CROSS sectional versus invasive imaging in patients with Heart Failure

Trial Protocol version 1.1

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Funded by NIHR HTA

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CROSS sectional versus invasive imaging in patients with Heart Failure (CROSS-HF)

Version (Date)	v1.1 (01-08-2024)
Trial Funding	NIHR HTA: 159132
Sponsor	University of Leeds
Clinical Trials Unit	Glasgow Clinical Trials Unit (GCTU), Robertson Centre for Biostatistics (RCB), Clarice Pears Building, Level 5, University of Glasgow, 90 Byres Road G12 8TB (UKCRC Registration Number 16)
Sponsor Reference	2024-NCT25
R&D Reference	
Ethics Reference	
IRAS Reference	332073
NIHR CRN Portfolio ID	50598
ISRCTN registry Ref:	xxxx (date registered: xxxx)
Trial website:	https://medicinehealth.leeds.ac.uk/directories0/dir-record/research-projects/1838/cross-sectional-versus-invasive-imaging-in-patients-with-heart-failure-cross-hf

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3.TRIAL SUMMARY
3.1 PROTOCOL VERSION HISTORY

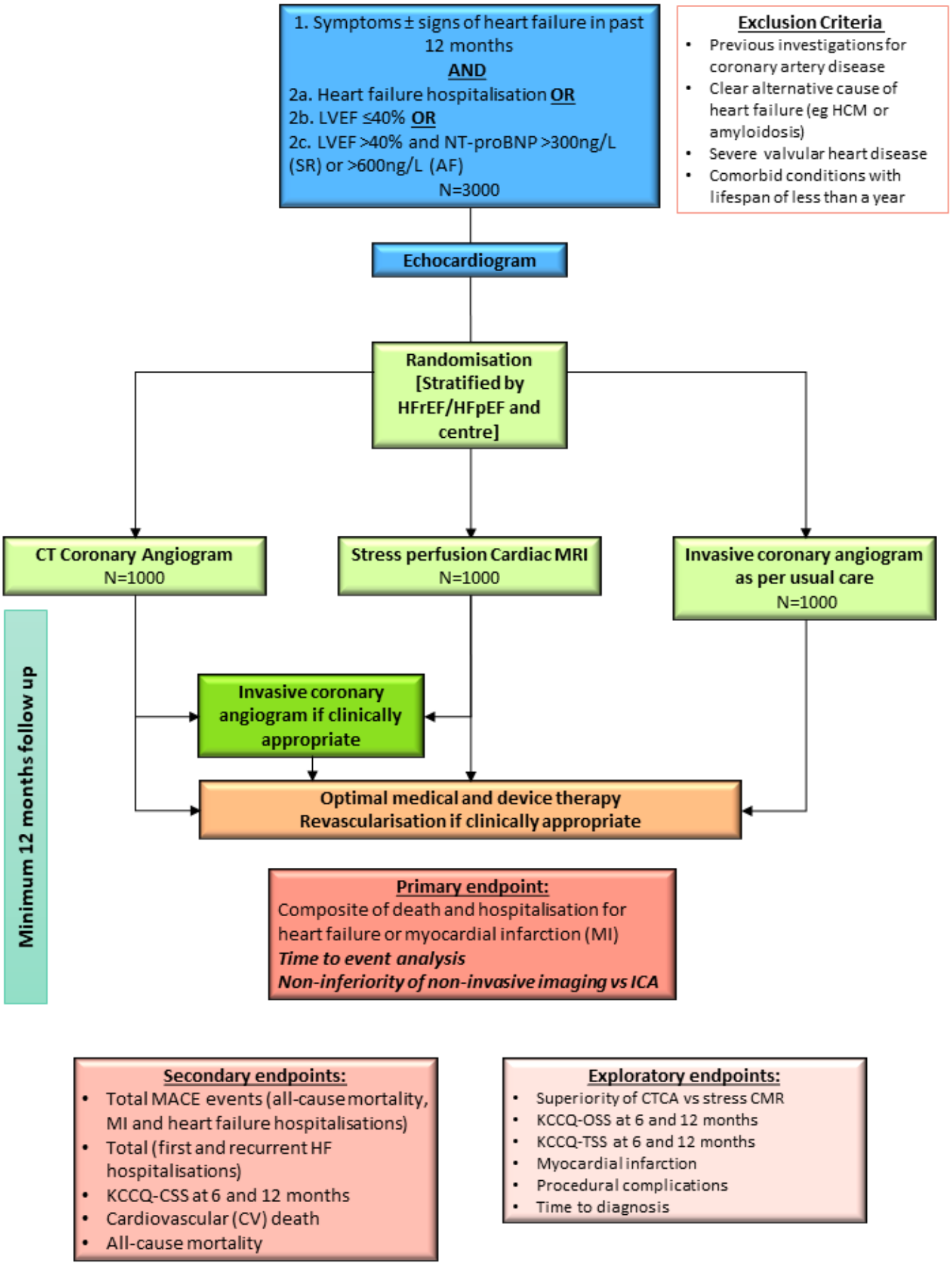
Version Stage	Version Number	Version Date	Protocol updated & finalised by;	Reasons for Update
Current	1.0	27/06/2024	N/A	First version

3.2 TRIAL SUMMARY

Trial Title	CROSS sectional versus invasive imaging in patients with Heart Failure (CROSS-HF)
Aim	To establish whether, in patients with heart failure, a strategy of non-invasive imaging with computed tomography coronary angiography (CTCA) or stress cardiovascular magnetic resonance (CMR) is non-inferior to invasive coronary angiography (ICA) in terms of major adverse cardiovascular events (MACE), patient reported outcome measures, and cost-effectiveness.
Trial Design	Multicentre, open-label randomised controlled trial with patients randomised 1:1:1 ratio to ICA, CTCA and stress CMR
Primary Outcome	Time to first MACE measured from randomisation for a minimum of 12 months: MACE defined as any of: • All cause death • Myocardial Infarction (MI) • Heart Failure Hospitalisation
Secondary Outcome	• Total MACE events (MACE is defined as all-cause mortality, MI and heart failure hospitalisations) • Total (first and recurrent) HF hospitalisations • KCCQ-CSS at 6 and 12 months • Total Cardiovascular (CV) deaths • Total all-cause mortality
Inclusion Criteria	1. Onset of symptoms ± signs of heart failure in past 12 months **AND** 2a. Non-elective heart failure hospitalisation (where heart failure was the primary reason for hospitalisation in the opinion of the investigator) **OR** 2b. Outpatients with LVEF ≤40% **OR** 2c. Outpatients with LVEF >40% and NT-proBNP >300ng/L (sinus rhythm) or >600ng/L (AF)

Major Exclusion Criteria	• Previous investigations for coronary artery disease (CAD), where CAD was identified as the cause of heart failure • Clear alternative cause of heart failure (e.g. cardiac amyloidosis or hypertrophic cardiomyopathy) • Severe valvular heart disease thought to be the main cause of heart failure • Comorbid conditions with lifespan of less than a year (in the opinion of the investigator)
Sample Size and Enrolment	• N=3000 • Expected set up start date 1st April 2024 • Expected first patient recruited by 1st October 2024 • Expected pilot phase completed by 1st July 2025 (9 months from opening) • Expected last patient recruited by 1st April 2028 • Expected last follow up assessment 1st April 2029 • At least 20 sites recruiting 5 patients per month

