FULL PROTOCOL TITLE OF THE STUDY

REvascularisation for heart failure with PReserved ejection fraction and Ischaemia: EValuation of Efficacy and mechanistic Description (REPRIEVED)

SHORT STUDY TITLE and ACRONYM

Coronary artery stents in heart failure with preserved ejection fraction

The REPRIEVED Trial

Chief Investigator: Dr Matthew Ryan

Co-sponsored by:

King's College London (KCL) and Guy's and St Thomas' NHS Foundation Trust (GSTFT)

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KEY STUDY CONTACTS

Chief Investigator	Dr Matthew Ryan (Senior Lecturer in Cardiology and Chief Investigator) Address: St Thomas' Hospital Campus, King's College London, Westminster Bridge Road, London, SE1 7EH, UK Phone: 020 7188 1041 Email: matthew.ryan@kcl.ac.uk
Clinical Trials Unit	London School of Hygiene & Tropical Medicine Address: Keppel Street, London, WC1E 7HT, UK Email: REPRIEVED@Lshtm.ac.uk
Trial Management Group	Dr. Matthew Ryan (Chief Investigator) Prof. Tim Clayton (Professor in Applied Medical Statistics) Mr Richard Evans (Senior Manager of the Clinical Trials Unit) Mr Steven Robertson (Senior Data Manager) Mrs Lynn Laidlaw (PPI Contributor) Mr Matthew Kwok (Trial Manager)
Funder	National Institute for Health and Care Research EME Programme Address: University of Southampton Phone: 023 8059 4304 Email: netsmonitoring@nihr.ac.uk
Emergency Telephone Contact *To be used **only** if emergency/urgent unblinding of trial treatment is required (24 hour)*	020 79272885 (If calling from outside the UK, please use +44 20 79272885)

SIGNATURE PAGE

The Chief Investigator and the R&D (Sponsor office) have reviewed this protocol. The investigators agree to perform the investigations and to abide by this protocol.

The investigator agrees to conduct the trial in compliance with the approved protocol, EU GCP, the UK Data Protection Act (2018), the Trust Information Governance Policy (or other local equivalent), the UK policy Framework for Health and Social Care research, the Sponsor's SOPs, and other regulatory requirements as amended.

Chief investigator

Dr Matthew Ryan

Signature Date

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CONTENTS PAGE

SIGNATURE PAGE 3

CONTENTS PAGE 4

1 LIST OF ABBREVIATIONS AND DEFINITIONS 8

2 SUMMARY/SYNOPSIS 10

3 INTRODUCTION 11

4 TRIAL OBJECTIVES AND PURPOSE 13

5 STUDY DESIGN & FLOWCHART 14

5.1 Study Design 14

5.2 Outcome definitions 15

5.3 Trial flowchart 23

5.4 Participating Trial Sites 24

5.5 Participant inclusion criteria 24

5.6 Participant exclusion criteria 24

5.6.1 Angina 25

6 STUDY PROCEDURES 25

6.1 Screening 25

6.1.1 Patient population for screening 25

6.1.2 Initial approach to patients 25

6.1.3 Sources of potential participants 25

6.1.4 Screening CT-FFR 26

6.1.5 Screening Logs 26

6.1.6 Responsibility for completing and reporting the screening log 26

6.2 Clinically referred participants 26

6.2.1 Self-referred participants 26

6.3 Consent 27

6.4 Randomisation 27

6.4.1 Stratification 27
6.4.2 Participant identification log 27
6.4.3 GP notification and medical records 28
6.5 Intervention 28
6.5.1 Arranging the trial intervention 28
6.5.2 On the day of the intervention 28
6.5.3 Timing of randomisation 28
6.5.4 Delivering the randomised treatment allocation 28
6.5.5 Post-intervention 29
6.5.6 Prescription of anticoagulants 29
6.6 Prescription of clopidogrel or placebo clopidogrel 29
6.7 Medical therapy 29
6.8 Blinding 30
6.8.1 Blinded and unblinded staff at trial sites 30
6.8.2 Randomisation notification emails 30
6.8.3 Blinding of the procedure 31
6.8.4 Emergency unblinding 31
6.9 Internal pilot study 31
6.10 Schedule of assessments for each visit 32
6.10.1 Baseline visit 32
6.10.2 PCI procedure visit 33
6.10.3 Discharge 33
6.11 Follow-up Procedures 33
6.12 Trial schedule 35
6.13 Radiology Assessments 36
7 LABORATORIES 36
7.1 Central/Local Laboratories 36

7.2 Sample Collection 36
7.3 Sample Analysis Procedures 36
8 END OF STUDY DEFINITION 37
9 ASSESSMENT OF SAFETY 37
9.1 Definition 37
9.2 Unexpected Serious Adverse Events 37
9.3 Unexpected Non-Serious Adverse Events 37
9.4 Reporting Unexpected Adverse Events 37
9.4.1 Assessment of Intensity 37
9.4.2 Assessment of Causality 37
9.5 Ethics Safety Reporting 38
10 TRIAL ORGANISATION 38
10.1 Trial Management Group 38
10.2 Trial Steering Committee 38
10.3 Patient Advisory Committee 38
10.4 Data Monitoring Committee 39
11 ETHICS & HRA APPROVALS 39
11.1 Required conditions before recruitment can start at trial sites 39
11.2 Amendments 39
11.3 Correspondence 39
12 COMPLIANCE AND WITHDRAWAL 40
12.1 Participant compliance 40
12.2 Withdrawal / dropout of participants 40
12.2.1 Recording participant withdrawal in the eCRF 40
12.2.2 Withdrawal due to an adverse event 40
12.3 Protocol Compliance 41
13 TRIAL DATA 42

