UK Heart Failure with Preserved Ejection Fraction Registry (UK HFpEF)

UK HFpEF Protocol v2.0 27/03/23 IRAS ID 314091

Study Sponsor:

Manchester University NHS Foundation Trust,
Research Office, 1st Floor Nowgen Centre,
Grafton Street,
Manchester,
M13 9WU

IRAS Project ID number: 314091

Sponsor number: B01434

Clinicaltrials.gov: NCT05441839

FUNDED BY
NIHR | National Institute for Health Research

British Heart Foundation

1 Signature pages

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirements.

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 investigation without the prior written consent of the Sponsor.

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

For and on behalf of the Study Sponsor:

Signature:

..... Date: ...../...../.....

Name (please print):

.....

Position:

.....

Chief Investigator:

Signature:

..... Date: ...../...../.....

Name: (please print):

.....

2 Table of Contents

3 General information

This document describes the UK HFpEF study and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoir or guide for the management of other patients.

Every care was taken in the drafting of the protocol, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the study, but centres entering patients for the first time are advised to contact the Sponsor to confirm they have the most up to date version.

This protocol defines the participant characteristics required for study entry and study procedures. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements. Waivers to authorise non-compliance are not permitted.

This protocol has regard for the Health Research Authority (HRA) guidance.

4 Key study contacts

Chief Investigator	Professor Chris Miller Cardiology Department, Wythenshawe Hospital, Manchester University NHS Foundation Trust, Manchester, M23 9LT Tel: 0161 291 3244 Email: christopher.miller@manchester.ac.uk
Study Coordinator	David Cotterell North West Heart Centre, First Floor, Research Office, Wythenshawe Hospital, Manchester University NHS Foundation Trust, Manchester, M23 9LT Tel: 0161 291 4075 Email: David.Cotterell@mft.nhs.uk
Sponsor	Dr Lynne Webster Manchester University NHS Foundation Trust, Head of Research Office, Research office, 1st floor Nowgen Centre, Grafton Street, M13 9WU Tel: 0161 276 3565 Email: Lynne.webster@mft.nhs.uk and Research.sponsor@mft.nhs.uk
Funder	National Institute for Health Research Email: academy-awards@nihr.ac.uk
Central blood sample repository	Dr Kristian Spreckley NIHR National Biosample Centre Units 2 & 3, Java Park, Bradbourne Drive, Tilbrook, MK7 8AT, UK Kristian.Spreckley@ukbiocentre.com

1.1 Additional contacts

The contact details of other individuals involved in the trial are detailed in documents supplementary to the protocol and stored in the Trial Master File:

Contact	Document Title
Executive Steering Committee	UK HFpEF Executive Steering Committee Membership
Working Group	UK HFpEF Working Group Membership
Principle investigators	UK HFpEF Participating Centres
Patient Advisory Group	UK HFpEF Patient Advisory Group Membership

5 Glossary

BMI	Body mass index
BSA	Body surface area
CI	Chief Investigator
CMR	Cardiovascular magnetic resonance
CRN	Clinical Research Network
ECG	Electrocardiogram
eCRF	Electronic case report form
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
LA	Left atrium
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MFT	Manchester University NHS Foundation Trust
MRI	Magnetic resonance imaging
NHS	National Health Service
NRES	National Research Ethics Service
NIHR	National Institute for Health Research
NYHA	New York Heart Association
PI	Principal Investigator
PISC	Participant Information Sheet and Consent form
R&D	Research & Development
REC	Research Ethics Committee
R&I	Research & Innovation
SOP	Standard Operating Procedure
ULN	Upper limit of normal

6 Study summary

Study title	UK Heart Failure with Preserved Ejection Fraction Registry
Short title	UK HFpEF
Study design	Prospective cohort study
Study participants	Inclusion criteria 1. Written informed consent 2. Diagnosis of HFpEF by a HF specialist (e.g., a cardiologist with HF expertise, a primary care physician with HF expertise, a secondary/tertiary care physician with HF expertise, a HF nurse specialist, a specialist HF pharmacist) 3. Natriuretic peptide levels measured Exclusion criteria 1. LV EF ever < 40%. (For clarity, patients with a previous LVEF below 40%, which has since improved to above 40%, are excluded) 2. Known infiltrative cardiomyopathy (e.g., amyloid, sarcoid, lymphoma, endomyocardial fibrosis) 3. Known active myocarditis, constrictive pericarditis, or cardiac tamponade 4. Known genetic hypertrophic cardiomyopathy or obstructive hypertrophic cardiomyopathy 5. Known arrhythmogenic right ventricular cardiomyopathy 6. Known severe primary valvular heart disease 7. Known idiopathic, heritable or drug-induced pulmonary arterial hypertension 8. Heart transplantation or ventricular assist device 9. Complex congenital heart disease Recruitment will be monitored; the proportion of participants with LV EF 40-49% will be limited to no more than 25% of the cohort.
Planned sample size	The funding from NIHR includes funding for establishing the study infrastructure and recruitment of the first 875 patients. Having demonstrated feasibility, further funding will be sought to continue recruitment, aiming for 10,000 patients.
Patient follow-up duration	10 years
Research Aims	To develop a large, deeply characterised cohort that will be a platform for collaborative clinical and translational HFpEF research, in order to: 1. Reclassify HFpEF into distinct diagnoses, where possible, based on disease mechanisms, clinical factors and outcome. 2. Evaluate whether patients in the distinct groups respond differentially to treatments, with the aim of predicting individual patient treatment response.

	3. Create a platform for clinical trials that: a. Matches mechanism of action of therapies (new, repurposed or previously discarded) with HFpEF subgroup/anticipated treatment response. b. Provides groups of patients readily available for recruitment to trials. c. Has data linkage in place for clinical outcomes. 4. Create a platform for identifying phenotypic and genetic factors that could be used as the basis for: a. Improving understanding of the causes of HFpEF. b. Developing diagnostics. c. Improving risk stratification. 5. Facilitate industry engagement by providing a single point of access for industry.

7 Roles and responsibilities

7.1 Funding and support in kind

Funder	Financial and non-financial support given
National Institute for Health Research (NIHR)	This study (reference NIHR301848) is funded by the NIHR Advanced Fellowship Programme. The views expressed in this publication are those of the authors and not necessarily those of the NIHR, NHS or the UK Department of Health and Social Care. NIHR will monitor progress against key milestones via the submission of regular progress reports.

7.2 Role of study Sponsor and funder

Manchester University NHS Foundation Trust are the sponsoring organisation and are legally responsible for the study. Manchester University NHS Foundation Trust is acting as sponsor for this study and is assuming overall responsibility for the initiation and management of the study. The Trust will provide permission to conduct the research and monitor the progress of that research. The research team all hold substantive or honorary contracts with the Trust and therefore the sponsor has influence over all aspects of the study design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results which are the responsibility of the research team.

NIHR have had no role in the study design other than through their external peer review process.

7.3 Roles and responsibilities of study management committees

7.3.1 Executive Steering Committee

The overall remit of the Executive Steering Committee is to provide leadership and oversight for UK HFpEF, and be responsible for its running and management. Refer to the Executive Steering Committee Terms of Reference for further details.

Membership is detailed in the UK HFpEF Executive Steering Committee Membership document, which is stored in the Trial Master File. Briefly, the Committee is chaired by the Chief Investigator. Membership includes people with expertise in disciplines involved in the study, patient representatives, Sponsor representative, project manager, and representatives of other aspects of the study that are felt to be of benefit by being part of the Committee.

The Committee usually meets monthly.