3.3 TRIAL FLOW CHART



4. GLOSSARY OF TERMS AND DEFINITIONS

4.1 TERMS

ACS	Acute coronary syndrome
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CCU	Coronary care unit
CMR	Cardiovascular magnetic resonance
CTCA	Computed tomography coronary angiogram
ECG	Electrocardiogram
EDC	Electronic data capture
ESC	European Society of Cardiology
eGFR	Estimated glomerular filtration rate
GCTU	Glasgow Clinical Trials Unit
GLM	Generalised linear model
HDU	High dependency unit
HES	Hospitalisation episode statistics
HbA1c	Haemoglobin A1C (glycosylated haemoglobin) test
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
ICA	Invasive coronary angiogram
ICER	incremental cost-effectiveness ratio
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive care unit
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention to treat
KCCQ	Kansas City cardiomyopathy questionnaire
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
NHPR	Non-hyperaemic pressure ratio
NHS	National Health Service
NTproBNP	N-terminal pro B-type natriuretic peptide test
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NMB	net monetary benefit
PCI	Percutaneous coronary intervention
PIL	Patient information leaflet
PPI	Patient and Public Involvement
PROMS	Patient reported outcome measures
QALY	Quality-adjusted life years
RCB	Robertson Centre for Biostatics
REC	Research ethics committee
SAE	Serious adverse event
SOP	Standard operating procedure
STICH-3 BCIS-4	Surgical Treatment for Ischemic Heart Failure British Cardiovascular Intervention Society
TIA	Transient ischaemic attack

TMG	Trial management group
TSC	Trial steering committee

4.2 STUDY DEFINITIONS

Heart Failure Classification (New York Heart Association Functional Classification)

- **Class I:** No Limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnoea
- **Class II:** Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnoea.
- **Class III:** Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation or dyspnoea.
- **Class IV:** Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency may be present, even at rest. If any physical activity is undertaken, discomfort is increased.

Heart Failure according to Left Ventricular Ejection Fraction

- Heart failure with reduced ejection fraction (HFrEF) defined as left ventricular ejection fraction (LVEF)≤40%.
- Heart failure with preserved ejection fraction (HFpEF) defined as LVEF>40%.
- Where image quality on initial echocardiogram prohibits assessment of LVEF by Simpson's biplane those with severe, moderate-severe and moderate left ventricular systolic dysfunction will be classified as HFrEF. Those with normal, mild or mild-moderate left ventricular systolic dysfunction will be classified as HFpEF.

Death

Classified into two categories, cardiovascular and non-cardiovascular as defined in the Standardized Data Collection for Cardiovascular Trials Initiative [1]:

a) Cardiovascular

- Death due to acute myocardial infarction (refers to a death by any mechanism (e.g. arrhythmia, sudden death, HF, stroke, pulmonary embolus, peripheral arterial disease) ≤ 30 days after myocardial infarction
- Sudden cardiac death (refers to a death that occurs unexpectedly and not within 30 days of an acute myocardial infarction).
- Death due to heart failure
- Death due to stroke
- Death due to complications of cardiovascular procedures
- Death due to cardiovascular haemorrhage (such as a non-stroke intracranial haemorrhage (e.g. subdural hematoma) or non-procedural or non-traumatic vascular rupture (e.g. aortic aneurysm).
- Death due to other cardiovascular causes refers to a cardiovascular death not included in the above categories but with a specific, known cause (e.g. pulmonary embolism or peripheral arterial disease).

b) Non-Cardiovascular

- Any other recorded cause of death

Heart Failure Hospitalisation

- Hospital admission (lasting >24 hours) for deteriorating symptoms or signs of heart failure, where there is a documented diagnosis of heart failure and the patient receives initiation or intensification

of treatment for heart failure. Initiation or intensification of treatment includes at least one of the following: increase in oral diuretic dose or addition of another oral diuretic; intravenous diuretic therapy; intravenous vasoactive therapy (vasodilator, inotrope or vasopressor); mechanical circulatory support; or cardiac transplantation.

- Elective admission for implantation or revision of cardiac devices will NOT constitute an endpoint.

Criteria for acute myocardial infarction[2]

The term acute myocardial infarction should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischaemia and with detection of a rise and/or fall of cardiac troponin values with at least one value above the 99th percentile URL and at least one of the following:

- Symptoms of myocardial ischaemia;
- New ischaemic electrocardiogram (ECG) changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology;
- Identification of a coronary thrombus by angiography or autopsy (not for type 2 or 3 MIs).

5. BACKGROUND

Each year 60,000 people are diagnosed with heart failure. In patients with neither history nor symptoms of coronary artery disease (CAD), occult CAD can still be identified in approximately 25% [3, 4]. Therefore, both NICE and European Society of Cardiology (ESC) guidelines recommend performing imaging to identify CAD [5, 6]. Whilst NICE does not specify the best test to identify CAD in heart failure there is guidance from ESC which only recommends either invasive coronary angiography (ICA) in intermediate-high risk patients (IIb, B) or CT coronary angiography (CTCA) in low-intermediate risk patients (IIa, C). Despite these recommendations there is widespread variation in practice with many patients not undergoing any investigations for CAD at all [7].

There is considerable variation in which imaging test, if any at all, is performed in patients presenting with heart failure in the NHS. This reflects a lack of clear evidence and variation in availability and expertise. There are no published data on the proportion of patients in the UK who undergo invasive angiography for investigation of heart failure, but registry data from Denmark and the USA suggest it may be between 17 and 35% [8, 9]. Despite advances in non-invasive imaging, registry data from Sweden suggests the proportion of patients with heart failure undergoing ICA is continuing to increase [10]. In our own unpublished pilot data of 502 patients referred for CMR from multiple hospitals in West and North Yorkshire for the workup of presumed non-ischaemic cardiomyopathy 97 (19%) underwent invasive angiography. In a recent study from Leicester 24/46 (52%) with HFrEF and 27/140 (19%) with HFpEF underwent ICA [11].

ICA is often perceived to be the best test for the diagnosis of CAD, but it is expensive, has a serious complication rate of 1% and is uncomfortable for patients. We have carried out extensive patient and public involvement consultation and it is clear that most patients would prefer to avoid ICA if possible. Despite this ICA is still performed in approximately 20% of patients presenting with heart failure.

It is possible to diagnose CAD using non-invasive cross-sectional imaging by CTCA or stress cardiovascular magnetic resonance (CMR). Both tests have been shown to have high sensitivity and specificity for identification of CAD in patients with angina pectoris [12, 13] but the evidence to support their use in patients presenting specifically with heart failure is lacking.

The high sensitivity and specificity of CTCA (sensitivity 97%, specificity 78%) and stress CMR (sensitivity 90%, specificity 80%) compared to ICA is well established [14]. However, there is very little evidence validating either test in patients presenting with heart failure. There are practical challenges in patients with heart failure that could impact the diagnostic accuracy such as poor contrast opacification in CTCA and reduced adenosine response in stress CMR. Therefore, there is a need to compare imaging pathways.

The only randomised evidence comparing cross sectional imaging modalities in heart failure is a study called IMAGE-HF conducted in Canada and Finland. In the CTCA portion (IMAGE-HF 1C) 246 patients were randomised to CTCA or ICA [3]. 93/121 (77%) patients randomised to CTCA avoided the need for further downstream ICA. There was a trend to cost saving in the CTCA arm, but this did not reach significance. There was no difference in clinical outcomes or quality of life, although the study was underpowered for this. A recent meta-analysis of just 5 studies suggested a pooled sensitivity of 99% and specificity of 94% for CTCA compared to ICA. However, given the sample size of the individual studies and their heterogenous nature it is relatively weak evidence.

