# Rationale and design of the United Kingdom Heart Failure with Preserved Ejection Fraction Registry

OPEN ACCESS

Original research

# Rationale and design of the United Kingdom Heart Failure with Preserved Ejection Fraction Registry

UK HFpEF Collaborative Group

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/heartjnl-2023-323049).

BHF Manchester Centre for Heart and Lung Magnetic Resonance Research, The University of Manchester, Manchester, UK

**Correspondence to**
Christopher A Miller;
christopher.miller@manchester.ac.uk

Received 6 June 2023
Accepted 26 August 2023



**To cite:** . *Heart* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/heartjnl-2023-323049

## ABSTRACT

**Objective** Heart failure with preserved ejection fraction (HFpEF) is a common heterogeneous syndrome that remains imprecisely defined and consequently has limited treatment options and poor outcomes.

**Methods** The UK Heart Failure with Preserved Ejection Fraction Registry (UK HFpEF) is a prospective data-enabled cohort and platform study. The study will develop a large, highly characterised cohort of patients with HFpEF. A biobank will be established. Deep clinical phenotyping, imaging, multiomics and centrally held national electronic health record data will be integrated at scale, in order to reclassify HFpEF into distinct subgroups, improve understanding of disease mechanisms and identify new biological pathways and molecular targets. Together, these will form the basis for developing diagnostics and targeted therapeutics specific to subgroups. It will be a platform for more effective and efficient trials, focusing on subgroups in whom targeted interventions are expected to be effective, with consent in place to facilitate rapid recruitment, and linkage for follow-up. Patients with a diagnosis of HFpEF made by a heart failure specialist, who have had natriuretic peptide levels measured and a left ventricular ejection fraction >40% are eligible. Patients with an ejection fraction between 40% and 49% will be limited to no more than 25% of the cohort.

**Conclusions** UK HFpEF will develop a rich, multimodal data resource to enable the identification of disease endotypes and develop more effective diagnostic strategies, precise risk stratification and targeted therapeutics.

**Trial registration number** NCT05441839.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Heart failure with preserved ejection fraction (HFpEF) is a common heterogenous systemic syndrome with limited treatment options.

### WHAT THIS STUDY ADDS

⇒ UK Heart Failure with Preserved Ejection Fraction Registry (UK HFpEF) is a prospective data-enabled cohort and platform study.

⇒ Rich, multimodal data resource to enable identification of endotypes and develop more effective diagnostic strategies, precise risk stratification and targeted therapeutics.

⇒ Platform for more effective and efficient trials, targeting interventions, consent in place for rapid recruitment, linkage for outcomes.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ UK HFpEF is a unique resource that will become a key platform for collaborative UK clinical and translational HFpEF research.

## INTRODUCTION

Heart failure (HF) is a major public health problem, with large and growing individual, societal and economic impacts.[1 2] In Western-type and developed countries, lifetime risk for HF is high, estimated to be between 1 in 5 and 1 in 3, and prevalence is expected to increase by around 50% over the next 20 years.[3 4] HF is the leading cause of hospitalisation for people aged over 65, with a subsequent 1-year mortality rate of more than 30%.[5 6] Quality of life is markedly impaired compared with other chronic diseases.[7] Importantly, there are substantial geographic, socioeconomic and ethnic disparities in HF incidence and outcomes.[8 9] The economic burden of HF on healthcare systems is considerable; in 2012, the estimated global cost of HF was $108 billion per annum, and in 2019 estimated costs were more than $24 000 per patient per year in the USA.[10 11]

Approximately half of patients with HF have a left ventricular ejection fraction (LVEF) that is not markedly abnormal. The Candesartan in HF Assessment of Reduction in Mortality and Morbidity (CHARM) trial programme gave rise to the term 'preserved' EF, referring to patients with an EF>40%. Rather than being based on biology, it was a pragmatic approach to distinguish this group from the better studied group of patients with HF and a lower EF, for whom evidence-based therapies already existed and for whom placebo was thus not an appropriate comparator, and because EF was available in all patients.[12 13] More recently, HF guidelines use the term HFpEF (heart failure with preserved ejection fraction) to designate a group with an LVEF>50%, and HF with mildly reduced EF for LVEF 41–49%, while also recognising that EF is a continuum, that its measurement is associated with error and that imaging guidelines from the same societies use different thresholds.[1 2]

Instead of being a single diagnosis, it is clear that HFpEF represents a heterogenous systemic syndrome. A wide range of cardiovascular and systemic disease mechanisms are described.[14] Patients typically have a range of long-term cardiometabolic and other conditions. Outcomes are also variable; around half of

deaths in patients with HFpEF are non-cardiovascular, and fewer than 20% of hospital admissions are due to HF.[15 16]

Understanding of HFpEF remains limited. For example, it is unclear why some people with cardiometabolic conditions develop HFpEF but most do not; there is a lack of pathophysiological features that reliably distinguish HFpEF from its risk factors and normal ageing; the marked heterogeneity in cardiovascular and 'extra-cardiovascular' phenotypes is unexplained; and predictors of outcomes are poorly defined.