7.3.2 Working Group

The overall remit of the Working Group is to input to the design, management and progress of UK HFpEF.

Membership is detailed in the UK HFpEF Working Group Membership document, which is stored in the Trial Master File. Briefly, the Committee is chaired by the Chief Investigator. Membership includes Executive Steering Committee members, site representatives, and representatives of other disciplines that are felt to be of benefit to the study.

The Working Group will usually meet approximately quarterly.

7.3.3 Patient Advisory Group

The overall remit of the Patient Advisory Group is to provide patient, carer and lay feedback to the UK HFpEF Executive Steering Committee. Refer to the Patient Advisory Group Terms of Reference for further details.

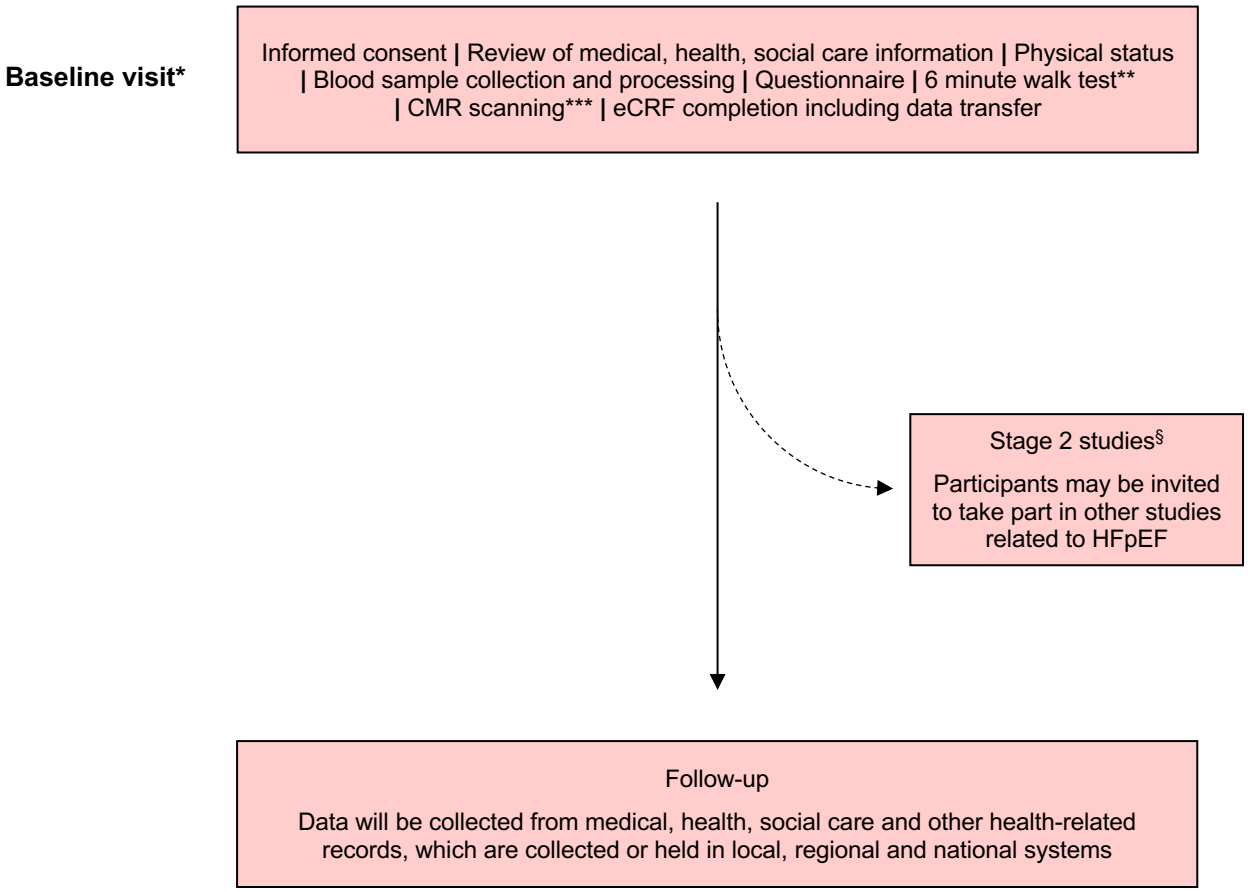
Membership is detailed in the UK HFpEF Patient Advisory Group Membership document, which is stored in the Trial Master File. Briefly, the Group comprises a Chair and approximately 5 other members. The Chair and members are patients with heart failure, carers of patients with heart failure, or other non-healthcare professionals with an interest in heart failure.

The Group shall meet regularly, initially monthly, and thereafter continue approximately quarterly, or as deemed necessary by the Executive Steering Committee.

7.4 Protocol contributors

Protocol development, including study design, conduct, clinical and scientific arrangements and writing, was led by the Executive Steering Committee, with detailed input from the Working Group and the Patient Advisory Group.

8 Study schematic



* May take place when patients are attending NHS facilitates for clinical care, including on the same day that consent is provided, or during a study visit. As much as possible, the assessments and procedures should take place on the same day, but if this is not possible, they could take place across more than one clinical attendance, or across, for example, a study visit and clinical attendances. See Section 15.1 for more details.

** Sub-study

*** For patients undergoing CMR as part of their clinical care (sub-study)

§ See section 14.4 for more details

9 Introduction

9.1 Background

Heart failure (HF), described as an epidemic, affects 1-2% of the adult population in developed countries.[1] It has a poor prognosis, representing the most common reason for hospitalisation in people aged over 65, and up to approximately 20-30% of patients die within a year of diagnosis.[2] Direct annual healthcare costs are almost £2-3 billion in England alone,[3] and as the population ages and HF risk factors, such as obesity, systemic hypertension and diabetes, become more prevalent, its impact is expected to rise further.[4]

Approximately half of patients with HF have a normal, or preserved, left ventricular ejection fraction (HFpEF).[5] Rather than being a single diagnosis, it has become clear that HFpEF represents a heterogeneous syndrome involving a range of pathophysiological mechanisms, clinical factors and outcomes.[6] However, to-date, HFpEF has generally been considered as a single disease entity. This 'one-size-fits-all' approach is a major reason why clinical trials of new therapeutic approaches have been characterised by efficacy failure, and treatment options remain very limited.[7-12] Patients, healthcare professionals and researchers recognise that "we are in dire need of new approaches".[13]

9.2 Rationale

Patients with HFpEF demonstrate a wide range of cardiovascular and systemic pathophysiology e.g. left ventricular diastolic and systolic dysfunction, hypertrophy, cardiomyocyte injury, myocardial fibrosis, atrial dysfunction, right heart dysfunction, vascular dysfunction and systemic inflammation.[6] Their presence in individual patients, and their association with outcome, are, however, variable, and there is overlap with patients without HFpEF.[14,15] It also remains unclear how the pathophysiological abnormalities relate to the range of comorbidities that are common in HFpEF, including obesity, diabetes, hypertension, atrial fibrillation, chronic kidney disease.

Several high profile phase III trials in HFpEF have shown potentially impressive efficacy in some subgroups of patients, but failed to prove significance over entire cohorts.[11,12] This is likely due to the 'one-size-fits-all' approach taken, with insufficient stratification of the various underlying disease mechanisms.

Machine learning techniques have been applied in attempts to reclassify HFpEF, but studies have generally used sparsely phenotyped trial data, and small cohorts with no or minimal disease mechanism data, and few have performed validation.[16-19] The resulting clusters have, therefore, been superficial and not advanced the field. Indeed, a recent editorial discussing these studies stated, "The most robust of statistical methodologies cannot circumvent the fact that faulty, incomplete, and imprecise data will lead to nonsensical output."[20] No study attempting to reclassify HFpEF has used a large, deeply phenotyped cohort that includes data regarding underlying disease mechanisms in conjunction with clinical and outcome data.