In IMAGE-HF 1B 500 patients with non-ischaemic heart failure were randomised to care with or without routine CMR [15]. They found the addition of CMR did not add to the diagnostic yield compared to standard

clinical care. However, it should be noted that stress CMR looking for identification of CAD was not performed in this study. In patients with angina, stress CMR has a higher specificity (meaning fewer false positive tests) than CTCA. In addition to detection of CAD, stress CMR gives additional information particularly about tissue characterisation which can be important diagnostically and prognostically in patients with heart failure i.e. CMR can unveil other causes of heart failure. However, stress CMR is less widely available than CTCA and has increased costs. Therefore, we will address in this trial whether the added benefits of stress CMR are worth the additional cost.

6. AIMS AND OBJECTIVES

6.1 AIMS

To establish whether, in patients with heart failure, a strategy of non-invasive imaging with computed tomography coronary angiography (CTCA) or stress cardiovascular magnetic resonance (CMR) is non-inferior to invasive coronary angiography (ICA) in terms of major adverse cardiovascular events (MACE).

To establish whether, in patients with heart failure, a strategy of non-invasive imaging compared to invasive coronary angiography leads to improved patient reported outcome measures (PROMS) and cost-effectiveness.

6.2 OBJECTIVES

To deliver a trial which leads to improved patient outcomes and experience by:

a) conducting a trial that is inclusive of patients with a wide range of ejection fraction, age, sex, ethnicities, socio-economic backgrounds and co-morbidities to make the findings generalisable

b) making participation in the trial as easy as possible for patients with no additional study visits and options to carry out all study activities remotely

c) collecting robust data on clinically important outcomes by review of electronic records

d) capturing the experience of patients participating in the trial by using quality of life questionnaires that will be comparable to other heart failure trials

e) to record patient acceptability of investigations using bespoke questions guided by patient and public involvement

f) encourage involvement of the multidisciplinary heart failure team (including specialist nurses and pharmacists) to take active research roles within the trial, with particular emphasis on the NIHR associate PI scheme

g) utilising an established network of centres with proven track records in delivering multi-centre randomised trials in cardiac imaging (CE-MARC 3, MR-INFORM), heart failure (IRONMAN, DAPA-HF, SUBCUT-HF II) and PCI and CABG teams (REVIVED and BCIS-4/STICH 3.0)

7. DESIGN

Health technologies being assessed: The health technology being assessed are invasive coronary angiography and non-invasive cross-sectional cardiac imaging (either CTCA or stress CMR). Both non-invasive imaging techniques are well established in the NHS for the assessment of patients with chest pain, although evidence in patients with heart failure is not as robust.

Trial Design: A multicentre, open-label, 3-arm, randomised (1:1:1) controlled clinical-effectiveness trial

Target population: Patients with a diagnosis of heart failure in the past 12 months where CAD has either been ruled out or not identified as cause of heart failure.

8. ELIGIBILITY

Patients will be required to satisfy the following criteria. Eligibility waivers to the inclusion / exclusion criteria are not permitted.

Inclusion Criteria

1. Onset of symptoms ± signs of heart failure in past 12 months **AND**

2a. Non-elective heart failure hospitalisation (where heart failure was the primary reason for hospitalisation in the opinion of the investigator) **OR**

2b. Outpatients with LVEF ≤40% **OR**

2c. Outpatients with LVEF >40% and NT-proBNP >300ng/L (sinus rhythm) or >600ng/L (AF)

In patients without HFrEF or prior hospitalisation NT-proBNP elevation will be required to make the diagnosis of heart failure. In line with contemporary trials of patients with HFpEF, such as DELIVER, FINEARTS and HERMES, there will be different NT-proBNP thresholds for patients in sinus rhythm (>300ng/L) and atrial fibrillation (>600ng/L)[16]. Sites who use BNP rather the following thresholds will be used for outpatients with LVEF>40%: 100 pg/ml (If in sinus rhythm)/300 pg/ml (if in atrial fibrillation).

In line with NICE guidelines, it is recommended that the diagnosis of heart failure is made by a heart failure specialist such as cardiologist with special interest, specialist nurse or pharmacist. We will support the NIHR associate PI scheme to encourage allied health professionals within the heart failure team to take on active leadership roles and responsibilities within the trial.

Exclusion Criteria

- Previous investigations for coronary artery disease (CAD), where CAD has been identified as cause of heart failure
- Clear alterative cause of heart failure (e.g. cardiac amyloidosis or hypertrophic cardiomyopathy)
- Severe primary valvular heart disease thought to be the main cause of heart failure
- Comorbid conditions with lifespan of less than a year (in the opinion of the investigator)

Only patients in whom the aetiology of heart failure is unclear should be recruited. For example, a patient with prior small MI several years previously with new onset heart failure would be eligible for recruitment. However, a patient with recent large MI presenting with subsequent heart failure would not be eligible as CAD has already been identified as the cause of heart failure.

9. RECRUITMENT PROCESS

All three arms of this trial are standard care in the NHS, and it is therefore considered very low risk to trial participants. The consent process has therefore been designed to be as accessible to patients and as inclusive as possible. The following pathways to recruitment will be available to patients to maximise inclusivity:

- **Consent during clinic:** Eligible patients will be given the patient information leaflet before or during clinic and will be given as long as they need to think about trial participation. They will have the opportunity to discuss the trial with members of the research team (on the trial delegation log). If they agree to participate in CROSS-HF they will be able to sign paper consent at the initial clinic appointment.
- **Consent after clinic:** Eligible patients who need longer to consider participation (or those who are identified later) will still be able to be recruited. To avoid additional trips back to the hospital participants will be able to complete either paper consent or over the phone (a researcher will read each statement to the patient) and sign on their behalf. A signed copy of the phone consent will be sent to the patient.
- **Inpatient consent:** Many patients newly presenting with heart failure are admitted to hospital and will be suitable for recruitment to CROSS-HF. The only patients who will be approached are those in whom an acute coronary syndrome has been excluded, and in whom the clinical plan is to discharge from hospital for further cardiac investigations as an outpatient. It is important to recruit these patients as they have increased risk and have been under-represented in previous heart failure trials. Timing of the study investigations will be at the discretion of site investigators.

9.1 SCREENING

Screening population

Inpatients with decompensated heart failure (as the primary cause of hospitalisation in the opinion of the investigators) and outpatients with onset of symptoms ± signs of heart failure in past 12 months. If a patient does not fulfil the eligibility criteria, then no data collection is required.

Patients who do not wish to participate

A site screening log will be kept, recording the number of patients that were eligible but who do not wish to participate in CROSS-HF including reasons for non-recruitment (e.g. physician choice, patient choice). Sites will be asked to provide numbers of eligible but non-consenting patients at regular intervals during the trial.

The right of the patient to refuse consent without giving reasons will be respected.

9.2 INFORMED CONSENT AND ELIGIBILITY

The Principal Investigator (PI) will retain overall responsibility for the conduct of research at their site, which includes the taking of informed consent of participants. They must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki 2013. If delegation of consent is undertaken, then details should be recorded within the site delegation log.

The research team or the clinical care team on the delegation log, will provide information (written/verbal/online video) about the trial prior to or during the routine clinic appointment. Before

discussion with potential participants a check will be made to establish that all the inclusion criteria are met and none of the exclusion criteria apply.

