2.3 Under Recognition and Challenges in Diagnosis

Despite its prevalence, HFpEF is difficult to diagnose and often under-recognised (6), leading to HFpEF 'Read codes' (a coded thesaurus of clinical terms used in primary care) being rarely used. In an analysis of CPRD data, less than 1% of Read codes for 674,669 total HF clinical events were indicative of HFpEF (10). Our analysis of 128 patients on HF registers in 2 practices found that 40% could be identified as HFpEF/ possible HFpEF through review of echocardiogram reports and other information, similar to an earlier audit of 775 patients (11).

2.4 Sub-optimal Management Strategies

Management of people with HFpEF is especially challenging. Although patients with LVSD have benefitted from pharmacologic and device treatments that have been shown to improve outcomes for LVSD, the same is not true for HFpEF (12). The mainstays of treatment are management of comorbidities and fluid status, requiring patients to monitor fluid retention, optimise blood pressure and potentially blood glucose, and manage symptoms, medications, diet and physical activity. Treatment burden for HFpEF is thus high, yet patients characterised by ageing, comorbidities, and frailty are especially challenged by self-management, and need pro-active support and timely communication with familiar health care providers (HCPs) especially across transitions in care (i.e. hospital to home) (13). There is little evidence specific to HFpEF on how to optimise this: two studies of HF self-management did not provide specific information regarding patients with HFpEF, or proportion in the sample (13, 14). We therefore propose to develop an optimised programme for primary-care based management of people with HFpEF suitable for subsequent deployment in a trial.

2.5 Impact on well-being and outcomes

The impact of HFpEF on patient well-being is substantial, although there are fewer studies than in patients with LVSD. Patients with HFpEF reported greater consequences of HF on their lives, more symptoms and the same or worse quality of life than those with LVSD (15, 16). In a large clinical trial of patients with HFpEF (n=3406) there was substantial impairment in quality of life, and 27% of patients had moderate to severe depression scores (17). Quality of life and self-rated health have been shown to be independent predictors of morbidity/mortality outcomes in HFpEF clinical trials (18, 19). Comorbid conditions have a greater impact on functional class and physical health status in patients with HFpEF compared to LVSD (20). Sarcopaenia (muscle wasting) was found in nearly 20% of 117 patients with stable HFpEF, and was associated with poorer exercise tolerance and quality of life (21). In a sample of 80 stable HFpEF patients 58% were classified as pre-frail (22). A systematic review of frailty in HF found prevalence of frailty to be 18-54% (including 21-27% with frailty phenotype in community-dwelling patients with HF), and associated with age $\geq$ 70 years and female sex (who are more likely to have HFpEF) (23).

In a study of newly diagnosed patients with HFpEF (n=193), 33% had a HF hospitalisation or cardiovascular death at mean follow-up of 22 $\pm$ 13 months (24). Chan and Lamm (25) found one-year mortality rates for HFpEF to be 10-25% in population-based and registry studies. Cardiovascular cause of death in epidemiological studies of HFpEF ranged from 39% to 58%, indicating substantial mortality from comorbid conditions as well (25). In-hospital mortality for HFpEF in studies is estimated at 2.5-6.5%, with 6 month mortality rates of 14-16%, similar to LVSD (25). USA data demonstrate a trend toward increasing hospitalisation for patients with HFpEF and decreasing hospitalisation for LVSD (26). Rehospitalisation rates of 29% within 60-90 days were found for both groups (26). However, a recent paper noted that we have little data on the 26% of patients with HF in primary care who have not

been hospitalised for HF (these were not specified as LVSD or HFpEF), but they also have a poor 5-year prognosis (5-year survival estimate of 44%) (27).

2.6 Rationale for Focus on Primary Care Management

Most hospital-based cardiology services focus on LVSD, and HF specialist nurse (HFSN) services are variable, with some limited to LVSD by design or by capacity to take on additional patients (8, 14). The majority of patients with HF are managed in primary care. HF is considered an ambulatory care sensitive condition amenable to community based interventions to reduce unplanned hospital admissions (28). Furthermore, the emphasis on managing comorbidities in HFpEF provides an impetus to focus on primary care management in collaboration with specialists. Primary care has an important role in managing the 'whole patient' rather than a single condition, and is uniquely situated to assess the burden of treatment for a patient and support minimally disruptive medicine (29) and holistic care, and prioritise coordination of care. Interventions recommended for improving management of patients with multiple conditions are to target specific problems or common combinations of comorbidities, and integrate within existing healthcare systems (30). The NICE guidelines on multi-morbidity (31) advocate focusing on interaction of conditions and treatments, patient preferences, needs and lifestyle factors, and improving coordination of care. The Royal College of General Practitioners (RCGP) issued a recent policy paper on the benefits of integrated care for patients with complex conditions described as patient-centred, primary care led, delivered by multi-professional teams working across professional boundaries (32). The report acknowledges that the implementation of integrated care is patchy at best, and previous studies in HF have shown difficulties in diagnosis, lack of HCP knowledge, often defined by poor organisation of services with fragmentation and discontinuity (7). A recent editorial noted that the fundamental problem was a lack of cohesive interaction between primary care, where HF care should be centred, and specialist input for advice and involvement at critical phases (33).