Studies aiming to identify factors that distinguish HFpEF that could be used for risk stratification have generally compared patients with HFpEF to healthy controls, differences between which are inevitable and not necessarily informative, and considered characteristics in isolation. HFpEF represents a complex interplay of multiple factors, for any given affected individual, making it very unlikely that any single characteristic would be identified, as has proven to be the case.

The analysis of genetic susceptibility to HFpEF is likely be important to enable the deconvolution of causal aetiological factors and therapeutic targets, however, to date genetic studies of HFpEF have been limited by sample size and limited phenotypic data. The development of an improved understanding of how genetic factors and downstream molecular phenotypes influence HFpEF has therefore been identified as a priority.[21]

9.3 Theoretical framework

The large and rapidly growing burden that HFpEF places on our healthcare systems mean there is a pressing need to better understand HFpEF and improve the management of patients with it. The recurrent lack of benefit of the one-size-fits-all approach mandates a new, personalised approach.

The UK HFpEF registry will be a key platform for collaborative UK clinical and translational HFpEF research. The aim is that multiple centres will collaborate and contribute patients such that the registry will provide deep phenotyping, linked to outcomes, in, ultimately, many thousands of patients. This will enable, for example, machine learning techniques to be applied at scale in order to reclassify HFpEF more powerfully. It will provide a platform for the development of diagnostics specific to the different HFpEF subgroups, and for more effective trials that will target groups of patients in whom new, repurposed or previously discarded treatments are expected to be effective. Moreover, it will provide cohorts of patients readily available for recruitment, with linkage in place for outcomes. It could be used to leverage commercial funding and participation, facilitated by simplified, single-point access for industry. It will enable scaled investigation aimed at understanding causes of HFpEF, improving risk stratification and providing better care.

10 Aims

To develop a large, deeply characterised cohort that will be a platform for collaborative clinical and translational HFpEF research, in order to:

1. Reclassify HFpEF into distinct diagnoses, where possible, based on disease mechanisms, clinical factors and outcome.
2. Evaluate whether patients in the distinct groups respond differentially to treatments, with the aim of predicting individual patient treatment response.
3. Create a platform for clinical trials that:
    a. Matches mechanism of action of therapies (new, repurposed or previously discarded) with HFpEF subgroup/anticipated treatment response.
    b. Provides groups of patients readily available for recruitment to trials.
    c. Has data linkage in place for clinical outcomes.
4. Create a platform for identifying phenotypic and genetic factors that could be used as the basis for:
    a. Improving understanding of the causes of HFpEF.
    b. Developing diagnostics.
    c. Improving risk stratification.
5. Facilitate industry engagement by providing a single point of access for industry.

11 Study design

Prospective cohort study.

12 Study setting

NHS secondary or primary care in the United Kingdom.

Criteria for the selection of sites will be determined by the Executive Steering Committee and Working Group and will be described in the supplementary document 'Site Suitability Assessment'.

Participating sites will be listed in the 'UK HFpEF Participating Sites' log, maintained separately to the protocol.

13 Study population

All individuals will be considered for inclusion in this study regardless of age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion and belief, sex, and sexual orientation, except where the study inclusion and exclusion criteria explicitly state otherwise.

13.1 Inclusion criteria

1. Written informed consent
2. Diagnosis of HFpEF by a HF specialist (e.g., a cardiologist with HF expertise, a primary care physician with HF expertise, a secondary/tertiary care physician with HF expertise, a HF nurse specialist, a specialist HF pharmacist).
3. Natriuretic peptide levels measured

13.2 Exclusion criteria

1. LV EF ever < 40%. (For clarity, patients with a previous LVEF below 40%, which has since improved to above 40%, are excluded)
2. Known infiltrative cardiomyopathy (e.g., amyloid, sarcoid, lymphoma, endomyocardial fibrosis)
3. Known active myocarditis, constrictive pericarditis, or cardiac tamponade
4. Known genetic hypertrophic cardiomyopathy or obstructive hypertrophic cardiomyopathy
5. Known arrhythmogenic right ventricular cardiomyopathy
6. Known severe primary valvular heart disease
7. Known idiopathic, heritable or drug-induced pulmonary arterial hypertension
8. Heart transplantation or ventricular assist device
9. Complex congenital heart disease

13.2.1 Note regarding LV ejection fraction criterion

Recruitment will be monitored; the proportion of participants with LV EF 40-49% will be limited to no more than 25% of the cohort.

13.3 Co-enrolment guidelines

Participants in UK HFpEF are free to participate in any other research studies; participation in other studies is not an exclusion to participating in UK HFpEF, and participation in UK HFpEF does not prevent participation in other studies.

Potential participants should be asked whether they are involved in any other research study as part of the baseline assessment, and this should be recorded in the study database.

Participants who have been enrolled in other HFpEF studies who have given consent for long-term follow-up and sharing of data may be included in the registry if all study criteria have been met.

14 Recruitment

In line with the "Saving and Improving Lives: The Future of UK Clinical Research Delivery" document, the process of recruitment is designed to be patient-centred. As much as possible, patients will be recruited 'where they are' in order to ensure that participation is as easy as possible, the cohort is as representative as possible, and the potential impact of factors such as COVID is minimised.

14.1 Participant identification

Potential participants may be identified from clinics, wards, diagnostic pathways and departments, electronic and paper-based health records, databases and waiting lists in secondary care.

Potential participants may be identified from clinics, diagnostic pathways, electronic and paper-based health records, databases and waiting lists in primary care.

Potential participants may be identified via recruitment platforms such as, but not limited to, CardioTrials (https://cardiotrials.org/), or The Heart Hive (https://www.thehearthive.org/).

Ethically approved posters, including paper and electronic versions, may be displayed in secondary and primary care, and disseminated via social media, patient groups, recruitment platforms and charities.

14.2 Participant approach

14.2.1 Secondary care

Potential participants will be approached by members of the clinical team (for example, clinicians, nurses, pharmacists, coordinators, and others who are appropriately trained) when attending hospital or community clinics for clinical care, for example, although not limited to, clinic appointments, appointments for tests, investigations or treatments, and admissions.

Potential participants may be given the Participant Information Sheet and Consent (PISC) form during the attendance at hospital and the study discussed with them. Potential participants will have time to read and digest the information and ask any questions they may have. Potential participants can decide to give consent immediately, in which case study procedures may be conducted on the same day. If potential participants wish to have longer to consider taking part, they may be contacted, for example by phone or email, at least seven days from when the PISC has been given, to discuss the study further, answer any questions and invite them for a study visit, or organise for them to undergo the study procedures at their next clinical attendance. A contact point is included in the PISC so that a potential participant can get in contact before seven days or at any other time.

Potential participants may be sent the PISC in advance of hospital attendance (by post, email, or other means).

If a hospital appointment takes place virtually (for example, a telephone or video clinic appointment), the study may be discussed during the appointment and the PISC may be sent (by post, email, or other means) to the potential participant. The potential participant may then be contacted, for example by phone or email, to discuss the study further, answer any questions and invite them for a study visit, or organise for them to undergo the study procedures at their next clinical attendance.

14.2.2 Primary care

Potential participants will be identified by members of the clinical team (for example, clinicians, nurses, pharmacists, coordinators, administrators and others who are appropriately trained). The clinical team will describe the study to the potential participant. This may happen when the potential participant is attending the primary care centre, or may happen by means such as phone call, email or message. If the potential participant

is agreeable, their details will be passed to the research team at the most appropriate secondary care centre, who will then invite them for a study visit.