13.1 Data to be collected 42
13.2 Electronic Case Report Form (eCRF) 42
13.2.1 eCRF access at site level 42
13.3 Data security 42
13.4 Data management 42
13.5 Personal Data Breaches 42
13.6 Data sharing 43
14 STUDY WITHIN A TRIAL (SWAT) 43
15 MONITORING AND AUDITING 44
15.1 Central statistical monitoring 44
15.2 Monitoring due to protocol non-compliance 44
15.3 Recording research conduct at site 44
16 STATISTICAL CONSIDERATIONS 44
16.1 Sample size calculations 45
17 FINANCING 45
18 INSURANCE AND INDEMNITY 45
19 Data responsibilities 46
19.1 Data controller 46
19.2 Data processors 46
20 INTELLECTUAL PROPERTY (IP) 46
21 REPORTING AND DISSEMINATION 46
22 REFERENCES 47
APPENDIX 1: NIHR INCLUDE Impaired Capacity to Consent Framework 50
APPENDIX 2: DATA FLOW DIAGRAM FOR DATA LEAVING TRUST/SITE PREMISES 51
APPENDIX 3: SAE Reporting Flow Diagram-Non CTIMPs 52
APPENDIX 4: Safety Reporting in Non-CTIMP Research 53
APPENDIX 5: PROTOCOL AMENDMENT HISTORY 54

1 LIST OF ABBREVIATIONS AND DEFINITIONS

AE	Adverse Event
AKIN	Acute Kidney Injury Network
ARC	Academic Research Consortium
BARC	Bleeding Academic Research Consortium
CABG	Coronary artery bypass graft
CAD	Coronary Artery Disease
CCS	Canadian Cardiovascular Society
CI	Chief Investigator - The overall lead researcher for a research project (Outside the UK the term Coordinating Investigator or Investigator may be used). Chief investigators are responsible for the overall conduct of a research project.
CMD	Coronary Microvascular Dysfunction
CNS	Central Nervous System
CFR	Coronary Flow Reserve
CT	Computed Tomography Scan
CTCA	Computed Tomography Coronary Angiogram
CT-FFR	Computed Tomography Fractional Flow Reserve
CTU	Clinical Trials Unit
Datix	Incident reporting and risk management platform
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDI	Equity, Diversity and Inclusion
FFR	Fractional Flow Reserve
GSTFT	Guys and St Thomas' NHS Foundation Trust
HFpEF	Heart Failure with preserved Ejection Fraction
HFrEF	Heart Failure with reduced Ejection Fraction
HRA	Health Research Authority
ICHOM	International Consortium for Health Outcomes Measurement
KCCQ-OSS	Kansas City Cardiomyopathy Questionnaire Overall Summary Score
KCL	King's College London
LVEF	Left Ventricular Ejection Fraction
MCID	Minimum Clinically Important Difference
MI	Myocardial Infarction
NHPR	Non-hyperaemic pressure ratio
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NT-pro-BNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
OAC	Oral anticoagulant
ORBITA	Objective Randomised Blinded Investigation with Optimal Medical Therapy or Angioplasty in Stable Angina (*Randomised Trial)*
PAC	Patient Advisory Committee
Participant	An individual who takes part in a clinical trial
PCI	Percutaneous Coronary Intervention

PI	Principal Investigator - An individual responsible for the conduct of the research at a research site. There should be one PI for each research site. In the case of a single-site study, the chief investigator and the PI will normally be the same person.
PIC	Participant Identification Centre
PPI	Patient and Public Involvement
PROMS	Patient Reported Outcome Measures
R&D	Research & Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SGLT2i	Sodium glucose cotransporter-2 inhibitor
SOP	Standard Operating Procedure
Sponsor	The organisation or partnership that takes on overall responsibility for proportionate, effective arrangements being in place to set up, run and report a research project.
SWAT	Study Within A Trial
TIA	Transient Ischemic Attack
TIMI	Thrombolysis In Myocardial Infarction
TMG	Trial Management Group
TSC	Trial Steering Committee
VARC	Valve Academic Research Consortium
VFR	Volumetric Flow Reserve
WPD	Working Practice Document

2 SUMMARY/SYNOPSIS

Title	*REvascularisation for heart failure with PReserved ejection fraction and Ischaemia: EValuation of Efficacy and mechanistic Description (REPRIEVED)*
Protocol Short Title/Acronym	*Coronary artery stents in heart failure with preserved ejection fraction: The REPRIEVED Trial*
Study Phase if not mentioned in title	*Phase II*
Is the study a Pilot?	*No*
IRAS Number	*330189*
REC Reference	*25/LO/0277 (London - Riverside REC)*
EDGE reference	*174792*
Study Duration	*Five years*
Methodology	*Prospective, multi-centre, randomised, double-blind, placebo procedure-controlled trial*
Health condition(s) or problem(s) studied	*Heart failure with preserved ejection fraction (HFpEF) and coronary artery disease*
Purpose of clinical trial	*To improve the quality of life of patients with HFpEF and coronary artery disease*
Primary objective	*To establish the efficacy of percutaneous coronary intervention at improving quality of life for patients with HFpEF and coronary artery disease*
Secondary objective (s)	*To examine the mechanistic link between ischaemia and quality of life in this population, and how this is modified by percutaneous coronary intervention*
End of study definition	*All study data collected and final database locked*
Number of Participants	*350*
Study Type	*Randomised controlled trial*
Human Tissue Samples (if applicable)	*Research bloods: 5ml blood for full blood count, 5ml for renal function, troponin and NT-pro BNP (only if not taken as part of standard of care at participating sites).*
Data collected/storage (if applicable)	*Data collection and processing at the London School of Hygiene & Tropical Medicine Clinical Trials Unit using an electronic data capture system hosted by Sealed Envelope Ltd.* *Subsequent transfer of final datasets (identifiable and pseudonymised) to King's College London for long term storage and secondary analysis.*