2.7 Improving Management of HFpEF

Management of comorbidities is thought to be key to managing HFpEF given that these conditions drive development and progression of HFpEF through promotion of inflammation (34, 35). Fluid management including use of diuretics are emphasised in guidelines (12). Banerjee (8) called for a focus on HFpEF, and treatment aimed at improving symptoms and quality of life through a multi-disciplinary approach (emphasising HF specialist nurses [HFSN]), supporting diuretic dose adjustment, and optimal management of hypertension and other comorbid conditions. HFSNs working in multi-disciplinary primary care teams are well-placed to provide education tailored to the patient, facilitate better communication and liaison among HCPs, and ensure coordination and continuity of care (14, 36, 37).

2.8 Lifestyle factors in HFpEF

Life-style factors are also important to address in management of HFpEF. Inactive patients with HFpEF compared to partially (1-89 minutes) or fully active patients ($\geq$ 90 minutes of self-reported physical activity per week), had a hazard ratio of 2.30 ($p = .047$) for all-cause mortality (sample n=209) (38). A recent meta-analysis of 6 trials (n=276) found that exercise training was safe and effective in improving cardiorespiratory fitness and quality of life in HFpEF (39). Weight loss has been little explored despite the role of obesity in the development of HFpEF. A small study of 100 patients with HFpEF (mean age 67, 80% women, mean BMI 39) found that those in the restricted calorie diet, exercise training, or diet

+ exercise arms showed improvement in fitness at 20 weeks compared to baseline and the control group. Both diet and exercise resulted in weight loss and improvement in symptoms (40).

2.9 Transitional Care in HFpEF

Carson, et al. (41) found a 18% rate of readmission in 30 days for patients with HFpEF in a large clinical trial, and post-hospitalisation events were highest in the first 30 days and returned toward baseline after 6 months. Importantly, many readmissions are due to non-cardiac causes (41, 42). Ensuring that patients hospitalised for HF are identified and followed-up is essential: in a recent linked database analysis, patients hospitalised for HF but without a matched primary care record of HF had a 5-year estimated survival of 22% (27). Transitional care interventions can be effective in preventing readmission, although a review and meta-analysis of transitional care after hospitalisation for HF found that high-intensity interventions (home visits combined with telephone follow-up, clinic visits or both) were the most effective (43).

3.0 Towards an optimised programme of care for patients with HFpEF.

Our starting point is the assumption that management of patients with HFpEF may be improved through a patient-centred, multi-professional team approach that includes comorbidity management, a flexible diuretic regimen, support for self-management, a healthy lifestyle, and timely specialist input when needed. Any programme of care will need to take into account potential treatment burden on the patient, and ensure that patient preferences are respected and patients are well supported. Implementation of a programme of management also needs to be feasible within primary care with programme components based on evidence, and an understanding of the mechanisms of effect. This component of the programme of research will focus on understanding the characteristics, needs, management and illness trajectory of patients with HFpEF.

4.0 Description of Project Protocol (Work Package 2b)

This work package of the study will use phenotyping and one-year follow-up of a community recruited cohort of patients with HFpEF or probable HFpEF to understand the characteristics and needs of this patient group. It involves a longitudinal cohort study conducted to identify patients with HFpEF in primary care and assess comorbidities, lifestyle factors, frailty, self-management, symptoms, quality of life, cognitive function, types of care received, management of risk factors and comorbidities, and one year morbidity and mortality. This will inform particular areas for assessment and management/self-management in the optimised programme. We will also apply to NHS Digital who are the data controllers of Hospital Episodic Statistics so we can check if participants have had any hospitals visits throughout the duration of the study.

4.1 Hospital Episodic Statistics

Hospitalisation and healthcare utilisation is an important outcome in this research. Therefore, part of the study involves exploring hospitalisation. This is achieved in two ways 1) consultation of the participant and 2) review and extraction of hospitalisation data from their general practice record. However, both of these methodologies carry a high risk of inaccuracy (for example, length of hospital stay may not be recalled by participants and there will always be a lag time between discharge and GP record update, such that it may be missed at the record review points). Therefore, an application to NHS Digital for Hospital Episodic Statistics data on all participants will be made. If permission to link the cohort of participants in this study to HES data collected on them is granted by NHS Digital, this data will be securely stored for a time-limited period (10 years) in line with good data handling practices. The linking, processing and storage of HES data will be outlined in a Data Sharing Agreement; although a consent based approach is being used, the legal basis for this linking, processing and storage will be under Article 61E/92J. The informed consent form contains an explicit statement relating to this aspect of data collection. HES data, like personal identifiable data, will be stored in the Secure Data Hosted Service (SDHS) managed by the University of Cambridge Clinical School Computing Service and in a similarly secure system at the University of Oxford (see section 11 for further details)..