9.3 RANDOMISATION

Randomisation to one of the three trial arms will be performed centrally using the RCB automated web randomisation system. Imaging assignment will be stratified by centre and ratio of HFpEF:HFrEF using randomly permuted blocks of varying size, with 1:1:1 allocation between the CTCA, stress CMR and invasive coronary angiography arms.

Study participants will be informed that they are free to withdraw consent for the study at any time.

10. TREATMENT PATHWAYS/INVESTIGATION DETAILS

10.1 TREATMENT PATHWAYS

Our sites will include both tertiary centres and district general hospitals to ensure that patients from as many locations and backgrounds are given the opportunity to participate. It will also optimise the generalisability of our findings to NHS patients and healthcare providers. Our overall aim is to open at least 20 sites recruiting >5 patients per month. Ten centres, comprising a mix of tertiary and secondary hospitals, have committed to opening the trial during the pilot phase and meeting the recruitment target of 5 per month.

Where patients have been recruited during an acute admission the timing of the trial investigation will be left to the discretion of the site team.

10.2 INVESTIGATION DETAILS

In keeping with the pragmatic design, all imaging tests will be conducted and reported on-site by independent cardiology or radiology NHS consultants with experience in the respective imaging modality. Individual sites can perform the tests as per usual care but as a guide the following investigation criteria will be recommended:

- **CTCA:** This will be as per usual care. 64-slice (or above) with heart rate control by betablockers and coronary vasodilation by nitrates. Vendor-specific radiation dose-reducing techniques such as prospective ECG-triggered image acquisition will be encouraged. A positive result will be recorded in the presence of any luminal stenosis ≥70% (≥50% left main stem) in a proximal coronary artery ≥2.5mm diameter.
- **Stress CMR:** This will be as per usual care. Performed on 1.5T or 3T system. Participants will be advised to avoid caffeine for 24 hours before the study. Adenosine infusion will be performed for a minimum of 3 min, at a rate of 140 µg/kg/min with up-titration to a maximum of 210 µg/kg/min. Patients with heart failure can have a blunted response to adenosine and uptitration will be encouraged. Alternatively, regadenoson can be used. A positive result will be recorded as ≥2 segments of stress induced hypoperfusion in segments without transmural infarction on late gadolinium enhancement imaging.
- **Invasive coronary angiography:** This will be as per usual care. Performed according to standard clinical protocols, with selective coronary injection and imaging from multiple views. Radial artery access will be encouraged.

***Inconclusive/uninterpretable test results (all three arms*)**: Patients with inconclusive first-line test results can have second line non-invasive testing or invasive angiography (as per usual care), based upon shared decision-making. This result will be recorded from the clinical report and a copy of the report uploaded to the eCRF.

***Ongoing Care*:** In line with both ESC and NICE guidelines [5, 6] we will encourage that all patients are managed by a core specialist heart failure multidisciplinary team (MDT) working in collaboration with the primary care team. Patients will be treated with guideline directed medical therapy as per usual care. Decisions about device therapy and revascularisation will be made by the clinical team using information from the imaging test they are randomised to [5, 6].

Patients undergoing CTCA or stress CMR may proceed to invasive angiography if deemed appropriate according to usual care. However, we will ask clinicians to avoid requesting the alternative non-invasive imaging test to minimise cross-over between arms.

Co-enrolment to other trials: Patients recruited to CROSS-HF will be allowed to be recruited to other trials, so long as it does not impact their participation in CROSS-HF. For example co-recruitment to STICH-3 BCIS-4,a NIHR funded trial comparing stenting and surgery for the management of patients with HF and LVEF≤40% will be possible. In usual care, the decision to choose between stents or surgery currently occurs following a discussion in a heart team meeting in the absence of evidence. In STICH-3 BCIS-4 assignment to stents or surgery will happen in a randomised manner in the trial. Co-recruitment to this trial will not affect any of the endpoints of CROSS-HF and will increase the chances of successful recruitment for both trials.

Recruitment Rate: The recruitment is planned over three and a half years (3 years assumed in sample size calculations, to compensate for ramping up of the recruitment at the start). Allowing for ramping up and the pilot phase, with 20 sites this equates to 5 randomisations per month per site.

Follow up: All follow up can be conducted remotely. Data for the primary and secondary endpoints (all cause death, myocardial infarction, heart failure hospitalisation, cardiovascular death, stroke, and revascularisation will be collected by review of primary and secondary care records at 6, 12 months and then annually for up to 4.5 years (or until 12 months after the last patient is recruited). Occasionally when information is not available in the medical records the site researchers may need to telephone patients for additional information.

Questionnaires including EuroQol EQ-5D-5L and Kansas City Cardiomyopathy Questionnaire (KCCQ) (see section 11.2) will be conducted at baseline, 6 and 12 months after randomisation. In addition, EuroQol EQ-5D-5L will be conducted annually for up to 4.5 years (or until 12 months after the last patient is recruited). Patient acceptability data will be collected at 6 months using a questionnaire created with input from the patient advisory group. A questionnaire on resource use will be collected at baseline and 12 months. With all questionnaires there will be the option to complete them on paper or online.

Longer-term Follow Up: We shall obtain consent for national data linkage (pending additional funding) to collect data on hospitalisations and deaths (dates and causes) from NHS England and Public Health Scotland, for up to 10 years after the end of the trial.

10.3 WITHDRAWAL FROM THE TRIAL

The patient will be free to withdraw from the trial at any time without giving reasons and without prejudicing any further treatment/care.

In line with usual clinical care, cessation or alteration of treatment regimens at any time will be at the discretion of attending clinical teams or the patients themselves. Where patients wish to withdraw from the trial, clarification of the extent of withdrawal will be sought and documented in the eCRF. It will be possible for patients to withdraw from future study questionnaires but still have follow up through review of electronic records and/or linkage with NHS England and Public Health Scotland.

10.4 INTERNAL PILOT

The internal 9-month pilot phase will test trial processes including recruitment and adherence. During the internal pilot detailed screening data will be collected from each site to determine the factors which are impacting recruitment, in addition to online discussions with the Principal Investigator at each site.

11. ASSESSMENTS/DATA COLLECTION

Participating sites will be expected to maintain a file of essential trial documentation (Investigator Site File) and to complete all electronic Case Report Forms (eCRFs) for the trial.

11.1 SUBMISSION OF TRIAL DATA

Electronic Case Report Forms (eCRF)

Trial data will be recorded by trial site research staff in the trial-specific eCRF designed and administered by the Robertson Centre for Biostatics (RCB) at the University of Glasgow. The participant's trial number plus full name, date of birth, postcode, email address, NHS number and CHI number in Scotland (for long term data linkage via NHS databases) and initials will be added to the eCRFs in order to identify the participant. This will be stored separately to clinical results, reports and demographic data, which will be pseudonymised with the patient's unique trial number. A query management tool within the eCRF will highlight to sites any missing or discrepant data queries.

11.2 BASELINE DATA

Baseline data (up to 6 months prior to randomisation):

- Demographics
- Medical History
- Questionnaires including EQ-5D-5L, KCCQ and resource use
- Medication (diuretic and 4 heart failure drugs only, no doses, from electronic patient records)
- Haemoglobin, eGFR, HbA1c, NTproBNP (if available),
- ECG: Atrial fibrillation, LBBB and upload
- Echocardiogram: LVEF and report upload

Ethnic diversity and inclusivity

- This trial will be inclusive of all patients affected by heart failure and in order to monitor this we will collect data on sex, ethnicity, occupation, living arrangements, education level, distance to nearest hospital, total household annual income.