3 INTRODUCTION

Heart failure with preserved ejection fraction

Heart failure with preserved ejection fraction (HFpEF) is a debilitating condition that accounts for over half of new diagnoses of heart failure, is increasing in prevalence and is associated with increased cardiovascular mortality compared to matched controls without HFpEF[1–4]. The primary symptoms are breathlessness, fatigue, peripheral oedema and effort intolerance. The condition is characterised by impairment of cardiac function due to structural cardiac abnormalities despite a normal left ventricular ejection fraction (LVEF) at rest[5]. Development of HFpEF is often associated with hypertension, diabetes, obesity and chronic kidney disease, particularly where these occur together and with increasing age[5,6]. It is estimated that 400,000 people in the UK have HFpEF, accounting for 2.5% of emergency hospital admissions and a significant proportion of the £2 billion per year that the NHS spends on heart failure treatment[7].

Widespread recognition of the condition has only been achieved in the last decade[8]. The prevalence of HFpEF is higher in women and minoritised ethnic populations, who have been under-served by interventional heart failure research[9–11]. Consequently, treatment remains under-developed and evidence-based treatment for HFpEF remains limited to only two repurposed antidiabetic drugs (sodium glucose cotransporter-2 inhibitors (SGLT2i) and semaglutide. SGLT2i are the only drug class to also reduce mortality, whilst semaglutide was tested only in patients with an obesity-HFpEF phenotype[12–17]. Current European guidelines recommend patients with HFpEF receive diuretics, SGLT2i and optimal treatment of comorbidities[8]. This contrasts sharply with heart failure with reduced ejection fraction (HFrEF), where evidence-based developments in drugs, devices and interventions have reduced mortality substantially over the past four decades[8].

Coronary artery disease in HFpEF

Coronary artery disease is an important contributor to the development of HFpEF. Observational and epidemiological studies have consistently shown a prevalence of coronary artery disease in HFpEF of 35-65%[18–24]. Epidemiological studies have found clear associations between prevalent coronary artery disease and incident HFpEF[25].

The mechanistic link between coronary artery disease and the development of HFpEF is hypothesised to be inducible myocardial ischaemia[26]. Inducible ischaemia (inadequate capacity to augment blood flow to meet the metabolic demands of the myocardium) may arise due to stenoses of the epicardial coronary arteries (epicardial coronary artery disease) or abnormalities of the arteriolar circulation (coronary microvascular dysfunction (CMD), though the effects on the myocardium are expected to be similar. The role of ischaemia in the pathogenesis of HFpEF is well recognised, though greater research focus has been given to CMD than epicardial coronary artery disease[27].

Studies in patients with HFpEF and CMD have demonstrated higher left ventricular work, oxygen demand and myocardial blood flow at rest but blunted rises in these indices during stress compared with controls[28]. This inadequate rise in supply relative to demand impairs left ventricular systolic and diastolic function during exertion, limiting cardiac reserve and resulting in detectable myocardial injury via troponin release after exercise[29]. This impairment of diastolic function also worsens ischaemia (as myocardial perfusion is dependent on diastolic ventricular relaxation) resulting in a deleterious cycle of ischaemia and impaired ventricular performance[30]. Patients may experience these effects as angina, breathlessness, effort intolerance or fatigue, often with significant overlap, and whether breathlessness represents an angina equivalent in patients with heart failure remains an important unanswered question.

In addition to the acute effects of ischaemia on symptoms and functional capacity in HFpEF, it is recognised that recurrent episodes of ischaemia result in chronic injury and myocardial fibrosis (which leads to persistent worsening of diastolic function)[21,31,32]. Longitudinal studies have shown larger deteriorations in LVEF over time in individuals with HFpEF and coronary artery disease, compared to those with HFpEF alone[20,33,34]. Developing the evidence base relating ischaemia from epicardial coronary artery disease to symptoms, fibrosis and longitudinal changes in left ventricular function in HFpEF would therefore complement ongoing parallel work relating to CMD.

Percutaneous coronary intervention

Percutaneous coronary intervention (PCI), also referred to as coronary angioplasty and stenting, is an established treatment for coronary artery disease when the patient presents with limiting angina despite optimal pharmacological therapy or an acute myocardial infarction[35]. Coronary patency is restored by balloon dilatation of significant coronary stenoses, followed by placement of a stent which enhances patency in the long term. The procedure is minimally invasive and associated with an in-hospital mortality of 0.14% and risk of myocardial infarction or stroke of 0.3%[36]. The cost of elective PCI in the NHS is modest compared to many other interventions (with an average tariff cost of £1782 for an elective procedure in 2019/20)[37]. Despite the causal association and mechanistic link between coronary artery disease and HFpEF, no randomised study has assessed the efficacy or mechanistic benefits of PCI in this population.