As a consequence, identification and management of patients with HFpEF remains challenging. A variety of diagnostic guidelines and algorithms exist, each comprising differing variables with varying measurement thresholds.[17 18] No single classification or score is able to determine the presence or absence of HFpEF. Treatment options are limited. Almost all phase III trials have been neutral, in part because study design has considered HFpEF to be a single disease entity. Indeed, it is noteworthy that subgroup analyses suggest that some agents might be effective in subgroups of patients with particular characteristics.[19–22] Sodium-glucose co-transporter-2 inhibitors are undoubtedly moving the field forward, improving quality of life and reducing the risk of HF hospitalisation, as well as prompting discussion around organisation of care.[15 16] No therapies, however, reduce mortality. The heterogeneity of patients with the same diagnostic label, lack of unified diagnostic criteria and limited treatment options have resulted in patients receiving inconsistent care.

It is with these factors in mind that the UK Heart Failure with Preserved Ejection Fraction Registry (UK HFpEF) has been conceived and designed. The overarching goal is that developing a large, deeply characterised cohort will enable novel understanding of HFpEF and identification of distinct disease endotypes, which will form the basis for more effective diagnostic strategies, precise risk stratification and targeted therapies, that will lead to improved quality of life and outcomes.

## DESIGN AND METHODS

### Overall study design and aims

UK HFpEF is a national prospective data-enabled cohort and platform study. It is a unique resource that will become a key platform for collaborative UK clinical and translational HFpEF research. The overarching objective is to provide genotyping and deep phenotyping, linked to outcomes, in a large cohort of patients. This will enable machine learning techniques to be applied in order to reclassify HFpEF into more distinct diagnoses. It will be a platform for the development of diagnostics specific to the different HFpEF subgroups, and for more effective trials that will target subgroups in whom new, repurposed or previously discarded treatments are expected to be effective. Moreover, it will provide cohorts of patients readily available for recruitment to such trials, with linkage in place for follow-up. It will enable scaled investigation aimed at understanding the causes of HFpEF, improving risk stratification and facilitating preventative intervention, and will leverage commercial funding and participation, facilitated by simplified, single-point, UK-wide access. Overall study design and aims are summarised in figure 1 and box 1.

### Oversight and governance

The study sponsor is Manchester University NHS Foundation Trust. The Executive Steering Committee is responsible for oversight of study conduct. The study was designed by the Executive Steering Committee, working in conjunction with a dedicated patient advisory group and a working group that includes representatives from sites expressing an interest in participating and other expertise such as data science, data governance and statistics. Membership of the study management committees is given in the online supplemental appendix.

Study set-up and initial recruitment are funded by the UK National Institute for Health and Care Research (NIHR) (NIHR301848). The funder had no role in study design other than through their external peer review processes. The study is supported by the NIHR–British Heart Foundation (BHF) Cardiovascular Partnership and the British Society for Heart Failure, is adopted onto the NIHR Clinical Research Network Portfolio (Central Portfolio Management System reference 52749) and registered at ClinicalTrials.gov (NCT05441839). Study website: https://www.ukhfpef.org/

### Patients

Eligibility criteria are summarised in box 2. Enrolment began on 7 October 2022 after approval. The study is being conducted in

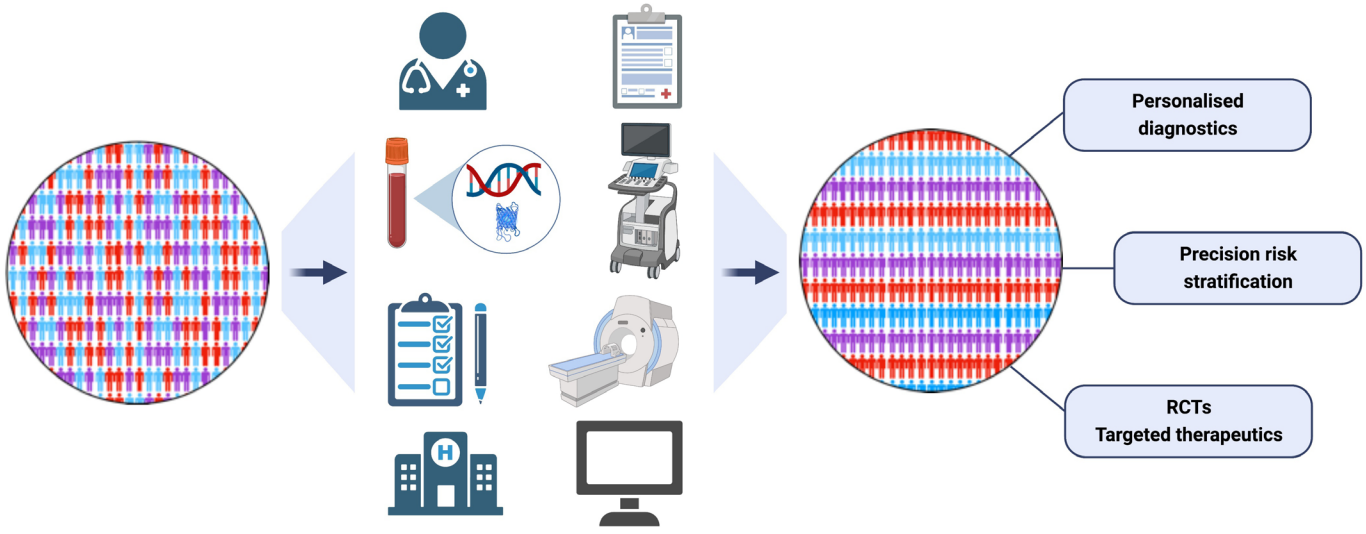


**Figure 1** UK Heart Failure with Preserved Ejection Fraction Registry (UK HFpEF) overview. UK HFpEF will develop a rich, multimodal data resource to enable the identification of disease endotypes and develop more effective diagnostic strategies, precise risk stratification and targeted therapeutics. Figure created with BioRender.com. RCTs, Hurandomised controlled trials.