4.2 Inclusion Criteria

Adult patients with diagnosed or suspected HFpEF (defined as: patients diagnosed with non-valvular HF that are i) not diagnosed with left ventricular systolic dysfunction or have a documented ejection fraction < 50%; or ii) do have a reported 'normal' or preserved EF, documented EF $\geq$ 50%, or reported diastolic dysfunction without moderate to severe systolic dysfunction) who:

- Have stable Class I – III New York Heart Association (NYHA) classification for chronic heart failure
- Have not been hospitalised for an exacerbation of their heart failure in the 6 weeks prior to screening
- Are able to communicate in English (both verbally and in writing)

4.2.1 Exclusion Criteria

Any patients who have:

- Any severe neuro-psychological or neuro-cognitive conditions that would confound outcome assessment
- NYHA Class IV classification for chronic heart failure receiving end of life care, or other life-threatening condition

4.3 Sample Size

Four sites (Cambridge, Oxford, Peterborough and London) will actively recruit for a total sample of 270 patients across all sites. It is probable that some of the patients recruited will not be confirmed as having HFpEF; we estimate that 25% will not have HFpEF (24), so our final sample will be 202 patients. From previous work we have found that 40% of patients on the HF registers can be identified as possible HFpEF (and searches may find additional patients). Oxford and Cambridge will each recruit 10-15 primary care practices with a HF register size of 50-100 patients (20 – 40 potential HFpEF

patients). If 50% of eligible patients participate in the study then each practice would yield 10 – 20 patients. Specialist secondary care site responsible for diagnosing HFpEF patients; they will contribute ~20 patients to the sample.

4.4 Sample Size Calculation

Our sample size calculation is based on the need for an adequate number of patients with HFpEF across England to allow us to confidently identify phenotypes, frequency of comorbid conditions, risk factors, frailty, lifestyle behaviours, and morbidity and mortality outcomes over 12 months. Using exemplar analyses in Stata we determined the precision with which estimates from a sample size of 200 could be made. For example, in a sample of 200 people, the 95% CI for an estimate of 10% prevalence in the HFpEF population in primary care would be from 6-15%. In population samples of people with HFpEF the prevalence of comorbidities/conditions ranged from 18-20% for sarcopaenia and frailty to 71% for hypertension, and one-year mortality was 10-25%. Thus we will have a high degree of precision to determine the prevalence of specific factors in patients with HFpEF in primary care.

5.0 Identifying Patients / Screening

Clinicians will review the records of patients on the heart failure (HF) register/clinic list to identify patients diagnosed with non-valvular HF that are i) not diagnosed with left ventricular systolic dysfunction or have a documented ejection fraction < 50%; or ii) do have a reported 'normal' or preserved EF, documented EF $\geq$ 50%, or reported diastolic dysfunction without moderate to severe systolic dysfunction. Clinicians will also conduct a search to find patients with possible HFpEF, who are not on the HF Register using specific medication and diagnostic codes. Patients will be sent an invitation letter or approached in clinic, provided information about the study and an informed consent, and asked to either return an expression of interest or consent form in person, by free post or e-mail, or to ring or speak to the research/clinical team if interested in participating in the study. One reminder mailing will also be sent if using this approach. Those interested will be followed up by telephone by the responsible clinician who will discuss the study, answer questions and schedule the patient for an assessment. Travel expenses will be reimbursed for the patients. If written consent has not been received, written informed consent will be obtained at the scheduled assessment visit 1. In secondary care, the cardiology research team will screen clinical records with the local PI. Those patients with confirmed diagnosis of HFpEF and a recent echo will be prioritised and invited to participate in the research.

6.0 Baseline Data Collection

Demographic and clinical information of consented patients (including current medications, hospitalisations and GP visits in the previous year, most recent blood pressure and blood glucose if appropriate, date of annual assessment, measures of multi-morbidity using Read codes) will be extracted from the patients' records in the practices/secondary care hospitals.