PCI is an attractive option to improve quality of life in patients with HFpEF and coronary artery disease. Treatment with PCI has been shown to improve myocardial perfusion and attenuate the development of systolic and diastolic dysfunction during exertion[38,39]. Long-term improvement in the ischaemic substrate may also reduce the development of myocardial fibrosis and progression to left ventricular systolic dysfunction which has been recognised in this population over longitudinal follow-up[21]. Furthermore, there are concerns that many first-line drugs traditionally used to treat ischaemia may worsen symptoms in patients with HFpEF. The use of beta blockers in HFpEF is associated with chronotropic incompetence, impaired exercise capacity and higher levels of natriuretic peptide, whilst chronic use of nitrates is associated with worsening endothelial function and reduced exercise capacity in this population[40–43]. A treatment which avoids these drug side effects whilst ameliorating ischaemia may therefore be beneficial. Factors which might attenuate the benefit of PCI include the high prevalence of coronary microvascular dysfunction in HFpEF which may leave a (lessened) ischaemic substrate after treatment and the extent of pre-existing cardiac remodelling which may not be reversible, as well as the systemic nature of the condition.

Despite these observational associations and mechanistic explanations for a potential benefit to PCI in HFpEF and coronary disease, the question remains unstudied. The ClinicalTrials.gov and ISRCTN registries report no trials of coronary revascularisation amongst 104 interventional HFpEF studies which are either recruiting or in set-up, though multiple studies are investigating the use of pharmacological treatment to mitigate ischaemia due to CMD or epicardial coronary artery disease in this population. National Institute for Health and Care Excellence (NICE) and international cardiology guidelines on the management of heart failure make no recommendations for the management of coronary artery disease in patients with HFpEF, contrasting with heart failure with reduced ejection fraction (HFrEF) where multiple recommendations are made based on high-quality randomised data[8,44,45]. Exploring the mechanistic links between ischaemia and symptoms in HFpEF and the efficacy of modifying them with coronary revascularisation is therefore a pressing and important question well suited to a phase-2 randomised trial.

4 TRIAL OBJECTIVES AND PURPOSE

Aims:

1. To establish the efficacy of PCI at improving quality of life for patients with HFpEF and coronary artery disease.

2. To examine the mechanistic link between ischaemia, quality of life and the change in these measures after PCI in this population.

Hypotheses:

Efficacy

In patients with HFpEF and coronary artery disease, treatment with PCI is associated with superior quality of life, measured with the KCCQ-OSS, compared to a placebo procedure.

Mechanistic

In patients with HFpEF and coronary artery disease:

- The severity of symptoms correlates with the extent of myocardial ischaemia measured by coronary flow reserve (CFR).
- Treatment of epicardial coronary disease by PCI will improve CFR.
- The change in quality of life following PCI correlates with pre-randomisation CFR and the change in CFR following PCI.

Objectives:

1. To determine the efficacy of PCI as a treatment for coronary artery disease in HFpEF.
2. To examine the mechanistic relationship between ischaemia and symptoms, and how changes in these relate following PCI, in patients with HFpEF and coronary artery disease.
3. To demonstrate the feasibility of a multicentre, placebo procedure controlled randomised trial of PCI in patients with HFpEF and coronary artery disease.
4. To co-produce this trial with patient representatives, to ensure it effectively addresses their needs and priorities.
5. To enrol an inclusive group of participants, ensuring representation of the population of those with HFpEF and coronary artery disease and that all individuals have the same opportunity of participation following the principles of equality, diversity and inclusion.
6. To create new, generalisable learning as to how diversity in interventional heart failure trials can be improved.
7. To inform the feasibility and design of a phase-III randomised controlled trial of clinical and cost effectiveness, should this study suggest efficacy.

5 STUDY DESIGN & FLOWCHART

5.1 Study Design

Research design: a phase II, multi-centre, randomised, double-blind, placebo procedure-controlled superiority trial comparing PCI to a placebo procedure in patients with HFpEF and coronary artery disease.

Randomisation: Patients with HFpEF and coronary artery disease will be randomised in a 1 to 1 manner to either PCI or placebo procedure using an online randomisation system in permuted blocks of varying size. Randomisation will be stratified by recruiting site.

Outcome measures:

- ***Primary efficacy:*** The primary efficacy outcome is the difference in KCCQ-OSS between treatment groups at 6-month follow-up. The Kansas City Cardiomyopathy Questionnaire (KCCQ) is the most widely used disease-specific tool for patient reported quality of life outcomes in heart failure, has been specifically validated in HFpEF and is the recommended tool for assessing functional and psychosocial outcomes in the International Consortium for Health Outcomes Measurement (ICHOM) standard outcome set for heart failure published in 2020[12,14,48,55,56].

- ***Primary mechanistic:*** The primary mechanistic outcome is the difference in CFR between treatment groups, after PCI has been performed in the PCI group. CFR is an independent predictor of future adverse cardiovascular events and allows us to determine the relationship between the severity of epicardial and microvascular disease and quality of life.