14.2.3 Recruitment platforms

Recruitment platforms such as CardioTrials are patient-centred digital platforms that grant patients the opportunity to participant in clinical studies that they are most suitable for.

Details of the study will be put onto the platform, including details of how to contact the research team. The platform allows patients to browse research studies that are available to participate in. From there, patients can choose the study that they may be interested in, view the relevant study information and contact the research team. The research team will then invite the patient for a study visit at the most appropriate secondary care centre.

14.3 Participant consent

Written informed consent is required for all participants.

It will be clearly stated that participation in the study is voluntary and that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal. The right of the patient to refuse consent to participate in the trial without giving reasons must be respected.

The person obtaining consent must be suitably qualified and experienced, and have been authorised to do so by the site Principal Investigator.

In obtaining and documenting informed consent, the person taking consent should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

The participant may, without being subject to any resulting detriment, withdraw from the trial at any time by revoking the informed consent. The rights and welfare of patients will be protected by emphasising to them that the quality of medical care will not be adversely affected if they decline to participate in this study.

Where possible, consenting may be performed via electronic devices, such as computers, tablets or phones. Electronic consent will take place with the patient present, and may take the form of simple electronic signatures, advanced electronic signatures, or qualified electronic signatures, or other means, depending on the system that is used at Site and with approval by Sponsor. Consenting may also take place via paper forms. The content of the electronic and paper consent will be the same, but presentation may differ.

If electronic consenting is used, a copy will be uploaded to the study administration database, a copy will be filed in the Investigator Site File/electronic equivalent (electronic or paper) and a copy will be filed in the participant's health record (electronic or paper) at the study site.

If paper consenting is used, the original signed form will be filed in the Investigator Site File, a copy will be uploaded to the study administration database, and a copy will be filed in the participant's health record (electronic or paper) at the study site.

14.4 Procedure for recruitment to 'Stage 2' studies

UK HFpEF will support recruitment of participants to other studies ('Stage 2' studies) according to participant characteristics.

Participant characteristics may include, for example, but are not limited to, clinical characteristics, imaging characteristics, circulating biomarker characteristics, genetic characteristics, or a combination.

Stage 2 studies may include, for example, but are not limited to, interventional trials, or studies evaluating patients with other research procedures. By providing patients who match the recruitment criteria for such Stage

2 studies, it means that research can be conducted more efficiently, and it gives patients who would like to take part in other studies the opportunity to do so. Such studies would require their own Research Ethics Committee approval and participant consent.

The consent form for UK HFpEF includes a section regarding consent to be contacted about Stage 2 studies. Participants will be invited to take part in no more than four Stage 2 studies in any 12 month period.

Applications to undertake Stage 2 studies involving the recall of participants will be reviewed and overseen by the Executive Steering Committee. It is generally expected that research data generated as part of Stage 2 studies would be deposited in the UK HFpEF study database, in order to, for example, further enhance participant characterisation and facilitate further data analyses.

14.4.1 Sample analyses

As part of UK HFpEF, a very wide range of analyses may be undertaken on the blood samples donated by participants, as described in section 15.3. Such sample analyses are an integral part of the study and are part of the UK HFpEF Research Ethics Committee approval. Depending on where samples are analysed, a Material Transfer Agreement may be required. See section 15.3 for further details.

If a particular sample analysis is deemed to be outwith that described in this protocol, the analysis may require a dedicated Research Ethics Committee approval, but use of the samples would not require participant re-consent.

15 Study assessments and procedures

15.1 Study schedule

The study schedule is outlined in Table 1. Assessments and procedures may be conducted when patients are attending NHS facilitates for clinical care, including on the same day that consent is provided, or during a study visit. As much as possible, assessments and procedures should take place on the same day, but if this is not possible, they could take place across more than one clinical attendance, or across, for example, a study visit and clinical attendances.

For example, participants undergoing cardiovascular magnetic resonance (CMR) imaging as part of their clinical care are unlikely to have the CMR on the same day as an out-patient clinic visit e.g., most study assessments and procedures could take place as part of the out-patient clinic visit, and the additional 5 minutes of CMR scanning could take place during the clinical CMR visit.

Table 1

Assessments and procedures	Visit*
Signed consent form	X
Review of medical, health, social care information	X
Physical status	X
Blood sample collection	X
Blood sample processing	X
Questionnaire	X
6 minute walk test**	X
CMR scanning***	X
eCRF completion including data transfer and query resolution	X

CMR = cardiovascular magnetic resonance

* May take place when patients are attending NHS facilitates for clinical care, including on the same day that consent is provided, or during a study visit. As much as possible, the assessments and procedures should take place on the same day, but if this is not possible, they could take place across more than one clinical attendance, or across, for example, a study visit and clinical attendances. See text above the table for further details.

** Sub-study

*** For patients undergoing CMR as part of their clinical care (sub-study)

15.2 Assessments and procedures

Study assessments and procedures, and the list of data fields to be collected, will be detailed in the Study Reference Manual. Briefly, they will include those listed below. Source documents, and the process of recording data, are described in the Source Document Agreement.

15.2.1 Review of medical, health, social care information

Information that may be collected includes, but is not limited to: medical history, diagnoses, prescriptions, medications, vaccinations, referrals to health professionals, laboratory tests, imaging, ECGs, other investigations, information on hospital attendances and admissions, lifestyle, and other health-related information.

15.2.2 Physical status

Physical status assessment may include, but may not be limited to, the following. Most of this information will usually be available from participants' health record, but where not, it will be measured:

- Symptoms: New York Heart Association (NYHA) Class, presence of orthopnoea, paroxysmal nocturnal dyspnoea.
- Signs: Blood pressure, pulse rate, height, weight, presence of peripheral oedema.
- Frailty: Assessment such as Rockwood Clinical Frailty Scale.

15.2.3 Blood sample collection and processing

Blood sampling will be performed for DNA extraction, plasma and serum. The total volume of blood collected will be up to 50 ml. Samples will undergo initial processing and storage at sites, before being transferred to a central repository (NIHR National Biosample Centre). Further details regarding collection, initial processing and storage, and transfer of samples to the central repository will be provided in the Study Reference Manual.

15.2.4 Questionnaire

The Minnesota Living with Heart Failure Questionnaire (MLHFQ) is a self-administered, validated, reliable, responsive and widely used heart failure-specific patient reported outcome measure, that characterises patient health-related quality of life within the functional and psychosocial domains.

15.2.5 Six minute walk test (sub-group)

Where possible, in terms of site logistics and participant characteristics, 6-minute walk testing will be performed according to standard protocols. The distance walked by participants at their own pace on a measured, flat, hard surface in a period of 6 minutes will be recorded.

15.2.6 CMR scanning (sub-group)

Where participants are undergoing CMR scanning as part of their clinical care, the CMR scans (i.e., images/data), will be uploaded to the study database (Trusted Research Environment – see section 16.4) for analysis, which may include, for example, automated analysis, modelling and artificial intelligence algorithms. Scans will be available in the study database for future analysis as new analysis techniques/new measurements of interest become available. CMR measurements may also be entered into the study database. CMR scanning may include up to approximately an additional 5 minutes of scanning above that which is considered part of the clinical scan, so that additional images can be acquired, and additional measurements made, for the study.