11.3 FOLLOW UP

Patients will be followed up for a minimum of 12 months. Follow up will continue until 1 year after the last patient is randomised. This duration has previously been used in effectiveness trials of cardiovascular imaging [18, 19].

6 month follow-up (± 28 days):

- Imaging report upload
- Questionnaires: EQ-5D-5L, KCCQ and acceptability (online, phone or post).
- Medication (as per baseline)
- Resource use (from review of electronic records):
    - Any other cardiac tests (stress CMR, CTCA, ICA)
    - Hospitalisation for cardiovascular cause (Days in CCU/Days in HDU/Days in ICU/Days in General Ward)
    - Outpatient appointments (cardiology or cardiothoracic surgery)

12 month follow-up (± 28 days):

- Any of the following events occurred from review of electronic records (category code list):
    - Death – cause if known
    - Revascularisation:
        - PCI: Date of PCI
          Elective/urgent
          Planned (Yes/No)
        - CABG: Date of PCI
          Elective/urgent
          Planned (Yes/No)
- Imaging report upload
- Questionnaires: EQ-5D-5L and KCCQ, resource use (online, phone or post)
- Medication (as per baseline)
- Resource use (from review of electronic records):
    - Any other cardiac tests (eCRF category code list – stress CMR, CTCA, ICA)
    - Hospitalisation for cardiovascular cause (category code list – Days in CCU/Days in HDU/Days in ICU/Days in General Ward)
    - Outpatient appointments (cardiology or cardiothoracic surgery)

Annual follow-up (± 28 days):

- Any of the following events occurred from review of electronic records (category code list):
    - Death – cause if known
    - Revascularisation:
        - PCI: Date of PCI
          Planned (Yes/No)
        - CABG: Date of PCI
          Planned (Yes/No)
- Imaging report upload
- Questionnaires: EQ-5D-5L
- Echocardiogram LVEF and report upload

- Resource use (from review of electronic records) :
    - Any other cardiac tests (eCRF category code list – stress CMR, CTCA, ICA)
    - Hospitalisation for cardiovascular cause (category code list – Days in CCU/Days in HDU/Days in ICU/Days in General Ward)
    - Outpatient appointments (cardiology or cardiothoracic surgery)

Longer-term follow-up (by remote data linkage with NHS records pending additional funding) for up to 10 years:

- Any of the following events occurred (category code list):
    - Death – cause if died
    - Myocardial infarction
    - Heart failure hospitalisation
    - Revascularisation:

        PCI: Date of PCI
        Planned (Yes/No)
        CABG: Date of CABG
        Planned (Yes/No)

Standard unscheduled CRFs:

- Withdrawal
- Serious Adverse Events (angiography complications and contrast reactions only)
- Death

11.4 SCAN UPLOAD

Study scans (ICA, CTCA, stress CMR) will be transferred to a central corelab at University of Leeds intermittently (e.g. every 6 months). These scan results will be used for future sub-studies (which will be subject to their own ethical and other approvals). The corelab analysis will not be used to influence decisions into how trial patients are managed but only for future research purposes.

11.5 LONG TERM FOLLOW UP

Individual sites will seek, for all randomised patients, the certified causes of death from medical records, the ONS or NHS England (England)/Public Health Scotland. Notification of deaths is independent of the patients' clinical follow-up (if they remain resident in the United Kingdom).

Details of late cardiovascular events (including Acute Coronary Syndrome, acute or planned revascularisation procedure, any heart failure hospitalisation) beyond the 12-month follow-up period may be obtained from hospital and GP records or from centralised NHS databases for a period of up to 10 years. An amendment will be submitted to the HRA to extend the study beyond the 5-year study period, when additional funding has been awarded.

11.6 DEFINITION OF END OF TRIAL

The end of the trial is defined as the date of last randomised patient has reached the minimum 12m follow up.

11.7 SCHEDULE OF EVENTS

	Eligibility	Baseline	Six months post randomisation	One year post randomisation	Annual follow-up	Long term data linkage
Usual Care						
Demographics and medical history	x					
LVEF Assessment	x					
Blood results (Hb, eGFR, HbA1c, NTproBNP if available)		x				
Electrocardiogram		x				
Echocardiogram upload		x			x	
Imaging Result upload (CTCA, stress CMR, ICA)			x			
Cardiac medication		x	x	x		
Research Activities						
Consent	x					
Confirmation of eligibility	x					
EQ-5D-5L questionnaire		x	x	x	x	
KCCQ questionnaire		x	x	x		
Resource use		x		x		
Acceptability questionnaire			x			
Primary endpoint			x	x	x	x
Secondary endpoint			x	x	x	
SAEs			x	x	x	

12. SERIOUS ADVERSE EVENTS PROCEDURES

12.1 GENERAL DEFINITIONS

A **Serious Adverse Event (SAE)** is defined in general as "any untoward medical occurrence or effect" that:

- results in death,
- is life-threatening*,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- consists of a congenital anomaly or birth defect,
- may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

*the term life-threatening refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

Related is defined as:

- A causal relationship between the intervention and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Unexpected is defined as:

- An adverse event which is not consistent with the information about the randomised imaging test (listed in 12.2.2)

12.2 OPERATIONAL DEFINITION & REPORTING PERIOD FOR AEs/SAEs

12.2.1 Expected AEs – Recorded in eCRF but not reportable

Due to the nature of heart failure and its treatment, patients are likely to experience adverse events throughout the course of the disease. The patient population may also have co-morbid disease and as such in this patient population, acute illness resulting in hospitalisation, new medical problems and deterioration of existing medical problems are expected. These events will be captured in the eCRF but will not be reportable.

12.2.2 Related SAEs – Reported within standard eCRF

Related SAEs (expected and unexpected) for the randomised investigation alone that occur within 30 days will be collected. Adverse Events that occur during the hospitalisation for the procedure will be recorded in the eCRF but will not reported in an expedited manner unless unexpected.

Data to inform the objectives (deaths or hospitalisations) will be recorded from medical records but not designated as SAEs for both study arms outside of the SAE reporting period.

The following SAEs are expected within the trial population and will be reported by the clinical research teams using in the eCRF including:

- Angiography complications
    - Vascular complications
    - Peri-procedural stroke
    - Peri-procedural MI
    - Allergic contrast reaction
- Allergic contrast reaction to either CTCA or stress CMR

12.2.3 Related & Unexpected SAEs – Expedited Reporting

All Related & Unexpected SAEs occurring within 30 days of an investigation (angiography, stress CMR, CTCA) must be reported by the clinical research team in the eCRF within one working day of the investigator becoming aware of the event.

For each Related & Unexpected SAE the following information will be collected:
- full details in medical terms with a diagnosis, if possible
- its duration (start and end dates if applicable)
- action taken
- outcome
- causality (i.e. relatedness to investigation), in the opinion of the investigator

Any follow-up information should be added to the same Related & Unexpected Serious Adverse Event eCRF as soon as it is available. Events will be followed up until the event has resolved or a final outcome has been reached. All Related & Unexpected SAEs will be reviewed by the Chief Investigator and subject to expedited reporting to the Sponsor (governance-ethics@leeds.ac.uk) within 1 working day and the main REC on behalf of the Chief Investigator within 15 days.