6.1 Assessment Visit 1

Assessment visit 1 will be conducted in a Clinical Research Facility setting or at the participant's home (subject to consent) and will include the following procedures:

Table 1	Assessment 1 Visit Procedures
Clinical Assessments	Height
	Weight
	Vital Sign measurement
	12-Lead Electrocardiogram[$]
	Ankle oedema and breathlessness scale
	Clinical Frailty Assessment
	SHARE Frailty Instrument
	Charlson Comorbidity Scale
	Montreal Cognitive Assessment
	6 Minute Walk Test[$]
Blood Sampling***	Blood Chemistry
	Full Blood Count
	HbA1c
	Natriuretic Peptides
	Creatinine Clearance
	Research Samples*
Patient Reported Outcome Measures (Questionnaires)	Hospital Anxiety and Depression Scale (HADS)
	Kansas City Cardiomyopathy Questionnaire (KCCQ)
	European Heart Failure Self-care Behaviours questionnaire (EHFScB)
	Symptom Status Questionnaire – HF (SSQHF)
	EQ-5D-5L
Physical Activity Monitoring	Participants will be invited to wear an Axivity accelerometer for 7 days in order to record physical activity and sedentary time
Transthoracic Echocardiogram	Measurement of specific parameters for atrial and ventricular structure and diastolic function (48)**
Pulse Wave Velocity*	Pulse wave velocity is a non-invasive measure of arterial stiffness that is made via a Sphygmocor.
Medical Record Review	Patient records will be reviewed to establish: Changes in medications and clinical conditions Emergency department visits and hospitalisations Assessment of recorded blood pressures, HbA1c, weight and other markers indicative of comorbidity management and progression Transitions (e.g. hospital to home) and types of care received (e.g. specialist services)

*Cambridge only sub-study

**At North West Anglia and Guys and St Thomas', a recent clinical echo may be accepted in lieu of a protocol driven echo provided the echo is ≤ 1 year previous and ≥ 3 diastolic parameters have been measured.

***At North West Anglia and Guys and St Thomas', a recent clinical blood sample result will be accepted provided it is ≤ 3 months prior to screening.

[$] These assessments may not be feasible if a home visit is undertaken

During Assessment Visit 1 participants will regularly be offered comfort breaks and refreshments to ensure they do not feel over-burdened by any research procedures. Participants attending the Cambridge Clinical Research Facility will be asked to donate additional samples of blood that will be stored for future analysis of emerging biomarkers. Samples will be stored for 10 years before being destroyed in line with the Human Tissue Act. At Cambridge, participants will also be asked to have a non-invasive assessment to establish arterial stiffness. PWV has been demonstrated as a highly reliable prognostic parameter for cardiovascular morbidity and mortality, however its value in HFpEF patients has not been established. The Cambridge site has expertise in this area and will conduct this additional sub-study.

7.0 Confirmation of diagnosis of HFpEF

Diagnosis of HFpEF will be confirmed by a panel of clinicians using the 2016 European Society of Cardiology (ESC) guidelines criteria (48), clinical information from the initial assessment and relevant echocardiographic data. The diagnosis will be based on clinical signs and symptoms of HF; preserved ejection fraction (EF) $\geq$ 50%; and evidence of structural heart disease (left ventricular hypertrophy or left atrial enlargement) and/or indices of diastolic dysfunction (disturbance in ventricular relaxation, distensibility or filling). An EF $\geq$ 50% is required for a diagnosis of HFpEF. Although elevated natriuretic peptides are included in the ESC diagnostic criteria, these are less useful in compensated patients. In the non-acute setting in untreated patients, BNP > 35 pg/mL or NT-proBNP > 125 pg/mL are considered the threshold for possible HF (48).

Participants not confirmed to have HFpEF will be thanked for their participation but not followed up further. With their consent, we will retain their baseline information for comparison with those patients found to have HFpEF. Information about the patients' clinical assessment will be shared with their General Practice, including confirmation or refutation of diagnosis of HFpEF.

8.0 Follow-up visit 2 (6 months)

Patients followed up at 6 months will repeat a similar but reduced panel of assessment as outlined in Table 2.

Table 2	Follow-Up Visit 2 (6 months) Procedures
Clinical Assessments	Height
	Weight
	Vital Sign measurement
	Ankle oedema and breathlessness scale
	Clinical Frailty Assessment
	SHARE Frailty Instrument
	6 Minute Walk Test[$]
Patient Reported Outcome Measures (Questionnaires)	Hospital Anxiety and Depression Scale (HADS)
	Kansas City Cardiomyopathy Questionnaire (KCCQ)
	European Heart Failure Self-care Behaviours questionnaire (EHFScB)
	Symptom Status Questionnaire – HF (SSQHF)
	EQ-5D-5L
Physical Activity Monitoring	Participants will be invited to wear an Axivity accelerometer for 7 days in order to record physical activity and sedentary time
Dietary Monitoring	24 hour diet recall*

*Cambridge site only
$ These assessments may not be feasible if a home visit is undertaken

9.0 Follow-up visit 3 (12 months)

Patients followed up at 12 months will repeat a similar but reduced panel of assessment as outlined in Table 3.