- ***Secondary outcomes:*** Key secondary outcomes include all-cause death and hospitalisation for heart failure. Further secondary outcomes include the efficacy of blinding (assessed using standard tools), the ICHOM standard outcome set for heart failure, individual components of the KCCQ (including total symptom score and clinical summary score), New York Heart Association (NYHA) functional class, difference in NT-pro-BNP at six months and difference in left ventricular ejection fraction (LVEF) and diastolic function (mitral E/e') at six months.

- **Secondary mechanistic:** Secondary mechanistic outcomes include change in invasively measured FFR, CFR and microvascular resistance from pre- to post-PCI in all target coronary arteries measured during the PCI procedure.

5.2 Outcome definitions

The following serious adverse events will be collected as secondary outcomes and are expected to occur during this study, and will not require additional reporting as SAEs (see section 7 below). Where possible, definitions are aligned with the ARC-2 consensus document.

Outcome	Endpoint definition
Death	Death from all-causes can be defined as one of the following classifications: **1. Cardiovascular death** Defined as any death resulting from cardiovascular causes. This may include death caused by: a. Acute MI b. Sudden cardiac, including unwitnessed death c. Heart Failure d. Stroke e. Cardiovascular procedures f. Cardiovascular haemorrhage g. Other cardiovascular cause **2. Non-cardiovascular death** Defined as any death not thought to be the result of a cardiovascular cause. This may include death caused by: a. Malignancy b. Pulmonary causes c. Infection (including sepsis) d. Gastrointestinal causes e. Accident or trauma f. Other non-cardiovascular organ failure g. Other non-cardiovascular cause **3. Undetermined** Defined as death not classified under any other category because of the absence of any relevant source documents. For endpoint determination these deaths will be classified as cardiovascular.
Myocardial infarction	Myocardial infarction will be defined according to the ARC-2 definition below. 1. **Spontaneous myocardial infarction (prior to or ≥48 hours after PCI/CABG)** Detection of a rise and/or fall of cardiac troponin I or T, with at least one value higher than the 99th percentile upper reference limit (URL) AND symptoms consistent with ischaemia OR dynamic electrocardiogram (ECG) changes (including ≥1mm ST elevation or ST depression, new left bundle branch block (LBBB) or >3mm T-wave

	inversion OR imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology. **2. Periprocedural MI (within 48 hours after PCI/CABG) including index procedure and subsequent unplanned revascularisation** Absolute rise in cardiac troponin I or T (from baseline) ≥ 35 times the URL AND new significant Q-waves or equivalent OR flow-limiting angiographic complications OR new "substantial" loss of myocardium on imaging. Flow-limiting angiographic complications are defined as loss of patency of a major vessel, graft or side branch, embolization, disruption of collateral flow, persistent slow flow or no reflow, major dissection, angiographic new occlusion or flow limiting stenosis in a coronary artery bypass graft or native coronary artery occlusion. **3. Significant periprocedural myocardial injury (within 48 hours after PCI/CABG) including index procedure and subsequent unplanned revascularisation** Absolute rise in cardiac troponin I or T (from baseline) ≥ 70 times the URL.
Stroke	Stroke will be defined using NeuroARC definitions as one of the following classifications: **Type 1: Overt Central Nervous System (CNS) injury – Acutely symptomatic brain or spinal cord injury** • **Type 1a Ischaemic stroke** Sudden onset of neurological signs or symptoms fitting with a focal or multifocal vascular territory within the brain, spinal cord or retina that persist for ≥ 24 hours or until death, with pathology or neuroimaging that demonstrates either CNS infarction in the corresponding territory (with or without haemorrhage) OR absence of other apparent causes (including haemorrhage), even if no evidence of acute ischaemia in the corresponding vascular territory is detected. OR Symptoms lasting <24 hours with pathology or neuroimaging confirmation of CNS infarction in the corresponding vascular territory. • **Subtype 1aH Ischaemic stroke with haemorrhagic conversions** Ischaemic stroke includes haemorrhagic conversions. These should be subclassified as Class A or B when conversion ischemic stroke is the

	primary mechanism and pathology or neuroimaging confirms a haemorrhagic conversion. Class A: Petechial haemorrhage: Petechiae or confluent petechiae within the infarction or its margins, but without a space-occupying effect. Class B: Confluent haemorrhage: Confluent haemorrhage or hematoma originating from within the infarcted area with space-occupying effect. • **Type 1b Symptomatic intracerebral haemorrhage** Rapidly developing neurological signs or symptoms (focal or global) caused by an intraparenchymal, intraventricular, spinal cord, or retinal collection of blood, not caused by trauma. • **Type 1c Symptomatic subarachnoid haemorrhage** Rapidly developing neurological signs or symptoms (focal or global) and/or headache caused by bleeding into the subarachnoid space, not caused by trauma. • **Type 1d Stroke not otherwise specified** An episode of acute focal neurological signs or symptoms and/or headache presumed to be caused by CNS ischemia or CNS haemorrhage, persisting ≥24 h or until death, but without sufficient evidence to be classified (i.e., no neuroimaging performed). • **Type 1e Symptomatic hypoxic-ischaemic injury** Non-focal (global) neurological signs or symptoms due to diffuse brain, spinal cord, or retinal cell death (confirmed by pathology or neuroimaging) in a nonvascular distribution, attributable to hypotension and/or hypoxia. **Type 2: Covert CNS injury – Acutely asymptomatic brain or spinal cord injury** • **Type 2a Covert infarction** Brain, spinal cord, or retinal cell death attributable to focal or multifocal ischemia, based on neuroimaging or pathological evidence of CNS infarction, without a history of acute neurological symptoms consistent with the lesion location. • **Subtype 2aH Covert infarction with haemorrhagic conversions** Covert CNS infarction includes haemorrhagic conversions. These should be subclassified as Class A or B when CNS infarction is the primary mechanism and neuroimaging or pathology confirms a haemorrhagic conversion.