15.3 Blood sample analyses

Details regarding sample storage will be provided in the Study Reference Manual. Multiple types of analyses will be performed on the donated samples. These will generate information that may, for example, improve understanding of disease mechanisms including genomics, facilitate clustering and identification of HFpEF subgroups, facilitate the development of diagnostics, support improved risk stratification, support improved

guidance of patient management, and improve or support other aspects of HFpEF research and patient management. The analyses may also facilitate recall of participants for Stage 2 studies.

Samples, and the data generated from the samples, will be linked to the other data, in order to, for example, allow relationships between data to be evaluated. For example, metabolomic data may be assessed in relation to genomic data and clinical data, to provide important insight into how metabolism is influenced by genomic variations, and how it contributes to disease pathogenesis, clinical manifestations, clustering and outcome.

As technology is continually advancing it is not possible to comprehensively list analysis methods that may be applied to samples in the future, but UK HFpEF will provide a powerful resource for evaluating emerging methodologies and analyses. Examples of the kinds of analyses and investigations likely to be undertaken on the samples are described below. Analyses may be conducted on samples from all participants, or from subgroups of participants, for example participants with certain characteristics.

Analyses of samples and data generation will be carried out by the most suitable provider. This may be within NIHR facilities, NHS facilities, research facilities or by independent commercial organisations ('industry'), and may take place in the United Kingdom or overseas, including outside of the European Economic Area and in the United States of America. All such analyses will be undertaken only on pseudonymised samples. Link tables will be retained within the UK HFpEF study administration database. Participant personal details, such as name, date of birth or address, will not be passed to external teams. The Executive Steering Committee will oversee these processes.

The release of samples for analysis will be subject to scientific review by the Executive Steering Committee and an appropriate Material Transfer Agreement. The Material Transfer Agreement is a legally binding document that will regulate the use of samples to ensure that standards are maintained. A condition of sample analysis is that data generated should be deposited in the UK HFpEF study database. This will enhance participant characterisation and facilitate further analyses.

15.3.1 Genomics

Participants will provide consent for genomic sequencing up to the level of the whole genome.

Genomic analyses will identify variations in the sequence of DNA. DNA sequencing may performed:

- in full (whole genome sequencing),
- partially, for example, by sequencing the protein-coding region of the genome (exome),
- partially, for example, genome-wide genotyping,
- in a targeted manner, for example, by genotyping single or small sets of genetic variants.

These analyses may be initiated at any time after recruitment. Genotype imputation processes, which predict or impute genotypes that are not directly assayed and thus can provide more detailed genetic information, may be used. Data from other omics platforms may also be analysed to determine overall quality of data and to provide normalisation. Data will be placed in the study database for analysis in conjunction with other data, as well as for use in recall studies.

15.3.2 Transcriptome analysis

Funding permitting, transcriptome analysis may be performed. Transcriptome analysis may be employed to evaluate gene expression patterns. This may include evaluation of RNAs involved in protein synthesis, RNAs involved in post-transcriptional modification or DNA replication, and regulatory RNAs. Analysis may include microarray analysis or RNA-sequencing, or other techniques. Data will be placed in the study database for analysis in conjunction with other data, as well as for use in recall studies.

15.3.3 Protein, lipid, carbohydrate, biochemistry, metabolomics and other analytes

Funding permitting, protein, lipid, carbohydrate, biochemical, metabolomic and other analyses may be performed on plasma and serum samples. As an example, proteomics technologies may be used to explore differences in protein expression profiles. Data will be placed in the study database for analysis in conjunction with other data, as well as for use in recall studies.

15.4 Study duration

Recruitment is expected to take approximately 5 years. Participants will remain in the study for 10 years from when they provide consent.

15.5 Withdrawal

Participants are free to withdraw consent at any time without providing a reason. Participants wishing to withdraw will be asked to select one of the following options:

1. **No further contact.** Withdrawal from further contact but allow their sample/s to be retained, research using their information and sample/s to continue, and collection of data from their medical, health, social care and other health-related records, from local, regional and national systems, to continue and be used for analysis.
2. **No further contact and no further analysis of sample/s.** Withdraw from further contact and have any of their remaining sample/s that have not already been used for analysis destroyed so that no further samples can be distributed for the generation of new data. However, they allow research using information already held about them, including from previous analysis of their sample/s, to continue, and they allow collection of data from their medical, health, social care and other health-related records, from local, regional and national systems, to continue and be used for analysis.
3. **No further contact and no further research using samples or information.** Withdraw from further contact. Any of their remaining sample/s that have not already been used for analysis will be destroyed so that no further samples can be distributed for the generation of new data. No further information from their medical, health, social care and other health-related records will be collected. No further research will be conducted using the information held about them.

Where the participant's preference cannot be confirmed, Option 1 will be implemented. This is explained in the Participant Information Sheet.

For participants choosing option 3, the study team will, from the time of confirmation of the withdrawal:

- Stop retrieving new data from local, regional and national systems.
- Not add new data from sample analyses to the study database.
- Bar the use of existing data in further analyses, but removal of data from integrated aggregation files, from data distributed through managed access, and from analyses already conducted, is not possible.
- Personal details such as name, date of birth or address, will be retained in archive so that a record remains available for retrieval of the initial consent and to have full documentation of the withdrawal process. Personal details such as name, date of birth or address will not be used after withdrawal for contacting of the participant for possible recall studies.

  For the avoidance of doubt:

- Samples already distributed for the purpose of analysis and measurement cannot be withdrawn.
- Remaining 'stock' samples will be destroyed.
- Data cannot be removed from all electronic media because of repeated back-ups and the existence of integration files containing aggregated data from the original individual level data.

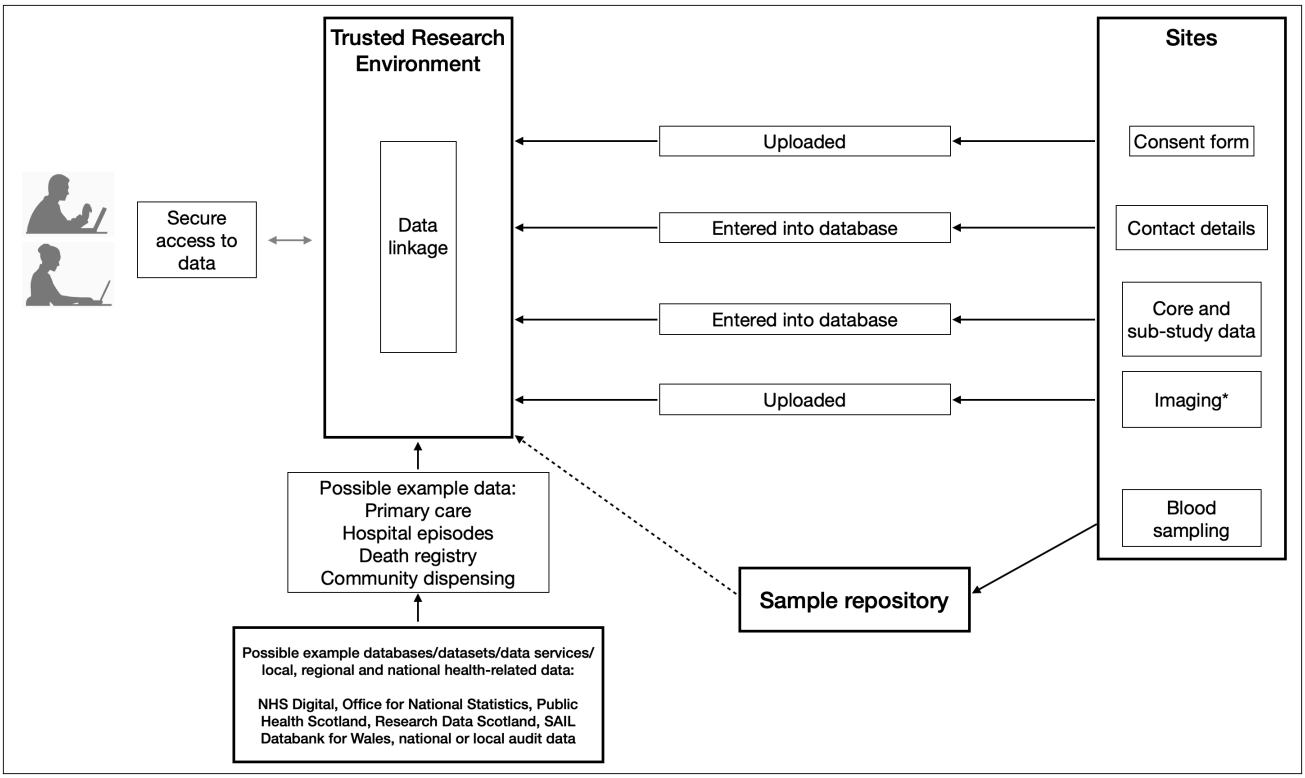
- Data may have been securely distributed, analysed or used in publications. This cannot be reversed or withdrawn.