12.2.5 Serious Adverse Events (SAEs) that Do Not Require Reporting

SAEs deemed to be unrelated to randomised investigation by the site PI (or delegated investigator) will not be reported.

12.2.6 Non-serious adverse events

Adverse Events (AEs) occurring during this timeframe must be recorded, assessed, reported and analysed in accordance with the UK Policy Framework for Health and Social Care Research and the study protocol. All AEs must be assessed for seriousness using the definitions above. Non-serious adverse events do not need to be reported within the eCRF but should be recorded within the patient's medical records.

12.3 RESPONSIBILITIES

Principal Investigator/Authorised Individual

1) Checking for SAEs when patients attend for routine treatment/follow-up
2) Judgement in assessing:
    - Seriousness
    - Causality
    - Expectedness
3) To ensure all Related & Unexpected SAEs are recorded and entered to the eCRF within 24 hours of becoming aware and to provide further follow-up information as soon as available
4) To report Related & Unexpected SAEs to local committees in line with local arrangements.

Chief Investigator or delegate

1) Assign relatedness and expected nature of SAEs where it has not been possible to obtain local assessment
2) Expedited reporting of Related & Unexpected SAEs to the main REC and Sponsor within required timelines
3) Review all events assessed as Related & Unexpected in the opinion of the local investigator, within the required timelines. In the event of disagreement between the local assessment and the Chief Investigator, local assessment may be upgraded or downgraded by the Chief Investigator prior to reporting to the main REC.

RCB

1) Preparing annual safety data for inclusion in reports Trial Steering Committee (TSC).
2) Notifying Investigators of Related & Unexpected SAEs (by email) which compromise patient safety.

Trial steering committee (TSC)

In accordance with the Trial Terms of Reference the TSC will periodically review safety data and unblinded overall data to determine patterns and trends of events, or to identify safety or trial conduct issues, which would not be apparent on an individual case basis.

13. OUTCOME MEASURES

13.1 PRIMARY ENDPOINT

Time to first composite endpoint measured from randomisation for a minimum of 12 months:

- All cause death
- myocardial infarction
- Heart failure hospitalisation

13.2 SECONDARY ENDPOINTS

- Total MACE events (MACE is defined as all-cause mortality, MI and heart failure hospitalisations)
- Total (first and recurrent) HF hospitalisations
- Total Cardiovascular (CV) death
- Total all-cause mortality
- KCCQ-CSS at 6 and 12 months
- EQ5D at 6 and 12 months

13.3 EXPLORATORY ANALYSES

- Superiority of CTCA vs stress CMR (time to event analysis of primary endpoint)
- KCCQ-OSS at 6 and 12 months
- KCCQ-TSS at 6 and 12 months
- Myocardial infarction
- Procedural complications
- Time to diagnosis (which will be impacted by NHS waiting lists)

14. SAMPLE SIZE

We will aim to recruit both outpatients and inpatients who have suffered decompensated heart failure who have poor outcomes (annualised major adverse cardiovascular event rates of 15-46% in trials) [20-22]. There are no prior trials of imaging strategy in heart failure on which to base a proposed non-inferiority margin. In MR-INFORM, a randomised trial of stress CMR vs ICA in patients with angina pectoris an absolute non-inferiority margin of 6% (equating to hazard ratio 1.6) was used. Non-inferiority hazard ratios vary in cardiovascular trials between 1.05 and 2.85 [23], and by selecting a non-inferiority margin at the very conservative end of this range we will maximise confidence in our findings.

The primary analysis will compare the two non-invasive strategies (combined) to the invasive strategy. Assuming 3.5 years recruitment, plus a year of follow-up (4.5 years maximum follow-up) and complete follow-up, there will be 90% power to demonstrate non-inferiority at a margin of HR=1.22 at 5% significance (i.e. one-sided $p<0.025$) with 982 per group (calculated using nQuery 9). Given the pragmatic study design and passive follow-up, we anticipate that withdrawals will be minimal and have therefore only increased the target by 2% (i.e. 3000 total, 1000 per arm).

The sample size calculation is based on recruitment over 3 years, with an additional year of follow-up (though we anticipate that recruitment will start slowly and increase, so we have allowed an additional 6 months to "ramp up"). To have 90% power to show non-inferiority (one-sided $p=0.025$), with a non-inferiority margin defined as a HR of 1.22 (which equates to a 6% absolute risk difference at 2 years), we require the observation of 1196 first events. Note, for a 1:1 randomisation this would be 1064 events, but in this study we are comparing the two non-invasive arms to the invasive arm as the primary analysis. The 2:1 randomisation implies that 1064 x 9 ÷ 8 events are required. Assuming recruitment at a constant rate over 3 years, plus an additional year of follow-up, this means recruitment of 982 per group (1964 non-invasive vs. 982 invasive).

To illustrate this further, 3 years of recruitment plus one year of follow-up implies an average of 2.5 years of follow-up per patient. An event rate of 35% over 2 years equates to 41.6 over 2.5 years (assuming exponential survival), so if we had a fixed follow-up of 2.5 years per patient, we would need to randomise a total of 1196 ÷ 0.416 = 2875 patients, or 959 per group, to observe 1196 events. This differs only slightly from the estimated 982 per group required when we have a variable follow-up time.

15. STATISTICAL ANALYSIS PLAN

15.1 GENERAL CONSIDERATIONS

Statistical analysis will follow a pre-determined plan [24]. All analyses will be conducted on the Intention-to-treat (ITT) population where a patient's diagnostic pathway will be that allocated at randomisation. A per-protocol population (PP) will also be defined for planned sensitivity analysis of the primary outcome and will include all participants according to the treatment randomised to, excluding participants who did not have sufficient exposure to their randomised investigation. This population will be defined in agreement with the external Trial Oversight Committee members.

15.2 FREQUENCY OF ANALYSIS

Interim reports will be presented to the independent Trial Oversight Committee in strict confidence at annual meetings. No formal interim unblended analyses of the primary outcome are planned.

Final analysis of the primary outcome measure will be following a minimum 12-month follow-up of all patients. Analysis of long-term outcomes is planned based on electronic health records.

15.3 ANALYSES OF PRIMARY OUTCOME MEASURE

Statistical analyses will follow a pre-determined statistical analysis plan, to be signed-off prior to any analyses being performed. All analyses will be conducted according to the intention-to-treat (ITT) principle, i.e. according to the diagnostic pathway allocated at randomisation. Initially, the two non-invasive pathways will each be compared for non-inferiority to the invasive standard of care. Subsequently the two non-invasive pathways will be compared for superiority against each other. All participants will be included in the analysis, up to the time of first event or censoring (being alive and event free). Unadjusted Kaplan-Meier estimates of survivor functions will be presented graphically. Survival between groups will be compared by a log-rank test, stratified by LVEF, and Cox Proportional Hazards regression, adjusted for LVEF. Differences between pathways will be reported as hazard ratios with 95% confidence intervals. Similar principles will be followed for other outcomes, using appropriate types of regression models. Missing data will not be imputed in main analyses, but multiple imputation methods may be applied in sensitivity analyses.

15.4 ANALYSES OF SECONDARY OUTCOME MEASURES

As a secondary analysis, we will perform a win ratio analysis of the hierarchy of death, number of hospitalisations, and quality of life. For each between-group comparison, all pairs of observations will be compared over the longest common follow-up time for each pair to determine the winner. Inclusion of a quality-of-life measure as the third level in the hierarchy of outcomes should ensure a high proportion of informative pairs. Alternative hierarchies will be explored in sensitivity analyses.

