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

UK HFpEF Collaborative Group

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 heterogeneous 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. 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. HF is the leading cause of hospitalisation for people aged over 65, with a subsequent 1-year mortality rate of more than 30%. Quality of life is markedly impaired compared with other chronic diseases. Importantly, there are substantial geographic, socioeconomic and ethnic disparities in HF incidence and outcomes. 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.

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.

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.

Instead of being a single diagnosis, it is clear that HFpEF represents a heterogeneous systemic syndrome. A wide range of cardiovascular and systemic disease mechanisms are described. Patients typically have a range of long-term cardiometabolic and other conditions. Outcomes are also variable; around half of
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Deaths in patients with HFrEF are non-cardiovascular, and fewer than 20% of hospital admissions are due to HF. Understanding of HFrEF remains limited. For example, it is unclear why some people with cardiometabolic conditions develop HFrEF but most do not; there is a lack of pathophysiological features that reliably distinguish HFrEF 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 HFrEF remains challenging. A variety of guideline-based algorithms exist, each comprising differing variables with varying measurement thresholds. No single classification or score is able to determine the presence or absence of HFrEF. Treatment options are limited. Almost all phase III trials have been neutral, in part because study design has considered HFrEF 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.

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. 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 HFrEF) has been conceived and designed. The overarching goal 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 HFrEF into more distinct diagnoses. It will be a platform for the development of diagnostics specific to the different HFrEF 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 HFrEF, 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.

**DESIGN AND METHODS**

**Overall study design and aims**

UK HFrEF 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 HFrEF 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 HFrEF into more distinct diagnoses. It will be a platform for the development of diagnostics specific to the different HFrEF 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 HFrEF, 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.

**Patients**

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

![Figure 1](https://heart.bmj.com/content/10.1136/heartjnl-2023-323049)

**Figure 1** UK Heart Failure with Preserved Ejection Fraction Registry (UK HFrEF) overview. UK HFrEF 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 therapies. Figure created with BioRender.com. RCTs, Hurandomised controlled trials.
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.

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.

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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 trials.

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HFpEF, heart failure with preserved ejection fraction.

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.

Patient-reported outcome measure
To characterise patient health-related quality of life, the Minnesota Living with Heart Failure Questionnaire is conducted.

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.
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 V10.11.0). In addition, patient-level data will be incorporated from national healthcare data services, such as NHS England, Digital Health and Care Northern Ireland...
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(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 British Heart Foundation Data Science Centre. 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 (NHBLI) 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 cancer.

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.


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 (NIHR302308) and the Manchester British Heart Foundation Accelerator Award (AA/18/14/34221). 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/13/3/30177 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/22/223036). SEP acknowledges support from the NIHR Barts Biomedical Research Centre. CM is directly and indirectly supported
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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 (RGF/21/110053) Grant support. MFF 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 HfP/E 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, Guebet 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.

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REFERENCES
UK Heart Failure with Preserved Ejection Fraction Registry:
rationale and design of UK HFpEF

Supplemental appendix
The UK HFpEF Collaborative Group

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Supplemental methods

Study duration

Participants will remain in the study for 10 years from when they provide consent. It is anticipated that at the end of the study, anonymised study data will be transferred to a managed-access research or scientific archive.

Authorship

A policy for authorship that follows the principles of the International Committee of Medical Journal Editors, written by the Executive Steering Committee and agreed by the Working Group, is in place (available at https://www.ukhfpef.org/).

Data Sharing

Participants are asked to provide consent for pseudonymised participant-level study data to be shared for research purposes. Requests for access to data are managed by the Executive Steering Committee. Release of data is subject to scientific review by the Executive Steering Committee and an appropriate Data Transfer Agreement. A Collaboration and Support Policy, written by the Executive Steering Committee and agreed by the Working Group, describes the framework for collaborations (available at https://www.ukhfpef.org/).
Supplemental Table 1. Core clinical laboratory investigations

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<td>Transferrin saturation</td>
</tr>
<tr>
<td>Thyroid stimulating hormone</td>
</tr>
<tr>
<td>Free T4</td>
</tr>
<tr>
<td>HBA1c</td>
</tr>
</tbody>
</table>

Additional clinical laboratory investigations, to record if available

| IgG  |
| IgA  |
| IgM  |
| Serum protein electrophoresis |
| Urine Bence Jones protein |
| Urine albumin : creatinine ratio |
| Urine dipstick proteinuria |

BNP = Brain natriuretic peptide; CRP C-reactive protein; eGFR = estimated glomerular filtration rate; hs = high sensitivity; Ig = Immunoglobulin; MCV = mean corpuscular volume; NTproBNP = N-terminal pro B-type natriuretic peptide.
Supplemental Table 2. Echocardiography protocol

Standard echo acquisition in line with the British Society of Echocardiography Minimum Dataset.¹

Key views and corresponding measurements are as follows:

<table>
<thead>
<tr>
<th>Key views</th>
<th>Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parasternal long axis 2D</td>
<td>LV end-diastolic dimension (cm)</td>
</tr>
<tr>
<td></td>
<td>LV end-systolic dimension (cm)</td>
</tr>
<tr>
<td></td>
<td>Maximum wall thickness (mm)</td>
</tr>
<tr>
<td>Parasternal long axis RV inflow CWD</td>
<td>TR $V_{max}$ (m/s)</td>
</tr>
<tr>
<td>Apical 4 chamber 2D</td>
<td>LV ejection fraction (%)</td>
</tr>
<tr>
<td>Apical 2 chamber 2D</td>
<td>LV ejection fraction (%)</td>
</tr>
<tr>
<td>Apical 4 chamber 2D GLS*</td>
<td>Peak GLS (%)</td>
</tr>
<tr>
<td>Apical 2 chamber 2D GLS*</td>
<td>Peak GLS (%)</td>
</tr>
<tr>
<td>Apical long axis 2D GLS*</td>
<td>Peak GLS (%)</td>
</tr>
<tr>
<td>Apical 4 chamber 2D optimised for LA volume</td>
<td>LA volume (cm$^3$)</td>
</tr>
<tr>
<td>Apical 2 chamber 2D optimised for LA volume</td>
<td>LA volume (cm$^3$)</td>
</tr>
<tr>
<td>Apical 4 chamber mitral valve PWD</td>
<td>$E V_{max}$ (cm/s)</td>
</tr>
<tr>
<td></td>
<td>$A V_{max}$ (cm/s)</td>
</tr>
<tr>
<td></td>
<td>DT (ms)</td>
</tr>
<tr>
<td>Apical 4 chamber mitral valve TDI</td>
<td>Lateral e' (cm/s)</td>
</tr>
<tr>
<td></td>
<td>Septal e' (cm/s)</td>
</tr>
<tr>
<td>Apical 5 chamber aortic valve CWD</td>
<td>AV $V_{max}$ (m/s)</td>
</tr>
<tr>
<td>Apical 4 chamber modified for RV/RA 2D</td>
<td>Basal RV diameter</td>
</tr>
<tr>
<td></td>
<td>Visual assessment of RV function</td>
</tr>
<tr>
<td>Apical 4 chamber modified for RV/RA CWD</td>
<td>TR $V_{max}$ (m/s)</td>
</tr>
<tr>
<td>Apical 4 chamber lateral tricuspid valve annulus MM</td>
<td>TAPSE (cm)</td>
</tr>
<tr>
<td>Apical 4 chamber right ventricle TDI</td>
<td>RV S' (cm/s)</td>
</tr>
<tr>
<td>Subcostal 2D +/- MM</td>
<td>IVC diameter (mm)</td>
</tr>
<tr>
<td></td>
<td>IVC diameter during inspiration (mm)</td>
</tr>
<tr>
<td>Multiple views</td>
<td>Mitral, aortic and tricuspid valve function</td>
</tr>
<tr>
<td></td>
<td>Pericardial effusion (present/absent)</td>
</tr>
</tbody>
</table>

¹ As permitted by image quality and local feasibility.

2D = Two-dimensional; A $V_{max}$ = Peak velocity in late diastole; AV $V_{max}$ = Aortic valve peak velocity; CWD = Continuous wave Doppler; DT = Flow deceleration time from peak E wave to end of E wave signal; E $V_{max}$ = Peak velocity in early diastole; GLS = Global longitudinal strain; IVC = Inferior vena cava; LA = Left atrium; LV = Left ventricle; MM = M-mode; PWD = Pulsed wave Doppler; RV = Right ventricle; TAPSE = Tricuspid Annular Plane Systolic Excursion; TDI = Tissue Doppler imaging; TR $V_{max}$ = Tricuspid regurgitation peak velocity;

**Supplemental Table 3. Cardiovascular magnetic resonance protocol**

<table>
<thead>
<tr>
<th><strong>Core</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Localisers</td>
</tr>
<tr>
<td>• CH4 cine.</td>
</tr>
<tr>
<td>• CH2 cine.</td>
</tr>
<tr>
<td>• CH3 cine.</td>
</tr>
<tr>
<td>• LVOT cine</td>
</tr>
<tr>
<td>• Aortic valve cine</td>
</tr>
<tr>
<td>• Gadolinium based contrast agent in line with local policy.</td>
</tr>
<tr>
<td>• LV short axis cine stack.</td>
</tr>
<tr>
<td>• TI Scout</td>
</tr>
<tr>
<td>• LGE segmented inversion recovery and PSIR. CH4, CH2, CH3 and short axis stack</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Supplemental</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• T1 mapping basal and mid short axis, before and after Gadolinium</td>
</tr>
<tr>
<td>• CH4 fat-water sequence.</td>
</tr>
<tr>
<td>• T2 mapping. Mid short axis.</td>
</tr>
<tr>
<td>• Aortic candy stick cine</td>
</tr>
<tr>
<td>• Cine perpendicular to the ascending and descending aorta at pulmonary bifurcation level, with measurement of blood pressure.</td>
</tr>
<tr>
<td>• Phase encoded velocity mapping perpendicular to the main pulmonary artery.</td>
</tr>
<tr>
<td>• 3D Dixon fat-water sequence, centred over the renal arteries.</td>
</tr>
<tr>
<td>• Perfusion imaging if being performed clinically</td>
</tr>
</tbody>
</table>

**Notes**

- 1.5T or 3T
- The protocol is split into core and supplementary sequences. It is expected that core sequences would be performed as part of a standard clinical CMR.
- As part of site set-up, the central study team will liaise with the site regarding the details of the CMR protocol appropriate for the site, and provide site-specific CMR guidance. The protocol is a guide.

CH = chamber; LGE = late gadolinium enhancement; LV = left ventricle; LVOT = left ventricular outflow tract; PSIR = Phase-sensitive inversion recovery; TI = inversion time.