	Class A: Petechial haemorrhage petechiae or confluent petechiae within the infarction or its margins, but without a space-occupying effect. Class B: Confluent haemorrhage: confluent haemorrhage originating from within the infarcted area with a space-occupying effect. • **Type 2b Covert haemorrhage** Neuroimaging or pathological evidence of CNS haemorrhage within the brain parenchyma, subarachnoid space, ventricular system, spinal cord, or retina on neuroimaging that is not caused by trauma, without a history of acute neurological symptoms consistent with the bleeding location. **Type 3: Neurological dysfunction – Acutely symptomatic without brain or spinal cord injury** • **Type 3a Transient ischemic attack (TIA)** Transient focal neurological signs or symptoms (lasting <24 h) presumed to be due to focal brain, spinal cord, or retinal ischemia, but without evidence of acute infarction by neuroimaging or pathology (or in the absence of imaging). • **Type 3b Delerium without CNS injury** Transient non-focal (global) neurological signs or symptoms (variable duration) without evidence of cell death by neuroimaging or pathology.
Hospitalisation	Hospitalisation will be defined by the Heart Failure Academic Research Consortium (HF-ARC) consensus document. Hospitalisation is defined as any hospital or virtual ward admission where length of stay is ≥24 hours, and will be classified as one of the following: 1. **Cardiovascular hospitalisation** Admission with a defined cardiovascular cause. This may include but are not limited to acute MI, arrhythmia or conduction system disturbance, cardiogenic shock, cardiovascular device failure, cardiovascular haemorrhage including tamponade, cardiovascular infection, cardiovascular procedure-related, HF (including both left and right ventricular dysfunction), peripheral arterial disease, thromboembolism, stroke, and sudden cardiac death. 2. **Heart failure hospitalisation** Admission with a primary diagnosis of heart failure. 3. **Non-cardiovascular hospitalisation** Admission with a defined non-cardiovascular cause. This may include but are not limited to gastrointestinal disorders including haemorrhage, hepatic failure, malignancies, mental deterioration not due to cerebrovascular disease, non-cardiovascular infections

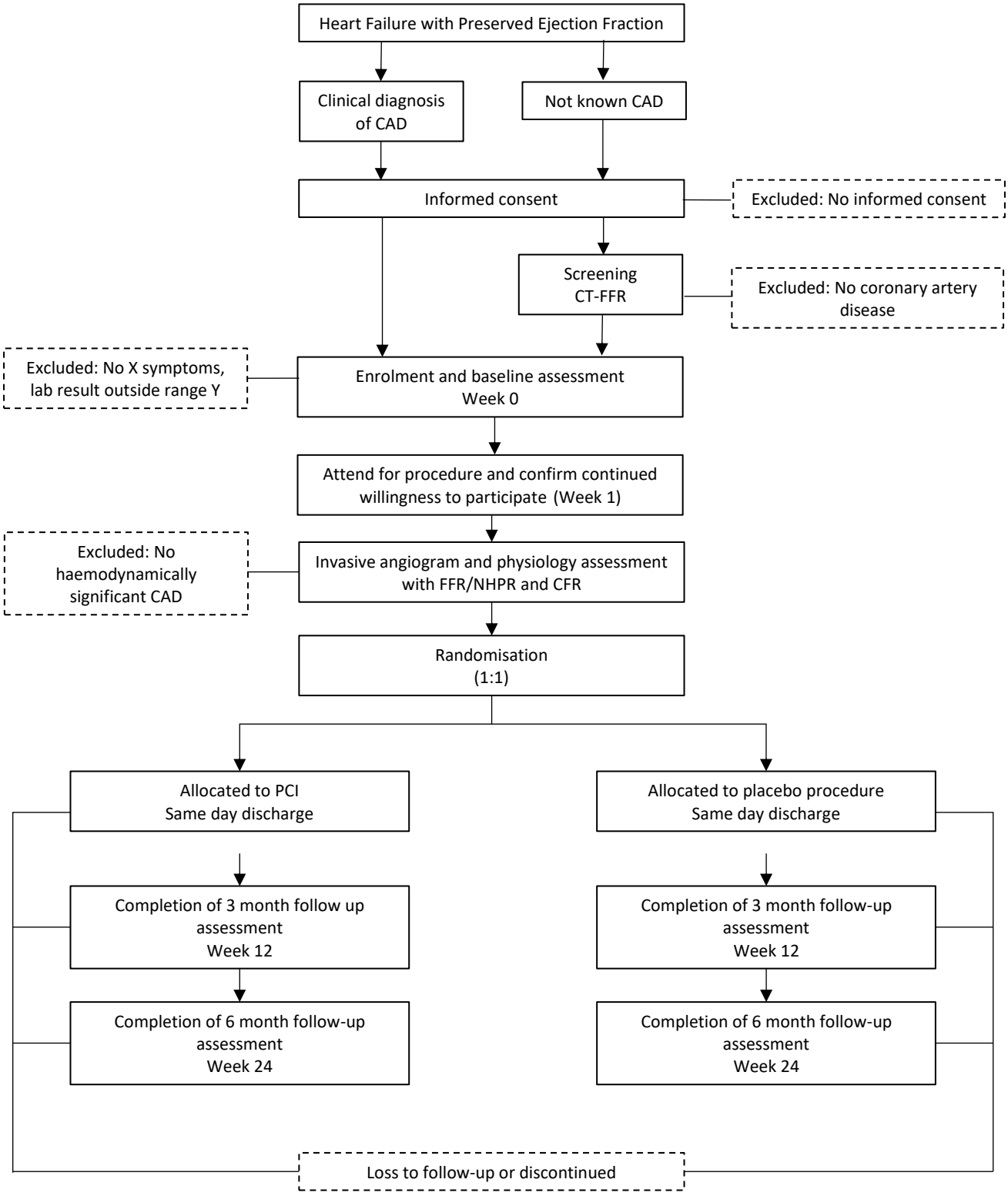
	and sepsis, renal failure, orthopaedic injuries, pulmonary disease, respiratory failure, attempted suicide, and trauma. **4. Hospitalisation due to unknown or undefined cause** Admission where there is identified primary cause or where the primary cause cannot be determined. **5. Elective hospitalisation** Admission for elective diagnostic or therapeutic procedures.
Atrial fibrillation	New-onset AF is defined as a new onset or a first detectable episode of AF, whether symptomatic or not, and will be classified as one of the following categories: 1. **Permanent or persistent** This includes persistent (lasts longer than 7 days), longstanding persistent (duration at least 12 months) or permanent (no further attempts to restore or maintain sinus rhythm). 2. **Paroxysmal** Episodes terminate within 7 days of onset.
Bleeding	Bleeding will be defined using the Bleeding Academic Research Consortium (BARC) 3 criteria as below: **Type 0:** No bleeding **Type 1** • Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional **Type 2** • Any overt, actionable sign of haemorrhage (e.g. more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation **Type 3** • Type 3a