The two non-invasive pathways will each be compared for non-inferiority to invasive standard of care for total MACE events (MACE is defined as all-cause mortality, MI and heart failure hospitalisations), total (first and recurrent) HF hospitalisations, KCCQ-CSS at 6 and 12 months, total Cardiovascular (CV) deaths, total all-cause mortality. Subsequently the two non-invasive pathways will be compared for superiority against each other.

15.5 EXPLORATORY ANALYSES

Procedural complications and time to diagnosis (which will be impacted by NHS waiting lists) will be compared between the two non-invasive pathways will each be compared for non-inferiority against invasive standard of care. Subsequently the two non-invasive pathways will be compared for superiority against each other.

15.6 MEASUREMENT OF COSTS AND OUTCOMES

The health economic evaluation will determine the cost-effectiveness of the three diagnostic strategies evaluated in the trial, from the perspectives of the UK NHS and personal social services, in line with the National Institute for Health and Care Excellence (NICE) guidance for health technology evaluation.[25] We will conduct the evaluation alongside the clinical trial over a 1-year time horizon and a model-based evaluation over a life-time horizon. We will capture all healthcare resource use in the three diagnostic arms (CTCA, stress CMR and ICA) over the duration of the trial. This will include resource use relating to treatment received (including setting and staff time required), hospitalisations, cardiac outpatient visits during follow-up.

Hospitalisation data will be captured using both the eCRF and linkage to centralised NHS databases. All other resource use data will be captured using a bespoke resource use questionnaire administered at baseline, 6- and 12-months post randomisation. For the within-trial analysis, mean total patient cost by trial arm will be estimated by applying national unit costs to healthcare resource use data. Quality of life data will be captured using the EuroQol EQ-5D-5L instrument, administered at baseline, 6 and 12 months post randomisation Quality-adjusted life years (QALYs) gained will be estimated using the baseline-adjusted area under the curve approach [26].

Where missing data are encountered, we will explore the assumptions regarding the missing data mechanism and decide upon an imputation method based on best practice. The mean total cost and mean total QALY gain per patient, according to randomisation group, will be estimated using a generalised linear model (GLM) and adjusting for trial minimisation factors and potential confounding factors. The appropriate family for the GLM will be selected based on the results of the modified Park's test. Cost-effectiveness at 12 months will be expressed as the incremental cost-effectiveness ratio (ICER) and net monetary benefit (NMB). We will assume a willingness-to-pay for QALY gains of £20,000. We will undertake probabilistic sensitivity analysis, using non-parametric bootstrapping, to explore the uncertainty in our results and plot the probability of cost-effectiveness on the cost-effectiveness acceptability curve. We will also undertake sensitivity analysis, using conceptual model-mediated regression analyses to explore the drivers – inputs

(imaging strategy), mediators (e.g. hospitalisations, procedural complications, time to diagnosis) of outcomes (costs and QALYs).

For the lifetime horizon, a health economic model will be developed. This will be informed by the existing literature. An initial scoping review did not identify any lifetime cost-effectiveness analyses of non-invasive imaging, compared with invasive coronary angiography, in patients with heart failure. However, there is clear evidence from patients with suspected angina that the choice of first-line test can influence downstream management and healthcare costs [27-29].

The health economic model will capture disease progression using health states which represent the natural history of people living with heart failure. Based on the existing literature, it is likely to be a decision-analytic model with multiple health states in which a patient with heart failure experiences a monthly transition probability of experiencing further complications or death. [30]. Other relevant model parameters will be informed by a targeted literature review. We will undertake a probabilistic sensitivity analysis using a 10,000-iteration Monte Carlo simulation. To reflect uncertainty in our model's parameter values, each parameter will be characterised as a probability distribution, in oppose to a point estimate, allowing us to explore the extent to which uncertainty in model parameters feed through into uncertainty in final modelled costs, life years, QALYs and overall cost-effectiveness.

15.7 ETHNICITY ANALYSIS

We plan to study the association between ethnicity, co-morbidities and outcomes in heart failure. Historically, traditional reporting of ethnicity has been poor in heart failure trials. In a recent meta-analysis of 414 trials only 38% reported ethnicity of participants. In those studies which have reported ethnicity, patients from ethnic minorities were under-enrolled relative to disease distribution [31]. This is particularly important as emerging data suggests the response to treatment and prognosis of patients with heart failure varies according to ethnicity with the highest event rates seen in black, then Asian patients with the lowest event rates in white patients [32].

We plan to collect self-reported data on ethnicity of all patients recruited to the trial. There is limited data on the relationship between ethnicity and outcomes in NHS heart failure patients which we will explore. As part of the trial eCRF we will collect data on duration of symptoms and referral pathway to investigate the hypothesis that impaired outcomes seen in ethnic minority patients are related to access to specialist healthcare.

16. DATA MONITORING

16.1 SOURCE DATA

ICH GCP defines source data as: 'All information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial'. The source data transcribed into the eCRF from the medical records must be accurate and verifiable. eCRF data will be checked for quality and completeness by the RCB. Missing data will be chased until it is received, confirmed as not available or the trial is at analysis. However missing data items

from participant-completed outcome measures will not be chased from participants (although missing questionnaire packs sometimes are). It is the responsibility of the site PI to ensure the accuracy of all data entered. Sites will be required to complete a source data plan. Source data worksheets can be provided to sites although are not mandatory. A Trial Monitoring Plan will be developed and a Meeting Group Monitoring Schedule including primary endpoint and safety data will be defined by the Trial Management Group (TMG) and agreed by the Trial Steering Committee (TSC) if necessary.

16.2 DATA COLLECTION

An eCRF, developed by the RCB (part of GCTU), will capture all data required to meet this protocol's requirements. Access to the eCRF will be restricted, via a study-specific web portal. Authorised site personnel will be able to make entries to their patients' data via the web portal. The Investigator or his/her designee will be responsible for all entries into the eCRF and will confirm that the data are accurate, complete and verifiable for all visits. Data will be stored in a MS SQL Server database.

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

16.3 DATA VALIDATION

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

16.4 DATA SECURITY

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

16.5 ARCHIVING

At the end of the trial, data will be securely archived in line with the Sponsor's procedures for a minimum of 10 years and for up to 20 years. Site data and documents will be archived at site. Following authorisation from the Sponsor, arrangements for confidential destruction will then be made.

17. QUALITY ASSURANCE AND ETHICAL CONSIDERATIONS

17.1 QUALITY ASSURANCE

The trial will be conducted in accordance with the principles of Good Clinical Practice in clinical trials as detailed by the Medical Research Council (1998), the UK Policy framework for Health and Social Care Research (*and Scottish Executive Health Department Research Governance Framework for Health and Social Care 2006 for studies conducted in Scotland)* and through adherence to RCB Standard Operating Procedures (SOPs).

Investigators are required to promptly notify the sponsor of a serious breach within 1 working day of the team's awareness (as defined in NRES SOP V7.6). A "serious breach" is defined as a breach of the protocol or of the conditions or principles of Good Clinical Practice (or equivalent standards for conduct of non-CTIMPs) which is likely to affect to a significant degree the safety or physical or mental integrity of the trial subjects, or the scientific value of the research. In the event of doubt the Investigator should contact the Trial Manager and CI immediately. All reported breaches will be reviewed by the Chief Investigator and are subject to expedited reporting to the Sponsor (governance-ethics@leeds.ac.uk) within 1 working day. Serious breaches need to be reported to the REC on behalf of the CI within 7 days.