Table 3	Follow-Up Visit 3 (12 months) Procedures
Clinical Assessments	Height
	Weight
	Vital Sign measurement
	12-Lead Electrocardiogram$
	Ankle oedema and breathlessness scale
	Clinical Frailty Assessment
	SHARE Frailty Instrument
	Montreal Cognitive Assessment (MOCA)
	6 Minute Walk Test$
Blood Sampling	Blood Chemistry
	Full Blood Count
	HbA1c
	Natriuretic Peptides
	Creatinine Clearance
Patient Reported Outcome Measures (Questionnaires)	Hospital Anxiety and Depression Scale (HADS)
	Kansas City Cardiomyopathy Questionnaire (KCCQ)
	European Heart Failure Self-care Behaviours questionnaire (EHFScB)
	Symptom Status Questionnaire – HF (SSQHF)
	EQ-5D-5L
	Recent Physical Activity Questionnaire*
Physical Activity Monitoring	Participants will be invited to wear an Axivity accelerometer for 7 days in order to record physical activity and sedentary time
Medical Record Review	Patient records will be reviewed to establish: Changes in medications and clinical conditions Emergency department visits and hospitalisations Assessment of recorded blood pressures, HbA1c, weight and other markers indicative of comorbidity management and progression Transitions (e.g. hospital to home) and types of care received (e.g. specialist services)

*Cambridge only
$ These assessments may not be feasible if a home visit is undertaken

10.0 Data Collection, Storage & Analysis

Data will be collected and stored in a number of methods:

Electronic transfer by computer network: All questionnaires and data in the study will be shared using only the patient's study identification number (therefore no identifiable data will be held in this system), and login to a secure system -REDCap - hosted by the University of Oxford CTU. REDCap is a secure web application for building and managing online surveys and databases. Access is given only to those who have completed relevant training, and access is gained via username and password log in, where data is only visible for the assigned research site. The REDCap database is built specific to the study requirements and fully validated prior to releasing to production. A full audit trail is logged within the system.

Personal Identifiable Data (PID): PID (names, addresses, telephone number, emails) belonging to participants is required to enable contact during the study. PID will be kept securely in a password protected database overseen by the Chief Investigator at Cambridge (for East of England participants) and the Principle Investigator at Oxford (for Oxford area participants). The areas that hold PID are locked down to enable only the authorised and authenticated members of the Research teams to access and maintain the data. PID will not be moving between research sites. On completion of the study, PID data collected at secondary care sites will be transferred to researchers at University of Cambridge to enable further follow-up of the cohort (subject to consent).

Manual files: Paper forms with PID or research data (expression of interest forms, paper questionnaires or consent forms) will be identifiable by a unique participant study ID number and stored in a locked filing cabinet in a locked room in the Institute of Public Health, University of Cambridge. Similar arrangements exist at the University of Oxford. All studies at the University of Oxford have to be registered with the Data Protection officer and data are held in accordance with the data protection act. Data containing personal information and allocated identifiers will be kept in a separate location to the anonymised data, both of which will be in locked filing cabinets, within rooms that are locked and have restricted access.

University computers: Electronic PID will be held using the Secure Data Hosted Service (SDHS) managed by the University of Cambridge Clinical School Computing Service. The SDHS is located on a firewall protected network (LAN) certified to ISO29001 security. The security policy can be accessed here: https://www.medschl.cam.ac.uk/research/information-governance/information-governance-policy/. Once uploaded to SDHS, access to PID will be accessible only by the research team using a 2-step authentication (password and security fob). Other data without personal identifiers will held on password-protected University Networked servers. A similar hosted secure system with the same certification will be used to hold PID at the University of Oxford. PID data collected at North West Anglia and Guys and St Thomas' will be entered on a database held on the Secure Data Hosted Service managed by University of Cambridge Clinical School Computing Service. For the duration of the study this data will only be visible to the local research team at North West Anglia and Guys and St Thomas'. However, on completion of the study, PID data will be managed by researchers at University of Cambridge to enable further follow-up of the cohort (subject to consent).

Analysis will include a description at baseline on demographic and clinical characteristics, laboratory and other test results, questionnaire scores and echocardiographic parameters using proportions and measures of central tendency as appropriate. Pre-specified baseline comparisons will determine differences by sex, obesity (BMI $\geq$ 30 kg/m^2), and presence of frailty. In addition to robust clinical information, we will be able to describe the cohort according to patient reported measures on activation, symptoms, self-management, HF specific quality of life and physical activity. Reported physical activity will be validated against information from activity monitors regarding both level of activity and time spent sedentary. A similar analysis will be conducted with data from the 6 and 12 month follow-up to determine changes in variables from baseline to 6 and 12 months. Data on outcomes (all cause and cardiovascular hospitalisations and mortality, length of stay in hospital,

readmissions and time frames of readmissions) will be collected over the 12 month period. These data will provide a deeper understanding of patients with HFpEF including distribution of characteristics, changes in variables over time, specific needs, and rates of specific outcomes.