A study withdrawal form will be initiated to ensure all necessary actions are undertaken.

16 Data management

16.1 Overview

Figure 1 below provides an overview of the expected flow and management of data. Further details are provided in the Data Management Plan.



*Imaging may include, for example, echocardiography and CMR

-- Samples will be linked to the other data

16.2 Data

Participants will be asked to provide consent for the collection and use for research of data relevant to their past and future health from medical, health, social care and other health-related records, which are collected or held in local, regional and national systems.

The data collected may include: general practice (GP) records, hospital records, national health-related data collected by national organisations (such as NHS Digital, the Office for National Statistics, Public Health Scotland, Research Data Scotland, the SAIL Databank for Wales), national or local audit data, or any other source of data relevant to participants' health.

Data will be linked. Data may be collected at baseline or at any stage thereafter.

16.2.1 Core data

Core data are data that should be collected on all participants at all sites. The list of core data fields is detailed in the Study Reference Manual. These may include, but are not limited to, the following:

- Participant personal details, such as, surname and given names, date of birth, sex, ethnicity, NHS number, contact details (including address, email and phone numbers, if available), and GP details.

  Participant personal details are needed in order to, for example:

- Contact participants to arrange study visits
- Retrieve information from medical, health and social care records, including electronic and paper-based information
- Retrieve medical, health, and social care data from local, regional and national systems and organisations such as, but not limited to, NHS Digital, the Office for National Statistics, Public Health Scotland, Research Data Scotland, the SAIL Databank for Wales, national or local audit data.
- Allow participants to be contacted regarding Stage 2 studies

- Medical history, diagnoses, co-morbidities, symptoms, signs, lifestyle, referrals
- Prescriptions, medications, vaccinations
- Physical status (see above)
- Laboratory tests
- ECG measurements

  ECG measurements will be recorded, and, where possible, the ECG itself, and the raw ECG data, may be uploaded to the study database.

- Echocardiographic measurements

  Echocardiograms (i.e., raw images/data), and other imaging modality images, may also be uploaded to the study database (Trusted Research Environment – see section 16.4) for analysis, which may include automated analysis/artificial intelligence algorithms. Scans will be available in the study database for future analysis as new analysis techniques/new measurements of interest become available.

- Data on hospital attendances and admissions, death registry information.

16.2.2 Other data

Other relevant data from the assessment and management that participants undergo/receive as part of their clinical care should also be recorded. For example, data from cardiac catheterisation, heart rhythm monitoring, exercise assessments, other imaging etc.

16.2.3 Sub-studies

Sub-studies will focus on specific aspects of HFpEF in addition to the core dataset, involving investigators/sites with an interest in these areas. This approach aims to ensure that the registry population is as representative of HFpEF as possible, whilst also providing a platform for more specific evaluations. Sub-studies will benefit from the data present in the wider registry, and the wider registry will benefit from data collected as part of the sub-studies.

Sub-studies may include, for example, invasive assessments, laboratory measurements, and other evaluations. Where such evaluations take place as part of clinical care, the data may be included in the registry. If a procedure is not part of the participant's clinical care i.e., if a procedure is conducted for research purposes, separate approval by a Research Ethics Committee and the Health Research Authority would be required.

16.2.4 Data from organisations such as NHS Digital

Medical, health and social care data organisations/data services/datasets, such as NHS Digital, the Office for National Statistics, Public Health Scotland, Research Data Scotland, the SAIL Databank for Wales and national and local audits, contain a large amount of often routinely-collected medical, health and social care data.

The benefits of incorporating data from sources such as these into UK HFpEF include: 1. It may mean substantially less data is required to be inputted at sites, for example, medical history and medication data; 2.

Data may be more accurate, comprehensive and contemporary; 3. Follow-up/outcome data, such as hospital admissions and death data, will be available. It is difficult to collect comprehensive outcome data at scale by other methods.

Data from such organisations/data services/datasets that may be collected, incorporated into the study database (Trusted Research Environment – see section 16.4) and used for research may include, but are not limited to: medical history, diagnoses, symptoms, signs, prescriptions, medications, vaccinations, referrals to health professionals, laboratory tests, imaging, other investigations, procedures, information on hospital attendances and admissions, death registry information, lifestyle, and any other health-related information.

16.3 Data management and governance

Manchester University NHS Foundation Trust (MFT), based in the UK, is the study Sponsor and will act as the data controller. MFT will put in place oversight arrangements appropriate to the requirements of the study.

Data will be held by MFT at their appropriately selected locations or facilities. Any such storage arrangements will be governed by the appropriate agreements.

A “privacy by design” approach will be adopted, whereby those whose role requires them to see personal data can do so, while other team members, and potentially approved external investigators, see only pseudonymised data.

16.4 Trusted research environment

Data will be stored in a ISO27001 certified Trusted Research Environment (TRE) commissioned by the British Heart Foundation Data Science Centre, based in the UK. ISO 27001 is an internationally recognised best-practice standard for information Security Management Systems.

A TRE enables highly secure research, including secure data storage, access, sharing, analysis and linkage, in a governed environment. It provides secure, audited data storage. Access is controlled, secure and role-based, on a named person basis only, with individual user authentication. Access will be determined by the Executive Steering Committee. It provides an accredited platform for NHS Digital data sharing framework agreements, which allows national health-related data collected by national organisations such as NHS Digital to be incorporated and linked. It also provides an analysis environment that supports statistical packages, meaning that data will generally be accessed, and statistical analyses will generally be performed, within the secure analysis area of the TRE. Access to the data, and the data that can be ‘seen’ as part of the analysis, will be determined by the Executive Steering Committee. Activity will be audited. Usually, outputs released from the secure analysis area will comprise reports or findings rather than the data itself. Reports or findings being outputted will be reviewed by the Executive Steering Committee, or a delegated member thereof, before they are released, to ensure that they are appropriate.

16.5 Participant confidentially

Participants will be given a unique participant identification number (pseudo-identifier). Study data will be held in a study database in the Trusted Research Environment (see section 16.4). The database will be de-identified and pseudonymised. Samples will also be stored in pseudonymised fashion.

Individual participant data from the multiple sources described, for example, data entered at sites, data obtained from blood sample analyses such as genomic data, and data from data services such as NHS Digital, will be linked in the Trusted Research Environment.