**Box 1 Aims of UK Heart Failure with Preserved Ejection Fraction Registry (UK HFpEF)**

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

⇒ Reclassify HFpEF into distinct diagnoses, where possible, based on disease mechanisms, clinical factors and outcome.

⇒ Evaluate whether patients in the distinct groups respond differentially to treatments, with the aim of predicting individual patient treatment response.

⇒ Create a platform for clinical trials that:
Matches mechanism of action of therapies (new, repurposed or previously discarded) with HFpEF subgroup/anticipated treatment response.
Provides groups of patients readily available for recruitment to trials.
Has data linkage in place for clinical outcomes.

⇒ Create a platform for identifying phenotypic and genetic factors that could be used as the basis for:
Improving understanding of the causes of HFpEF.
Developing diagnostics.
Improving risk stratification.

⇒ Facilitate industry engagement by providing a single point of access for industry.

HFpEF, heart failure with preserved ejection fraction.

**Box 2 Eligibility criteria for UK Heart Failure with Preserved Ejection Fraction Registry (UK HFpEF)**

**Inclusion criteria**

⇒ Written informed consent.

⇒ Diagnosis of HFpEF by an HF specialist (eg, a cardiologist with HF expertise, a primary care physician with HF expertise, a secondary/tertiary care physician with HF expertise, an HF nurse specialist, a specialist HF pharmacist).*

⇒ Natriuretic peptide levels measured.

**Exclusion criteria**

⇒ LVEF ever <40%.† (For clarity, patients with a previous LVEF below 40%, which has since improved to above 40%, are excluded.)‡

⇒ Known infiltrative cardiomyopathy (eg, amyloid, sarcoid, lymphoma, endomyocardial fibrosis).

⇒ Known active myocarditis, constrictive pericarditis or cardiac tamponade.

⇒ Known genetic hypertrophic cardiomyopathy or obstructive hypertrophic cardiomyopathy.

⇒ Known arrhythmogenic right ventricular cardiomyopathy.

⇒ Known severe primary valvular heart disease.

⇒ Known idiopathic, heritable or drug-induced pulmonary arterial hypertension.

⇒ Heart transplantation or ventricular assist device.

⇒ Complex congenital heart disease.

*Original text (diagnosis of HFpEF by a cardiologist with HF expertise, or a primary care physician with HF expertise, or a heart failure nurse) clarified in a protocol amendment.
†Note regarding LVEF: recruitment will be centrally monitored; the proportion of participants with LVEF 40–49% will be limited to no more than 25% of the cohort.
‡Original text (LVEF<40% (at screening or any previous measurement)) clarified in a protocol amendment.
HF, heart failure; LVEF, left ventricular ejection fraction.

accordance with the principles of Good Clinical Practice and the World Medical Association Declaration of Helsinki. All participants provided written informed consent.

### Study procedures

The study protocol, participant information sheet and consent form are available at https://www.ukhfpef.org/

### Recruitment

It is expected that the majority of patients will be recruited via HF services, including outpatient clinics and inpatient wards. Patients can also be identified by primary care physicians with HF expertise, or express an interest in participating directly via patient-centred recruitment platforms such as CardioTrials (https://cardiotrials.org/), in which case they will be invited to the most appropriate secondary care centre. Reasons for non-recruitment will be recorded in a screening log.

### Baseline evaluations

Study assessments and procedures are illustrated in figure 2. The study uses data collected as part of clinical care supplemented with study-specific data.

#### Personal data

Participant personal details are collected in order to retrieve medical, health and social care data from local, regional and national data systems and organisations, and to allow participants to be contacted regarding stage 2 studies (see below).

#### Medical, health and social care information

Data collected include demographics, medical history, HF history, medications, laboratory investigations, ECG, echocardiography and other investigations that participants may undergo as part of their clinical care, for example, cardiac catheterisation, cardiopulmonary exercise testing, exercise echocardiogram, heart rhythm monitoring, nuclear scintigraphy. Date of each item is also captured.

To standardise the clinical evaluation that patients with HFpEF receive across the UK, and data collection, a core set of laboratory investigations are advised (online supplemental appendix). Similarly, there is a standardised echocardiography protocol, in line with the British Society of Echocardiography minimum data set (online supplemental appendix).

Pseudonymised ECGs and echocardiogram digital imaging and communications in medicine (DICOM) images are uploaded to the study database, where they are available for central analysis, including using automated artificial intelligence (AI) algorithms.