The data will also provide us information about confirmed prevalence of HFpEF, response rates to recruitment, and retention/drop out. We will ask patients about preferred means of communication, use of social media, mobile telephones and email, and consent to be contacted about the next phase of this programme of work. Initial analysis of baseline data from the cohort will support identification of areas of priority in management and self-management of comorbidities and other factors such as frailty, depression, symptoms, cognitive impairment and physical activity that should be addressed in an optimised management programme. Following patients over time will also help us identify the best measures with which to monitor patients in clinical practice. Quantitative data from the cohort study will also be discussed in conjunction with information from the qualitative research undertaken in a separate related work package (WP2a).

11.0 Longitudinal Cohort Study Timetable Phase 1 October 2017 to January 2019

Initial preparations will include submission of HRA ethics and governance application(s); adverts for RA posts in sites, recruitment and training of research staff (Oct 2017 – Jan 2018 in Cambridge and Oxford). The initial Investigators' meeting will be held in October 2017.

11.1 Longitudinal Cohort Study Timetable Phase 2 January 2018 – January 2019

A steering group will be formed, and a Patient Advisory Group will be developed (although additional people may be added throughout the first year). The systematic review will be completed, disseminated and submitted for publication. Recruitment of patients for cohort study and baseline data collection will be nearing completion in Cambridge and Oxford. Analysis of baseline data from cohort study completed and disseminated to sites. Six month follow-up data of cohort beginning in July 2018.

11.2 Longitudinal Cohort Study Timetable Phase 3 January 2019 – May 2020

During the 2nd year we will complete 6 and 12 month data collection from the cohort and analyse follow-up data. We plan to submit papers and reports from the baseline cohort study. Completion of 12 month cohort data analysis, and submission of papers and reports.

12,0 COVID-19 impact study

The original study set out to characterise a cohort of patients with HFpEF. The panel of participants who agreed to and are stilled enrolled in this research 'consented to be contacted about future research'. It has become clear that the COVID-19 pandemic has necessitated a whole scale change in the way healthcare is currently and potentially will be conducted in the future. Patients with long term conditions like HFpEF are particularly affected by these changes as they are 1) vulnerable to COVID-19 and may have been asked to undertake additional protective measures (shielded); 2) require regular monitoring to ensure their condition is not deteriorating or they are experiencing

adverse events; 3) often have poor baseline health which may be adversely affected by changes to society and healthcare. Healthcare professionals too will have experienced changes as they are at increased risk due to frequent exposure to COVID-19, may have had to undertake different clinical duties as resource is restructured to cope with the pandemic or have had to change the way they perform care due duties.

Many of these changes experienced by patients and providers will have long term implications and it is important we establish the perspectives of patients with condition like HFpEF. Therefore, we intend to recall patients who provided consent to contact study. There will be no exclusion criteria, the inclusion criteria is ongoing consent to contact. These participants will be invited to take part in this sub-study that explores their views and experiences. A letter of invite will be send along with the new information about the study, a consent form and the possible options of participation (YES/NO interview or YES/NO survey). Confidentiality and data protection arrangements set out for the original study will be maintained.