Identifying participant personal details, such as name, full date of birth, NHS number, address and contact details, will be held separately in the Trusted Research Environment, in a study administration database. An electronic copy of participants’ consent form will be uploaded and stored securely alongside their personal

details in the study administration database. The link between the pseudo-identifiers and participant personal details will be kept securely in the study administration database.

Participant personal details are needed in order to, for example:

- Retrieve information from medical, health and social care records, including electronic and paper-based information
- Retrieve medical, health, and social care data from local, regional and national systems and organisations such as, but not limited to, NHS Digital, the Office for National Statistics, Public Health Scotland, Research Data Scotland, the SAIL Databank for Wales, national or local audit data.
- Allow participants to be contacted regarding Stage 2 studies

Sites may also hold personal details of participants recruited at their site so that participants can be contacted to arrange study visits.

The study team are aware that keeping personal data safe is of paramount importance to participants, and this is one of the key reasons why a Trusted Research Environment is being used. Only a very small number of named members of the study team, determined by the Executive Steering Committee, will be able to access participant personal details in the study administration database. Other researchers who work with the data will have no access to participant personal details. Personal details will not be released. The Executive Steering Committee will oversee these processes.

In some circumstances, for example to fulfil General Data Protection Regulation (GDPR) data access requests, it may be necessary to combine participant study data with their personal details. All study team members who would undertake such activity will have GCP training, approval from the Executive Steering Committee and specific approval from the study Sponsor.

16.6 Gift nature of data and sample

It will be explained in the Participant Information Sheet that in taking part in the study, participants donate their data and blood sample as a gift, without receiving a payment.

16.7 Reporting of sample analyses

UK HFpEF does not intend to undertake analysis of data generated by genotyping or sequencing of DNA samples to identify variants that may have clinical significance, and hence does not plan to provide feedback of genetic findings. This is in line with other national cohort studies such as NIHR BioResource. The primary purpose of such genomic analysis is to study aspects such as potential novel subsets and clusters of disease and co-morbidities. It will also facilitate recall of participants for other research studies (Stage 2 studies). If a recall research study involves identification and use of genomic information of clinical significance, the arrangements for communicating findings will be described in the Research Ethics Committee application of the recall study.

Most of the data generated as a consequence of analysis of the samples provided (for example proteomic or metabolomic profiling) are unlikely to be clinically significant, and if findings have clinical significance, then the effect size of the observation is likely to be small.

16.8 Data access and analysis

Access to the data will be determined by the Executive Steering Committee.

Study investigators and analysts accessing data will require individual user authentication. Data will generally be accessed, and analyses will generally be performed, within the secure analysis area of the Trusted Research Environment. Access to the data, and the data that can be ‘seen’ as part of the analysis, will be determined by the Executive Steering Committee. Activity will be audited. Usually, outputs released from the secure analysis

area will comprise reports or findings rather than the data itself. Reports or findings being outputted will be reviewed by the Executive Steering Committee, or a delegated member thereof, before they are released, to ensure that they are appropriate.

Sometimes it may be necessary for data, including imaging, to be released from the Trusted Research Environment for analysis. For example, where bespoke analysis algorithms or programming are required, such as automated scan analysis, modelling and artificial intelligence algorithms, or where specific statistical software is required. In such circumstances, access, and the data that can be 'seen', will be determined by the Executive Steering Committee. Data outputted will be pseudonymised and will be reviewed by the Executive Steering Committee, or a delegated member thereof, before they are released. Identifying participant personal details such as name, address, date of birth, will not be released.

16.9 Data sharing

Participants will be asked to provide consent for pseudonymised study data, including, for example, individual patient-level data, scans and any other study data, to be shared for research purposes with investigators or organisations, including independent commercial organisations ('industry'), in the United Kingdom or overseas, including outside of the European Economic Area and in the United States of America. Participant personal details such as name, address, date of birth, will not be shared.

Requests for access to the data will be managed by the Executive Steering Committee. Release of data to investigators or organisations requesting access, whether they reside within or outside the UK, will be covered by a Data Transfer Agreement. The Data Transfer Agreement is a legally binding document that will regulate the use of data to ensure that standards are maintained.

16.10 Data archiving

It is anticipated that at the end of the study, anonymised study data, including genotype and phenotype data, will ultimately be transferred to a managed-access research or scientific archive such as the European Genome-Phenome Archive.

16.11 Release of personal information for Stage 2 studies

See section 14.4. Applications to undertake Stage 2 studies involving UK HFpEF participants will be reviewed and overseen by the Executive Steering Committee.

17 Statistical considerations

17.1 Sample size

The purpose of UK HFpEF is to recruit a large, deeply characterised cohort of patients with HFpEF in order to identify distinct subgroups based on disease mechanisms, clinical factors and outcomes, improve understanding of the causes of HFpEF, provide the basis for developing and evaluating new therapies and diagnostics, and improve risk stratification. Ultimately, the aim is to improve the quality of life and outcome of patients with HFpEF.

An exact sample size to address all of these questions is difficult to provide. Using the NIHR BioResource as a guide, several possible exposures and outcomes that would be of relevance to HFpEF and HFpEF subgroups have been explored. A large cohort provides adequate power to address many of these questions, with appropriate adjustment, with examples given below (reproduced from the NIHR Immune Mediated Inflammatory Diseases [IMID] BioResource protocol). Based on these calculations, we aim to ultimately recruit 10,000 patients.

Current funding from NIHR includes funding for setting up the study infrastructure and recruitment of approximately the first 875 patients. Having established the study, commenced recruitment, and demonstrated feasibility, further funding will be sought to complete recruitment.

Example sample sizes required to identify different odds ratios in a case control study (1:1 matching) according to putative exposure in the control group. (Reproduced from the NIHR IMID BioResource protocol).

Exposure in controls	Sample size required for each odds ratio (80% power, 95% confidence level)		
	Odds ratio 1.2	Odds ratio 1.5	Odds ratio 2.0
0.05	9176	1770	560
0.1	4890	960	310
0.2	2800	562	190

Example sample sizes required to identify different risk ratios in a cohort study according to the putative exposure and cumulative incidence of the outcome. (Reproduced from the NIHR IMID BioResource protocol).

Frequency of exposure	Cumulative rate of outcome in unexposed	Risk ratio to be detected	Sample size required Exposed	Sample size required Unexposed
50%	5%	3	160	160
		2	475	475
		1.5	1550	1550

	1%	3	870	870
		2	2500	2500
		1.5	8150	8150
10%	5%	3	75	665
		2	235	2115
		1.5	810	7280
	1%	3	400	3600
		2	1240	11170

18 Ethical and regulatory considerations

18.1 Ethical considerations

The study will abide by the principles of Good Clinical Practice (GCP), the World Medical Association Declaration of Helsinki and the UK Policy framework for Health and Social Care research, as amended from time to time.

Study procedures are documented. All are standard, non-invasive, well tolerated procedures with minimal associated risk.

The research team explored the ethical considerations for the study with a dedicated Patient Advisory Group. The Group felt that the burden being placed on participants is acceptable, that the procedures involved are appropriate and that there are no barriers to taking part.

18.2 Peer review

The study has been reviewed by NIHR through their independent, external, expert peer review process.

18.3 Regulatory review and compliance

Before the start of the study, a favourable opinion will be sought from an independent NHS Research Ethics Committee (REC) for the study protocol, informed consent forms and other relevant documents.

No participants will be enrolled into this study prior to the study receiving REC and Health Research Authority (HRA) approval, and until local site R&D approval has been obtained.

The study team at MFT will be responsible for maintaining the Trial Master File, which will contain the study approval documentation, including all correspondence with relevant authorities such as REC and HRA, and in which all current and superseded study documents will be retained.