#### Physical status

Data collected include HF symptoms and signs, New York Heart Association (NYHA) class, blood pressure, pulse rate, height, weight and Rockwood Clinical Frailty Scale.[23]

#### Patient-reported outcome measure

To characterise patient health-related quality of life, the Minnesota Living with Heart Failure Questionnaire is conducted.[24]

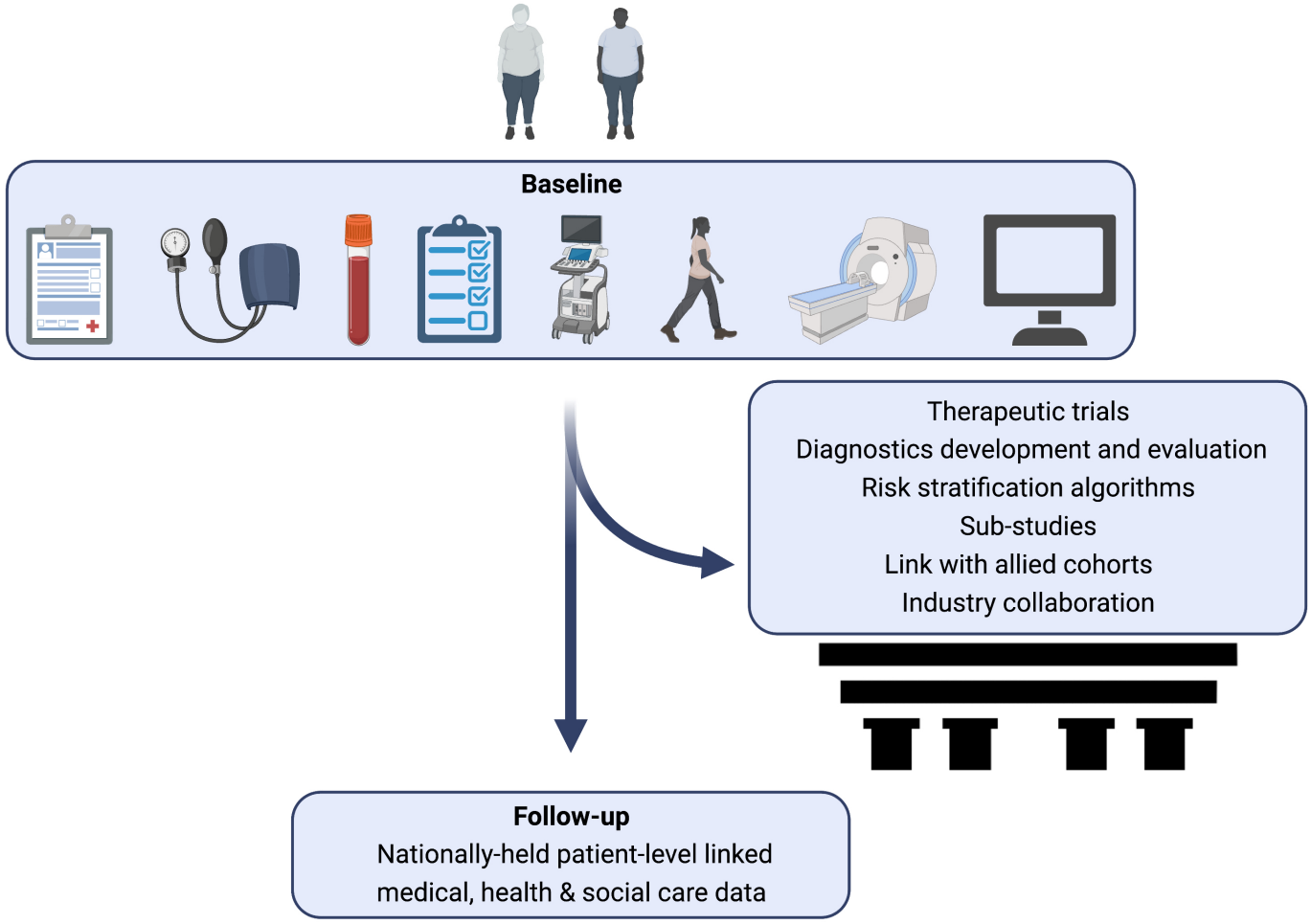


**Figure 2** UK Heart Failure with Preserved Ejection Fraction Registry (UK HFpEF) study design. Baseline assessments use data collected as part of clinical care supplemented with study-specific data. Recruitment to other heart failure with preserved ejection fraction (HFpEF)-related studies, such as clinical trials and evaluation of diagnostics, will be supported. Follow-up will be incorporated from national healthcare data services. See text for further details. Figure created with BioRender.com.

### Blood sampling

Up to 50 mL of blood is collected and aliquoted (plasma (10 aliquots), serum (10 aliquots), buffy coat (4 aliquots)), before being transferred for central storage at NIHR National Biosample Centre.

## Substudies

Substudies will focus on specific aspects of HFpEF in addition to the core data set, involving investigators and sites with a particular interest. This approach ensures that the registry population is as representative of HFpEF as possible, while also providing a platform for more specific evaluations. Substudies will benefit from the data present in the wider registry, and the wider registry will benefit from data collected as part of the substudies. Substudies may include, for example, invasive assessments. Example substudies included from the outset are:

### Exercise capacity

Where possible, in terms of site logistics and participant characteristics, 6-min walk testing is performed.[25]

### Cardiovascular MRI

Where participants are undergoing cardiovascular MRI (CMR) as part of their clinical care, a standardised protocol is advised (online supplemental appendix). This includes approximately 5 min of additional research imaging above that considered part of the clinical scan. The pseudonymised DICOM images are uploaded to the study database, where they are available for central analysis.