	○ Overt bleeding plus haemoglobin drop of 3 to <5 g/L* (provided haemoglobin drop is related to bleed) ○ Any transfusion with overt bleeding • Type 3b ○ Overt bleeding plus haemoglobin drop ≥5 g/dL* (provided haemoglobin drop is related to bleed) ○ Cardiac tamponade ○ Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/haemorrhoid) ○ Bleeding requiring intravenous vasoactive agents • Type 3c ○ Intracranial haemorrhage (does not include microbleeds or haemorrhagic transformation, does include intraspinal) ○ Subcategories confirmed by autopsy or imaging or lumbar puncture ○ Intraocular bleed compromising vision **Type 4: CABG-related bleeding** • Perioperative intracranial bleeding within 48 hours • Reoperation after closure of sternotomy for the purpose of controlling bleeding • Transfusion of ≥5 units whole blood or packed red blood cells within a 48-hour period • Chest tube output ≥2L within a 24-hour period **Type 5: fatal bleeding** • Type 5a ○ Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious • Type 5b ○ Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation
Vascular complication	Vascular complications will be defined according to the Valve Academic Research Consortium 2 (VARC-2) criteria as below: **Major complication** • Aortic dissection or aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudo-aneurysm OR • Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, haematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure) *leading to* death, life-threatening or major (VARC) bleeding, visceral ischaemia, or neurologic impairment OR

	• Distal embolisation (non-cerebral) from a vascular source requiring surgery or resulting in death, amputation, limb or visceral ischaemia, or irreversible end-organ damage OR • Unplanned endovascular or surgical intervention resulting in death, major (VARC) bleeding, visceral ischaemia, or neurologic impairment OR • New ipsilateral lower extremity ischaemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram • Surgery for access site-related nerve injury OR • Permanent access site-related nerve injury **Minor complication** • Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, haematomas, percutaneous closure device failure) *not leading to* death, life-threatening or major (VARC) bleeding, visceral ischaemia, or neurological impairment OR • Distal embolisation treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage OR • Unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication OR • Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolisation, or stent-graft) **Percutaneous closure device failure** • Failure of a closure device to achieve haemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning)
Acute renal failure	Acute kidney injury is defined according to the Acute Kidney Injury Network (AKIN) criteria as any of the following: **1.** Increase in serum creatinine ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours; or **2.** Increase in serum creatinine ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or **3.** Urine volume <0.5 mL/kg/h for 6 hours.

Repeat revascularisation	Repeat revascularisation will be defined according to the ARC-2 criteria as one of the following classifications: **1. Target lesion** Defined as the treated segment including the 5-mm margin proximal and distal to the stent/scaffold **2. Target lesion revascularisation** Target lesion revascularisation is defined as a repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion. **3. Target vessel** The target vessel is defined as the entire major intervened coronary vessel including side branches. **4. Target vessel revascularisation** Target vessel revascularisation is defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel including the target lesion. **5. Target vessel non-target lesion revascularisation** Target vessel nontarget lesion revascularisation is defined as any repeat percutaneous intervention or surgical bypass of the target vessel for pre-existing disease, disease progression or other reasons unrelated to the target lesion as defined above.

5.3 Trial flowchart



5.4 Participating Trial Sites

Participants will be recruited at NHS hospital trusts within the United Kingdom based on site suitability as assessed by the study team. A current list of recruiting sites can be found on the trial website (http://www.lshtm.ac.uk/REPRIEVED). Participants will be identified in the course of their clinical care at these participating sites. Potential participants will also be able to self-refer for involvement in the trial.