17.2 ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 64th World Medical Association General Assembly, Edinburgh, Scotland, 2013. Informed written consent will be obtained from the patients prior to randomisation/registration into the trial. The right of a patient to refuse participation without giving reasons must be respected. The participant must remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment. The trial will be submitted to and approved by a main Research Ethics Committee (main REC), the Human Research Authority (HRA) and the appropriate Site Specific Assessor for each participating centre prior to entering patients into the trial.

17.3 CLINICAL GOVERNANCE ISSUES

To ensure responsibility and accountability for the overall quality of care received by participants during the trial period, clinical governance issues pertaining to all aspects of routine management will be brought to the attention of the TSC and, where applicable, to individual NHS Trusts.

17.4 MONITORING

The study Monitoring Plan outlines the timelines and methods of site monitoring and will be maintained by the GTCU. The degree of monitoring will be proportionate to the risks associated with the study. Risk will be assessed on an ongoing basis by the GTCU and the CI, and adjustments made accordingly (in conjunction with the Sponsor).

17.5 REGULATORY COMPLIANCE

All imaging within this study is routine clinical care nonetheless The protocol and study documentation will be reviewed by a Medical Physics Expert and Clinical Radiation Expert to ensure that it confirms with Ionising Radiation (Medical Exposure) Regulations.

18. DATA PROTECTION AND PATIENT CONFIDENTIALITY

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

- Personal information will be collected via the eCRF to facilitate the process for patient reported outcome questionnaires and to enable record linkage to be carried out. These data items will be encrypted and only those individuals who require to see these data, i.e. the person performing the

record linkage and site research team staff or study monitor, as appropriate, will be able to view them. All electronic data will be held securely in accordance with ISO 27001 at the RCB, part of the GCTU. All Centre staff are required to sign confidentiality agreements and to follow Standard Operating Procedures in accordance with Good Clinical Practice and ISO certification. Personal information may also be shared with University of Leeds for data linkage.

- The trial data managers, statisticians, health economists or any other staff who will perform data related tasks will only be able to access depersonalised data where the participant's identifying information is replaced by a unique study identifier.
- Only those that have been trained and approved will be able to enter or view any data via the web portal. Each site can only see their own patient's data. Patient consent forms will be stored at the study site in a secure location accessible only to study teams.
- where copies of source documents is required (such as scans and reports), the participant's name must be obliterated by site before sending and only the unique patient trial identifier used.
- Scans and reports transferred to the Corelab at University of Leeds will be stored on a secure server.

If a participant withdraws consent from further trial treatment their data will remain on file and will be included in the final trial analysis.

19. STATEMENT OF INDEMNITY

The University, when acting as Sponsor, has insurance cover in force, which meets claims against it and where those claims arise from the Universities own negligence in its role and activities relating to the study (and which is subject to the terms, conditions and exceptions of the relevant policy). Clinical negligence indemnification will rest with the participating NHS Trust under standard NHS arrangements.

20. TRIAL ORGANISATIONAL STRUCTURE

20.1 INDIVIDUALS AND INDIVIDUAL ORGANISATIONS

Trial Sponsor: In accordance with the UK Policy Framework for Health and Social Care Research, the Sponsor of the study is the University of Leeds. Responsibilities for conduct are delegated as below.

Chief Investigator: as defined by the UK Policy framework for Health and Social Care Research, is responsible for the design, management and reporting of the trial. The CI will be responsible for the day to day running of the trial including obtaining HRA and local site approvals, clinical set-up, ongoing management including training, monitoring reports and promotion of the trial.

Robertson Centre for Biostatistics, part of Glasgow Clinical Trials Unit: The RCB will have responsibility for data management and analysis in accordance with the UK Policy framework for Health and Social Care Research . The RCB will provide data management according to applicable RCB SOPs, including, randomisation design and service, database development and provision, protocol review, trial design, and statistical analysis for the trial.

CROSS-HF Clinical Research Nurse (CRN): The CRNs based at recruiting sites will be responsible for the day-to-day management of the trial, patient recruitment, obtaining informed consent, randomisation, liaison with medical staff, CRF completion and annual follow-up assessments.

20.2 GROUPS

Trial Management Group (TMG): The TMG, comprising the Chief Investigator, RCB team, grant co-applicants and a CROSS-HF CRN will be assigned responsibility for the clinical set-up, on-going management, promotion of the trial, and for the interpretation and publishing of the results. Specifically the TMG will be responsible for (i) protocol completion, (ii) oversight of CRF development, (iii) obtaining approval from the main REC and supporting applications for Site Specific Assessments, (iv) completing cost estimates and project initiation, (v) nominating members and facilitating the TSC, (vi) reporting of serious adverse events, (vii) monitoring of screening, recruitment, treatment and follow-up procedures, (vii) auditing consent procedures, data collection, trial end-point validation and database development.

Trial Steering Committee (TSC): The role of the TSC is to provide overall supervision of the study. The TSC will provide advice on data and safety aspects of the study and, on consideration, recommend any appropriate amendments/actions for the study as necessary. The TSC acts on behalf of the funder and Sponsor.

Meetings will occur at least annually with increased frequency as needed. In addition, feasibility reviews will be performed and overseen by the TSC at the following time points:

- At the end of the completion of the vanguard stage: to review participant recruitment rates and safety data
- At 80% recruitment: to review safety data and event rates

Data Monitoring Committee (DMC)

The role of the DMC is to provide advice on data and safety aspects of the study. Meetings of the Committee will be held at least annually to review safety data, the interim analysis completed at 80% follow-up or as necessary to address any issues. The DMC is advisory to the TSC and can recommend premature closure of the study to the TSC. Minutes from the DMC meetings will be agreed by the members and distributed to the Sponsor and Funder.

Patient and Public Involvement (PPI) Group: Patients and non-medical patient leaders from two organisations reviewed and contributed to the study design: Cardiomyopathy UK and British Society for Heart Failure Patient Group. A representative from each of these groups will sit on the TSC.

21. PUBLICATION POLICY

The trial will be registered with ISRCTN registry prior to the start of recruitment.

The success of the trial depends upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship and contributorship. Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions. These state that authorship credit should be based only on substantial contribution to:

- conception and design, or acquisition of data, or analysis and interpretation of data
- drafting the article or revising it critically for important intellectual content
- and final approval of the version to be published
- and that all these conditions must be met (www.icmje.org).

All collaborators will be listed as contributors for the main trial publication, giving details of roles in planning, conducting and reporting the trial. The CROSS-HF team should be acknowledged in all publications, as should the funder NIHR. Other key individuals will be included as authors or contributors as appropriate and at the discretion of the CROSS-HF TMG. Any disputes relating to authorship will be resolved by the TSC.

The Chairs and Independent members of the TSC will be acknowledged, but will not qualify for full authorship, in order to maintain their independence.

To maintain the scientific integrity of the trial, data will not be released prior to the first publication of the analysis of the primary endpoint, either for trial publication or oral presentation purposes, without the permission of the Trial Oversight Committee. In addition, individual collaborators must not publish data concerning their participants which is directly relevant to the questions posed in the trial until the first publication of the analysis of the primary endpoint.

The funder, the NIHR, has adopted an open access policy for all funded research which means that an electronic copy of all peer-reviewed published papers must be accessible via the UKPMC website.

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