12.0 References

1. Guidance NIfHaCE. Chronic Heart Failure: National Clinical Guideline for Diagnosis and Management in Primary and Secondary Care. London: Royal College of Physicians (UK) National Clinical Guideline Centre.; 2010.
2. National Heart Failure Audit. April 2014 - March 2015.
3. Borlaug BA. The pathophysiology of heart failure with preserved ejection fraction. Nature reviews Cardiology. 2014.
4. Lam CS, Donal E, Kraigher-Krainer E, Vasan RS. Epidemiology and clinical course of heart failure with preserved ejection fraction. European journal of heart failure. 2011;13(1):18-28.
5. Pedrotty DM, Jessup M. "Frailty, thy name is woman": syndrome of women with heart failure with preserved ejection fraction. Circulation Cardiovascular quality and outcomes. 2015;8(2 Suppl 1):S48-51.
6. Deaton C, Benson J. Time for correct diagnosis and categorisation of heart failure in primary care. The British journal of general practice : the journal of the Royal College of General Practitioners. 2016;66(652):554-5.
7. Simmonds R, Glogowska M, McLachlan S, Cramer H, Sanders T, Johnson R, et al. Unplanned admissions and the organisational management of heart failure: a multicentre ethnographic, qualitative study. BMJ open. 2015;5(10):e007522.
8. Banerjee P. Heart failure with preserved ejection fraction: A clinical crisis. International journal of cardiology. 2016;204:198-9.
9. Clark AM, Flynn R, Hsu ZY, Haykowsky M. Heart failure with preserved ejection fraction: health services implications of a stealth syndrome. European journal of cardiovascular nursing : journal of the Working Group on Cardiovascular Nursing of the European Society of Cardiology. 2013;12(4):316-7.
10. Edwards DD, C. Unpublished data. 2016.
11. Deaton C. Unpublished data from Greater Manchester and Cambridgeshire practice records.
12. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 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)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. European heart journal. 2016.
13. Fry M, McLachlan S, Purdy S, Sanders T, Kadam UT, Chew-Graham CA. The implications of living with heart failure; the impact on everyday life, family support, co-morbidities and access to healthcare: a secondary qualitative analysis. BMC family practice. 2016;17(1):139.
14. Glogowska M, Simmonds R, McLachlan S, Cramer H, Sanders T, Johnson R, et al. Managing patients with heart failure: a qualitative study of multidisciplinary teams with specialist heart failure nurses. Annals of family medicine. 2015;13(5):466-71.
15. Gallacher K, May CR, Montori VM, Mair FS. Understanding patients' experiences of treatment burden in chronic heart failure using normalization process theory. Annals of family medicine. 2011;9(3):235-43.
16. Hoekstra T, Lesman-Leegte I, van Veldhuisen DJ, Sanderman R, Jaarsma T. Quality of life is impaired similarly in heart failure patients with preserved and reduced ejection fraction. European journal of heart failure. 2011;13(9):1013-8.
17. Hamo CE, Heitner JF, Pfeffer MA, Kim HY, Kenwood CT, Assmann SF, et al. Baseline distribution of participants with depression and impaired quality of life in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial. Circulation Heart failure. 2015;8(2):268-77.
18. Komajda M, Carson PE, Hetzel S, McKelvie R, McMurray J, Ptaszynska A, et al. Factors associated with outcome in heart failure with preserved ejection fraction: findings from the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE). Circulation Heart failure. 2011;4(1):27-35.

19. Inkrot S, Lainscak M, Edelmann F, Loncar G, Stankovic I, Celic V, et al. Poor self-rated health predicts mortality in patients with stable chronic heart failure. European journal of cardiovascular nursing : journal of the Working Group on Cardiovascular Nursing of the European Society of Cardiology. 2015.
20. Edelmann F, Stahrenberg R, Gelbrich G, Durstewitz K, Angermann CE, Dungen HD, et al. Contribution of comorbidities to functional impairment is higher in heart failure with preserved than with reduced ejection fraction. Clinical research in cardiology : official journal of the German Cardiac Society. 2011;100(9):755-64.
21. Bekfani T, Pellicori P, Morris DA, Ebner N, Valentova M, Steinbeck L, et al. Sarcopenia in patients with heart failure with preserved ejection fraction: Impact on muscle strength, exercise capacity and quality of life. International journal of cardiology. 2016;222:41-6.
22. Reeves GR, Whellan DJ, Patel MJ, O'Connor CM, Duncan P, Eggebeen JD, et al. Comparison of Frequency of Frailty and Severely Impaired Physical Function in Patients >/=60 Years Hospitalized With Acute Decompensated Heart Failure Versus Chronic Stable Heart Failure With Reduced and Preserved Left Ventricular Ejection Fraction. The American journal of cardiology. 2016;117(12):1953-8.
23. Jha SR, Ha HS, Hickman LD, Hannu M, Davidson PM, Macdonald PS, et al. Frailty in advanced heart failure: a systematic review. Heart failure reviews. 2015;20(5):553-60.
24. Dalos D, Mascherbauer J, Zotter-Tufaro C, Duca F, Kammerlander AA, Aschauer S, et al. Functional Status, Pulmonary Artery Pressure, and Clinical Outcomes in Heart Failure With Preserved Ejection Fraction. Journal of the American College of Cardiology. 2016;68(2):189-99.
25. Chan MM, Lam CS. How do patients with heart failure with preserved ejection fraction die? European journal of heart failure. 2013;15(6):604-13.
26. Oktay AA, Rich JD, Shah SJ. The emerging epidemic of heart failure with preserved ejection fraction. Current heart failure reports. 2013;10(4):401-10.
27. Koudstaal S, Pujades-Rodriguez M, Denaxas S, Gho JM, Shah AD, Yu N, et al. Prognostic burden of heart failure recorded in primary care, acute hospital admissions, or both: a population-based linked electronic health record cohort study in 2.1 million people. European journal of heart failure. 2016.
28. Wallace E, Smith SM, Fahey T, Roland M. Reducing emergency admissions through community based interventions. BMJ (Clinical research ed). 2016;352:h6817.
29. May C, Montori VM, Mair FS. We need minimally disruptive medicine. BMJ (Clinical research ed). 2009;339:b2803.
30. Smith SM, Wallace E, O'Dowd T, Fortin M. Interventions for improving outcomes in patients with multimorbidity in primary care and community settings. The Cochrane database of systematic reviews. 2016;3:Cd006560.
31. Multimorbidity: clinical assessment and management. NICE guideline. 2016.
32. Mathers NP, V.; Thomas, M. GENERAL PRACTICE AND THE INTEGRATION OF CARE: AN RCGP POLICY REPORT.
33. McDonald K, Gallagher J. The practice gap in heart failure-the elephant in the room. European journal of heart failure. 2017;19(3):301-3.
34. Franssen C, Chen S, Hamdani N, Paulus WJ. From comorbidities to heart failure with preserved ejection fraction: a story of oxidative stress. Heart (British Cardiac Society). 2016;102(4):320-30.
35. Shah SJ, Gheorghiade M. Heart failure with preserved ejection fraction: treat now by treating comorbidities. JAMA : the journal of the American Medical Association. 2008;300(4):431-3.
36. Tierney S, Kislov R, Deaton C. A qualitative study of a primary-care based intervention to improve the management of patients with heart failure: the dynamic relationship between facilitation and context. BMC family practice. 2014;15:153.
37. Focus on Heart Failure. 10 recommendations to improve care and transform lives. APPG on heart disease.
38. Doukky R, Mangla A, Ibrahim Z, Poulin MF, Avery E, Collado FM, et al. Impact of Physical Inactivity on Mortality in Patients With Heart Failure. The American journal of cardiology. 2016;117(7):1135-43.