## Blood sample analyses

Multiple types of analyses will be performed on the donated samples including genomic, transcriptomic, proteomic, lipidomic, metabolomic and biochemical analyses, dependent on future funding. Participants provide consent for sequencing up to the level of the whole genome. Data generated from the samples will be linked with the other data.

## Data flow and management

Figure 3 provides an overview of the flow and management of data. Data collected at sites are entered via a secure Research Electronic Data Capture (REDCap, version 12.4.11) web application.[26] Consent forms and pseudonymised ECGs are uploaded via REDCap, and pseudonymised echocardiogram and CMR DICOM files are uploaded via REDCap using a secure file transfer system (ownCloud V.10.11.0). In addition, patient-level data will be incorporated from national healthcare data services, such as NHS England, Digital Health and Care Northern Ireland

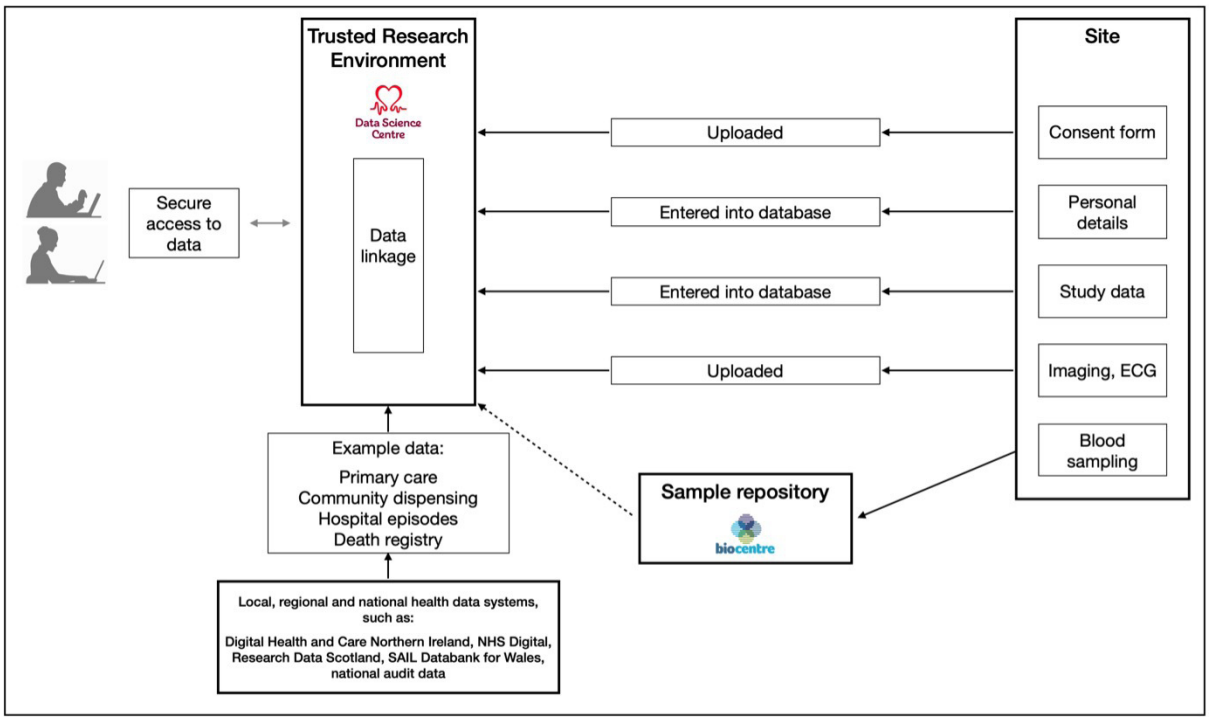


**Figure 3** UK Heart Failure with Preserved Ejection Fraction Registry (UK HFpEF) data flow and management. Data collected at sites are entered and uploaded via a secure web application. Patient-level data will be incorporated from national healthcare data services. Data are stored in an accredited Trusted Research Environment in collaboration with the British Heart Foundation Data Science Centre. See text for further details. NHS, National Health Service; SAIL, Secure Anonymised Information Linkage.

(Northern Ireland), Research Data Scotland (Scotland) and Secure Anonymised Information Linkage Databank for Wales (Wales). Such data include primary care, community dispensing, hospital episode and death registry data.

Data are stored in an accredited Trusted Research Environment in collaboration with the BHF Data Science Centre, part of Health Data Research UK, the UK's Institute for Health data science. The Trusted Research Environment enables highly secure and privacy-preserving data storage, access, sharing, analysis and linkage in a well-governed environment. Access, determined by the Executive Steering Committee, is controlled, secure and role based on a named person basis only, with individual user authentication. The Trusted Research Environment provides an accredited platform to enable data sharing framework agreements with national data organisations and services, allowing the data described above to be incorporated and linked at participant level. It also provides an analysis environment that supports statistical software. Activity is audited and outputs are reviewed by the Executive Steering Committee before they are released. REDCap and ownCloud are hosted within the Trusted Research Environment.