The Principal Investigator at each site will be responsible for maintaining a study Site File, in which study documentation relevant to the site, including, for example, current and superseded study documents, will be retained.

The Chief Investigator is responsible for producing annual reports as required, including annual progress reports to the REC.

The Chief Investigator will submit a final report at the conclusion of the study to the Sponsor and the REC within the timelines defined in the regulations.

If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.

During the life of the study, there may be amendments to the study protocol and/or documentation. Substantial amendments will not be implemented until REC review is in place and local approvals have been obtained. All amendments and regulatory communications will be filed in the Trial Master File and Site Files.

18.4 Amendments to the protocol

Any amendments to the study protocol shall be reviewed by the Sponsorship team prior to submission. Any non-substantial amendments shall be notified to the HRA, and any substantial amendments, along with amended documentation, shall be approved by the REC, and HRA, prior to implementation, as per nationally agreed guidelines. The Chief Investigator, or designee, will work with the R&I department to put the necessary arrangements in place to implement the amendment and to confirm their support for the study as amended.

18.5 Source documents

Source documents will be as set out in the Source Document Agreement.

18.6 Records retention and archiving

Records will be retained for 10 years in accordance with the Manchester University NHS Foundation Trust SOP on record retention. The Principal Investigator at each site, or a nominated deputy, will be responsible for all research related documents. Individuals responsible for data who leave their site must inform the R&D team at their site of who will be acting as the custodian of that data.

After an End of Study Notification has been completed, and has been declared and acknowledged by the REC, the following procedures will be adhered to:

Research documents less than 10 years old will be kept on site by the PI to facilitate access for audit, information, etc. Where it is not possible to store the documents on site, the PI will arrange for off-site storage via the R&D Directorate. It will be ensured that the documents can be accessed, with short notice if required. A log will be kept by the PI of the documents stored, which will include the following information: box number (1 of 1 etc.), study ID, study name, PI, date of storage, date to be destroyed, emergency contact details, Sponsor and contact details.

Research documents more than 10 years old will be destroyed. Prior to destruction, a log will be made of all the documents that are being destroyed.

18.7 Monitoring and quality control

Trial monitoring is carried out to ensure that the rights and well-being of participants are protected during the course of a study. The study will be subject to the audit and monitoring regime of Manchester University NHS Foundation Trust in line with applicable Manchester University NHS Foundation Trust SOPs and policies. The study will have, as a minimum, an annual survey sent out for completion by a member of the research team.

18.8 Indemnity

The NHS indemnity scheme will apply to this study to ensure it meets the potential legal liability of the Sponsor, equipment, employer and investigators/collaborators for harm to participants arising from the management, design and conduct of the research. No arrangements will be made for the payment of compensation in the unlikely event of harm.

19 Publication and dissemination

It is intended that results of analyses of study data will be reported and disseminated in reports, academic journal publications and presentations.

An Authorship Policy will be developed. Individual investigators should not submit any part of their individual data for publication without the prior consent of the Executive Steering Committee. Study results will be reported according to best practice, including, for example, CONSORT statements, and the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected.

Lay summaries of the findings will be posted to the study website and links to these summaries may be posted on patient group websites. The summaries will be written in conjunction with the Patient Advisory Group. Presentations will be made to patient groups, with members of the Patient Advisory Group involved.

20 References

1 Luscher, T. F. Heart failure: The cardiovascular epidemic of the 21st century. *Eur Heart J* **36**, 395-397, doi:10.1093/eurheartj/ehv004 (2015).

2 Ponikowski, P. *et al.* 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* **37**, 2129-2200, doi:10.1093/eurheartj/ehw128 (2016).

3 House of Commons Library. NHS Funding and Expenditure. (2019).

4 Chang, P. P. *et al.* Trends in Hospitalizations and Survival of Acute Decompensated Heart Failure in Four US Communities (2005-2014): ARIC Study Community Surveillance. *Circulation* **138**, 12-24, doi:10.1161/CIRCULATIONAHA.117.027551 (2018).

5 Owan, T. E. *et al.* Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* **355**, 251-259, doi:10.1056/NEJMoa052256 (2006).

6 Lewis, G. A. *et al.* Biological Phenotypes of Heart Failure With Preserved Ejection Fraction. *J Am Coll Cardiol* **70**, 2186-2200, doi:10.1016/j.jacc.2017.09.006 (2017).

7 Yusuf, S. *et al.* Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet* **362**, 777-781, doi:10.1016/S0140-6736(03)14285-7 (2003).

8 Massie, B. M. *et al.* Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med* **359**, 2456-2467, doi:10.1056/NEJMoa0805450 (2008).

9 Redfield, M. M. *et al.* Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA* **309**, 1268-1277, doi:10.1001/jama.2013.2024 (2013).

10 Redfield, M. M. *et al.* Isosorbide Mononitrate in Heart Failure with Preserved Ejection Fraction. *N Engl J Med* **373**, 2314-2324, doi:10.1056/NEJMoa1510774 (2015).

11 Pitt, B. *et al.* Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* **370**, 1383-1392, doi:10.1056/NEJMoa1313731 (2014).

12 Solomon, S. D. *et al.* Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. *N Engl J Med* **381**, 1609-1620, doi:10.1056/NEJMoa1908655 (2019).

13 Shah, S. J. Precision Medicine for Heart Failure with Preserved Ejection Fraction: An Overview. *J Cardiovasc Transl Res* **10**, 233-244, doi:10.1007/s12265-017-9756-y (2017).

14 Zile, M. R. *et al.* Prevalence and significance of alterations in cardiac structure and function in patients with heart failure and a preserved ejection fraction. *Circulation* **124**, 2491-2501, doi:10.1161/CIRCULATIONAHA.110.011031 (2011).

15 Shah, A. M. *et al.* Cardiac structure and function and prognosis in heart failure with preserved ejection fraction: findings from the echocardiographic study of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) Trial. *Circ Heart Fail* **7**, 740-751, doi:10.1161/CIRCHEARTFAILURE.114.001583 (2014).

16 Cohen, J. B. *et al.* Clinical Phenogroups in Heart Failure With Preserved Ejection Fraction: Detailed Phenotypes, Prognosis, and Response to Spironolactone. *JACC Heart Fail* **8**, 172-184, doi:10.1016/j.jchf.2019.09.009 (2020).

17 Segar, M. W. *et al.* Phenomapping of patients with heart failure with preserved ejection fraction using machine learning-based unsupervised cluster analysis. *Eur J Heart Fail* **22**, 148-158, doi:10.1002/ejhf.1621 (2020).

18 Kao, D. P. *et al.* Characterization of subgroups of heart failure patients with preserved ejection fraction with possible implications for prognosis and treatment response. *Eur J Heart Fail* **17**, 925-935, doi:10.1002/ejhf.327 (2015).

19 Shah, S. J. *et al.* Phenomapping for novel classification of heart failure with preserved ejection fraction. *Circulation* **131**, 269-279, doi:10.1161/CIRCULATIONAHA.114.010637 (2015).

20 Ahmad, T., Desai, N. R. & Januzzi, J. L. Heart Failure With Preserved Ejection Fraction: Many Emperors With Many Clothes. *JACC Heart Fail* **8**, 185-187, doi:10.1016/j.jchf.2019.11.004 (2020).

21 Porrello, E. R. & Delbridge, L. M. D. HFpEF-Time to Explore the Role of Genetic Heterogeneity in Phenotypic Variability: New Mechanistic Insights Offer Promise for Personalized Therapies. *Circulation* **140**, 1607-1609, doi:10.1161/CIRCULATIONAHA.119.042496 (2019).

21 Appendices