39. Pandey A, Parashar A, Kumbhani DJ, Agarwal S, Garg J, Kitzman D, et al. Exercise training in patients with heart failure and preserved ejection fraction: meta-analysis of randomized control trials. Circulation Heart failure. 2015;8(1):33-40.
40. Kitzman DW, Brubaker P, Morgan T, Haykowsky M, Hundley G, Kraus WE, et al. Effect of Caloric Restriction or Aerobic Exercise Training on Peak Oxygen Consumption and Quality of Life in Obese Older Patients With Heart Failure With Preserved Ejection Fraction: A Randomized Clinical Trial. JAMA : the journal of the American Medical Association. 2016;315(1):36-46.
41. Carson PE, Anand IS, Win S, Rector T, Haass M, Lopez-Sendon J, et al. The Hospitalization Burden and Post-Hospitalization Mortality Risk in Heart Failure With Preserved Ejection Fraction: Results From the I-PRESERVE Trial (Irbesartan in Heart Failure and Preserved Ejection Fraction). JACC Heart failure. 2015;3(6):429-41.
42. O'Carroll GW, D.; O'Connell, E.; O'Hanlon, R.; Kenny, C.; McDonald, K. Re-admission patterns in patients following first admission for heart failure: Heart failure with preserved ejection fraction as compared with heart failure with reduced ejection fraction. Embase European Heart Journal. 2015.
43. Vedel I, Khanassov V. Transitional Care for Patients With Congestive Heart Failure: A Systematic Review and Meta-Analysis. Annals of family medicine. 2015;13(6):562-71.
44. Coulter AR, S.; Dixon, A. Delivering better services for people with long-term conditions. Building the house of care. The Kings Fund. 2013.
45. Peters DH. The application of systems thinking in health: why use systems thinking? Health research policy and systems. 2014;12:51.
46. Stalter AM, Phillips JM, Ruggiero JS, Scardaville DL, Merriam D, Dolansky MA, et al. A Concept Analysis of Systems Thinking. Nursing forum. 2016.
47. Spencer L RJ, O'Connor W, Morrell G, Ormston R. Ritchie J, Lewis J, McNaughton Nicholls C, Ormston R Qualitative research practice: A guide for social science students and researchers. Sage 2014. 2014.
48. 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). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. European journal of heart failure. 2016.
49. McMillan SS, Kelly F, Sav A, Kendall E, King MA, Whitty JA, et al. Using the Nominal Group Technique: how to analyse across multiple groups. Health Services and Outcomes Research Methodology. 2014;14(3):92-108.

Appendix 1: Protocol Version History

Version Number	Version Date	HRA Approval Date
1.0	31 August 2017	13/03/2018
2.0	04 January 2018	30/04/2018
3.0	03 January 2019	09 Feb 2019
4.0	23 April 2019	