## Participant confidentiality

Participants are given a unique participant identification number. Deidentified, pseudonymised study data are held in the 'UK HFpEF Research Data' database in the Trusted Research Environment. Personal data and uploaded consent forms are held in a separate 'UK HFpEF Consent & Personal Information' database in the Trusted Research Environment. The link between the pseudoidentifiers and participant personal details is kept securely in the Consent & Personal Information database. Only a small number of appropriately trained, named study team members determined by the Executive Steering Committee can access the identifiable information.

## Stage 2 studies

A key aim of the study is to be a platform to support recruitment to other HFpEF-related studies, such as clinical trials of novel and repurposed therapies and evaluation of diagnostics. The genotyping and deep phenotyping mean that patients who meet recruitment criteria for other studies can be readily identified and contacted, enabling efficient recruitment and more effective research, for example, allowing mechanism of action of a new therapy to be matched with anticipated individual treatment response. The data linkage may be used to support collection of clinical outcomes for these other studies. Importantly, the process provides patients who would like to take part in other studies the opportunity to do so.

UK HFpEF participants are asked to provide consent to being contacted regarding up to four stage 2 studies in any 12-month period. It is generally expected that data generated from stage 2 studies will be deposited in the UK HFpEF database.

## Industry collaboration

In line with the NIHR–BHF Cardiovascular Partnership strategy, an important objective is to develop appropriate industry collaborations. Private sector partnership provides opportunity for resource and expertise to support HFpEF research, and to access novel technologies at an early stage to facilitate innovative research and more rapid translation. The Executive Steering Committee will retain control of commercial relationships, which are anticipated to be on a project-by-project basis. Multiple industry partners are expected rather than exclusivity. As a prerequisite, data generated must be deposited back into the

study database. All participants are made aware of the potential for industry collaboration in the participant information sheet and are specifically asked to provide consent to their data and samples being shared with industry.

Additional methods are found in the online supplemental appendix.

## DISCUSSION

UK HFpEF realises the full potential of the UK healthcare system and clinical research infrastructure for cardiovascular research. The study combines research-specific data, with clinical data available via individual patient records at sites, nationally held patient-level healthcare data, contemporary imaging and biobanking, at scale, from all four nations. It is supported by the NIHR–BHF Cardiovascular Partnership, which brings together NIHR and BHF research infrastructure, and the NIHR Clinical Research Network. It is a vanguard for the BHF Data Science Centre, specifically its 'Enabling Cohorts' thematic area, and samples are stored centrally in the NIHR National Biosample Centre. The study aims to link with similar projects internationally, such as the National Heart, Lung and Blood Institute (NHLBI) HeartShare programme,[27] and other large studies investigating allied pathophysiology, such as the UK Pulmonary Arterial Hypertension Cohort Study.

Precision medicine requires detailed characterisation, at scale, and digital technologies to make sense of the data optimally. UK HFpEF will develop a rich, multimodal data resource that integrates deep clinical phenotyping, imaging, multiomics and electronic health records in a large cohort. Machine learning algorithms will be applied to reclassify HFpEF into subgroups, improve understanding of disease mechanisms underlying the development and progression of HFpEF and identify novel biological pathways, new molecular targets and validation of existing targets. Together, these will form the basis for developing diagnostics and targeted therapeutics specific to subgroups. Moreover, the study will be a platform for more effective and efficient trials, focusing on groups of patients in whom interventions are expected to be effective, with consent in place to facilitate rapid recruitment, and linkage in place for follow-up. While existing HF registries aim to address important knowledge gaps, UK HFpEF will focus on HFpEF and combine extensive phenotyping with genetic data at scale to enable systems biology approaches. Similar approaches have yielded important translational insights into other high burden diseases such as type 2 diabetes; however, a lack of available data sets has stymied the application of these approaches to HFpEF.

Previous attempts to reclassify HFpEF with machine learning techniques suggest that distinct subgroups may exist, but have been limited by sparse characterisation and often small retrospective cohorts. The resulting clusters have, therefore, been superficial and not advanced the field. The analysis of genetic susceptibility to HFpEF is likely to be important for deconvoluting causal factors and therapeutic targets: to date, however, genetic investigations have been restricted by sample size and limited phenotyping.

Recruitment criteria are pragmatic. There are no widely accepted evidence-based HFpEF diagnostic criteria, and the field is rapidly evolving. Requiring a diagnosis of HFpEF by a healthcare professional with specialist HF expertise provides specificity, and means the cohort reflects current practice. It was felt important to document natriuretic peptide levels in all patients, but given the lack of consensus regarding appropriate thresholds, and because levels are confounded by factors common to this patient group, no threshold is specified. Instead, the cohort will be used to develop new criteria, while also evaluating existing criteria and scoring systems.

An LVEF threshold of 40% was chosen, after extensive Steering Committee and working group discussion, for a number of reasons: (1) the guideline-designated LVEF cut-offs are recognised within the guidelines as being 'arbitrary'[1]; (2) LVEF measurement is associated with substantial variation[28]; (3) of the eight phase III HFpEF trials currently listed on ClinicalTrials.gov as 'recruiting' or 'active not recruiting', seven have an entry LVEF criterion of less than 50%, and thus an LVEF threshold of 40% permits investigation of the patients that are being included in HFpEF trials[29]; and (4) fundamentally, the aim of the study is to move the field forward, so that patient evaluation and intervention become based on the underlying biology.

Including patient-level linked electronic medical, health and social care record data from national data services provides several advantages. It will add retrospective information to enrich medical history data, and prospective information to enable longitudinal follow-up of health-related outcomes. Less manual data input is required, and as more data become available via national services, manual data input should reduce further. Community-prescribing data are accurate and contemporary, and hospital episode and death data, which would otherwise be challenging to collect at scale, are comprehensive.

Having raw DICOM image data available centrally will facilitate development and application of current and future AI image analysis algorithms, data from which will be incorporated into the wider machine learning analyses. The study provides the opportunity for synergistic training and development of clinically and non-clinically trained individuals.

In summary, UK HFpEF will develop a rich, multimodal data resource to enable novel understanding of HFpEF, which will form the basis for more effective diagnostic strategies, precise risk stratification and targeted therapies.

**Collaborators** The UK HFpEF Collaborative Group is a group authorship for this manuscript: Executive steering commitee: C A Miller, A Al-Mohammad, J Beezer, E Columbine, D Cotterell, S Fisher, N Hartshorne-Evans, L Humphreys-Davies, R Hyland, R T Lumbers, G P McCann, M F Paton, M C Petrie, S Robinson, C Sudlow. Patient Advisory Group: L Humphreys-Davies, N Hartshorne-Evans, R Cleverley, A Smith, M Wardle, S Worsnop. UK-wide Network and Working Group: R T Lumbers, C Manisty, J Moon, S E Petersen, S Balakrishnan Nair, C Sudlow, A Clegg, J Gosai, M Shanmuganathan, C Bhagra, C Deaton, J Bateman, J Llewellyn, R Williams, A Venkatamaran, R Schiff, A L Clark, J Mayet, M R Wilkins, L A Penn, P Le Page, S O'Driscoll, A M Shah, R Zakeri, K O'Gallagher, M Mayr, K Gatenby, J P Greenwood, S Plein, P Kanagala, C A Miller, F Soltani, R Arnold, S Kunhunny, A K McDiarmid, A Zaman, M C Petrie, C Berry, M Dweck, C Lang, I Mordi, P Garg, M Dewhurst, K Hann, D P Ripley, T Green, F Magdy, S Neubauer, O Rider, S K Prasad, C Bucciarelli-Ducci, A J Ludman, A Bakhai, T Jackson, A Al-Mohammad, D Austin, M Chapman, J Beezer, P Campbell, L J Anderson, A Flett, P Haydock, P Patel, R Steeds, P Banerjee, R Chahal, G P McCann, I Squire, S Dodd, N Peek.

**Contributors** All authors inputted to study design and are involved with study delivery. The manuscript was drafted by CAM and all authors provided critical input and review. CAM is responsible for the overall content as guarantor.

**Funding** Study set-up and initial recruitment is funded by NIHR (reference NIHR301848). CAM, Advanced Fellowship, is funded by NIHR. CAM acknowledges support from the Manchester NIHR Biomedical Research Centre (NIHR203308) and the Manchester British Heart Foundation Accelerator Award (AA/18/4/34221). CS is Director of the British Heart Foundation Data Science Centre (at Health Data Research UK), which is funded by the British Heart Foundation. MCP and CB are supported by the British Heart Foundation Centre of Research Excellence Award (RE/13/5/30177 and RE/18/6/34217+). JM and MRW acknowledge support from the Imperial NIHR Biomedical Research Centre and the British Heart Foundation Imperial Centre of Research Excellence. JM is supported by a British Heart Foundation Consultant Research Award (FS/CRA/22/23036). SEP acknowledges support from the NIHR Barts Biomedical Research Centre. CM is directly and indirectly supported

by the University College London Hospitals (UCLH) and Barts NIHR Biomedical Research Centres. SP acknowledges funding from the British Heart Foundation (CH/16/2/32089). MM is a British Heart Foundation Chair Holder (CH/16/3/32406) with British Heart Foundation Programme (RG/F/21/110053) Grant support. MFP holds a NIHR Clinical Lectureship and acknowledges support from a British Heart Foundation Innovation Fund award. GPM is funded by an NIHR Research Professorship (RP-2017-08-ST2-007) and receives support for work in HFpEF from the NIHR Leicester Biomedical Research Centre and NIHR Leicester Clinical Research Facility. RZ, Advanced Fellowship, is funded by NIHR. RTL acknowledges support from the University College London Hospitals NHS Trust NIHR Biomedical Research Centre and the British Heart Foundation UCL Research Accelerator.

**Disclaimer** The funder had no role in study design other than through their external peer review processes and was not involved in the preparation, drafting or editing of this manuscript. 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.

**Competing interests** CAM has served on advisory boards for AstraZeneca, Boehringer Ingelheim and Lilly Alliance, Novartis, and PureTech Health; serves as an advisor for HAYA Therapeutics; and has received speaker fees from Boehringer Ingelheim and Novo Nordisk, conference attendance support from AstraZeneca and research support from Amicus Therapeutics, AstraZeneca, Guerbet Laboratories, Roche and Univar Solutions. RTL has received research grants from Pfizer and has provided consultancy for FITFILE and HealthLumen. SEP provides consultancy to Circle Cardiovascular Imaging, Calgary, Alberta, Canada.

**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants and was approved by the NHS Health Research Authority and the London-Fulham Research Ethics Committee (IRAS project ID: 314091) (REC reference: 22/PR/0543). Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data sharing not applicable as no data sets generated and/or analysed for this study. No data were analysed or available for this registry protocol manuscript.



## REFERENCES

1 McDonagh TA, Metra M, Adamo M, *et al*. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;42:3599–726.
2 Heidenreich PA, Bozkurt B, Aguilar D, *et al*. 2022 AHA/ACC/HFSA guideline for the management of heart failure: executive summary: a report of the American college of cardiology/American Heart Association joint committee on clinical practice guidelines. *J Am Coll Cardiol* 2022;79:1757–80.
3 Savarese G, Lund LH. Global public health burden of heart failure. *Card Fail Rev* 2017;3:7–11.
4 Huffman MD, Berry JD, Ning H, *et al*. Lifetime risk for heart failure among white and black Americans: cardiovascular lifetime risk pooling project. *J Am Coll Cardiol* 2013;61:1510–7.
5 National heart failure audit summary report [Healthcare Quality Improvement Programme]. 2022. Available: https://www.nicor.org.uk/heart-failure-heart-failure-audit/ [Accessed Dec 2022].
6 Virani SS, Alonso A, Aparicio HJ, *et al*. Heart disease and stroke statistics-2021. *Circulation* 2021;143:e254–743.
7 Juenger J, Schellberg D, Kraemer S, *et al*. Health related quality of life in patients with congestive heart failure: comparison with other chronic diseases and relation to functional variables. *Heart* 2002;87:235–41.
8 Conrad N, Judge A, Tran J, *et al*. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. *Lancet* 2018;391:572–80.
9 Lawson CA, Zaccardi F, Squire I, *et al*. 20-year trends in cause-specific heart failure outcomes by sex, socioeconomic status, and place of diagnosis: a population-based study. *Lancet Public Health* 2019;4:e406–20.
10 Cook C, Cole G, Asaria P, *et al*. The annual global economic burden of heart failure. *Int J Cardiol* 2014;171:368–76.
11 Urbich M, Globe G, Pantiri K, *et al*. A systematic review of medical costs associated with heart failure in the USA (2014-2020). *Pharmacoeconomics* 2020;38:1219–36.
12 Pfeffer MA, Swedberg K, Granger CB, *et al*. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-overall programme. *Lancet* 2003;362:759–66.
13 Pfeffer MA, Shah AM, Borlaug BA. Heart failure with preserved ejection fraction in perspective. *Circ Res* 2019;124:1598–617.
14 Lewis GA, Schelbert EB, Williams SG, *et al*. Biological phenotypes of heart failure with preserved ejection fraction. *J Am Coll Cardiol* 2017;70:2186–200.
15 Anker SD, Butler J, Filippatos G, *et al*. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med* 2021;385:1451–61.
16 Solomon SD, McMurray JJV, Claggett B, *et al*. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med* 2022;387:1089–98.
17 Pieske B, Tschöpe C, de Boer RA, *et al*. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the heart failure association (HFA) of the European society of cardiology (ESC). *Eur Heart J* 2019;40:3297–317.
18 Reddy YNV, Carter RE, Obokata M, *et al*. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. *Circulation* 2018;138:861–70.
19 Elkholey K, Papadimitriou L, Butler J, *et al*. Effect of obesity on response to spironolactone in patients with heart failure with preserved ejection fraction. *Am J Cardiol* 2021;146:36–47.
20 Anand IS, Claggett B, Liu J, *et al*. Interaction between spironolactone and natriuretic peptides in patients with heart failure and preserved ejection fraction: from the TOPCAT trial. *JACC Heart Fail* 2017;5:241–52.
21 Anand IS, Rector TS, Cleland JG, *et al*. Prognostic value of baseline plasma amino-terminal pro-brain natriuretic peptide and its interactions with Irbesartan treatment effects in patients with heart failure and preserved ejection fraction: findings from the I-PRESERVE trial. *Circ Heart Fail* 2011;4:569–77.
22 Solomon SD, Vaduganathan M, L Claggett B, *et al*. Sacubitril/valsartan across the spectrum of ejection fraction in heart failure. *Circulation* 2020;141:352–61.
23 Rockwood K, Song X, MacKnight C, *et al*. A global clinical measure of fitness and frailty in elderly people. *CMAJ* 2005;173:489–95.
24 Rector TS, Kubo S, Cohn J. Patients' self-assessment of their congestive heart failure: part 2: content, Reliability and validity of a new measure, the Minnesota living with heart failure questionnaire. *Heart Fail* 1987;3:198–209.
25 ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;166:111–7.
26 Harris PA, Taylor R, Thielke R, *et al*. Research electronic data capture (REDCap)--A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377–81.
27 Shah SJ, Butler J, Shah SH, *et al*. Accelerating therapeutic discoveries for heart failure: a new public-private partnership. *Nat Rev Drug Discov* 2022;21:781–2.
28 Pellikka PA, She L, Holly TA, *et al*. Variability in ejection fraction measured by echocardiography, gated single-photon emission computed tomography, and cardiac magnetic resonance in patients with coronary artery disease and left ventricular dysfunction. *JAMA Netw Open* 2018;1:e181456.
29 Available: ClinicalTrials.gov [Accessed 23 Dec 2022].