It is anticipated that >100 patients per site per year will meet inclusion criteria and be considered for the study; it is recognised that there is underdiagnosis of both HFpEF and coronary artery disease, and attempts will be made at each site to increase detection of coronary artery disease in patients diagnosed with HFpEF and vice versa.

5.5 Participant inclusion criteria

1. A diagnosis of HFpEF, defined by the European Society of Cardiology (ESC) criteria[8], as:

    a. Symptoms of heart failure (New York Heart Association (NYHA) class II-IV) ***and***
    b. Left ventricular ejection fraction ≥ 50% ***and***
    c. NT-pro-BNP > 125 pg/ml in sinus rhythm or > 365 pg/ml in atrial fibrillation ***and***
    d. One or more of the following objective signs of left ventricular diastolic dysfunction:
        i. Invasively measured left ventricular end diastolic pressure ≥ 15 mmHg at rest or ≥ 25 mmHg on exercise (directly measured or estimated via pulmonary capillary wedge pressure)
        ii. Estimated pulmonary artery systolic pressure > 35mmHg or tricuspid regurgitation velocity > 2.8 m/s on echocardiography
        iii. Left atrial volume index > 34ml/m^2 in patient in sinus rhythm or left atrial volume index > 40ml/m^2 in atrial fibrillation
        iv. Relative left ventricular wall thickness > 0.42
        v. Left ventricular mass index ≥ 95 g/m^2 in females or ≥ 115 g/m^2 in males
        vi. Mitral E/E' ratio > 9

    plus

2. Significant coronary artery disease defined as:

    a. Functionally significant disease in at least one major proximal epicardial coronary artery (British Cardiovascular Intervention Society Jeopardy Score ≥ 4) which is suitable for PCI and has a fractional flow reserve (FFR) ≤0.80 measured with FFR, non-hyperaemic pressure ratio (NHPR) ≤ 0.89, or estimated with computational fluid dynamics during invasive angiography (e.g. VFR) or CT-FFR.

Assessments of left ventricular ejection fraction and coronary anatomy must have been performed within 12 months prior to enrolment.

5.6 Participant exclusion criteria

Exclusion criteria are:

1. Age <18 years
2. People without capacity to provide informed consent

3. PCI contraindicated or not feasible on coronary angiography or screening CTCA
4. Contraindication to clopidogrel/dual antiplatelet therapy
5. Recent acute myocardial infarction or coronary revascularisation (within 90 days)
6. Enrolment in another interventional study which may affect study outcomes
7. Severe chronic obstructive pulmonary disease (GOLD stage ≥ 3)
8. Haemoglobin ≤80 g/L
9. Other cardiac diagnosis as a cause for HFpEF (hypertrophic cardiomyopathy, untreated severe left sided valvular disease, cardiac amyloidosis)

Eligibility will be determined by the investigators at the recruiting site.

5.6.1 Angina

Angina is not an exclusion criterion, as patients with HFpEF may experience ischaemia as breathlessness, angina, fatigue or effort intolerance, or a combination of these symptoms, all of which may impair quality of life and all of which may be modified by PCI. There is also no specific evidence of the effectiveness of PCI at relieving angina in HFpEF, where the mechanisms driving symptoms differ substantially from patients without heart failure. Finally, specific clinician attributed terms often fail to adequately capture the complexity of symptoms and lived experience of patients with HFpEF.

However, where angina is the sole symptom, participants would not be eligible for inclusion as they would not meet the inclusion criteria for Symptoms of Heart Failure, as angina is not a direct symptom of the condition.

6 STUDY PROCEDURES

6.1 Screening

6.1.1 Patient population for screening

All patients who have a potential diagnosis of HFpEF and coronary artery disease should be screened for eligibility.

6.1.2 Initial approach to patients

The initial approach to potential trial participants must be performed by members of the direct care team. A member of the direct care team must obtain verbal agreement from the patient before the research team contacts the patient and accesses their data for screening.

6.1.3 Sources of potential participants

It is recommended to screen from the following sources:

- Patients referred to the Heart Team for consideration of revascularisation or heart failure optimisation
- Patients seen in outpatient clinics for the assessment or management of coronary artery disease
- Patients seen in outpatient clinics for the assessment or management of HFpEF
- Patients admitted to hospital who are referred for invasive or non-invasive assessment for coronary artery disease
- Patients admitted to hospital with decompensated heart failure with a new or prior diagnosis of HFpEF

6.1.4 Screening CT-FFR

Consenting potential participants who meet the diagnostic criteria for HFpEF but have not recently been investigated for coronary artery disease will undergo screening CT coronary angiography with FFR assessment (CT-FFR) to determine the presence of coronary artery disease. Patients confirmed to have significant coronary artery disease (FFR≤0.80 in at least one main epicardial vessel) will be enrolled in the randomised trial. All potential participants attending this appointment and those enrolled in the trial will receive travel expenses and a £10 gift voucher as a token of appreciation for their participation. Feasibility of PCI will be assessed prior to randomisation from invasive angiography or novel techniques for PCI planning from CTCA to ensure the maximal number of enrolled patients are randomised[47].

6.1.5 Screening Logs

Full detailed screening logs of all patients screened for inclusion in the trial will be completed at sites, and will be requested periodically by the CTU. It is anticipated that during the pilot phase screening logs will be requested monthly, and afterwards will be requested every three months.

Only patients who complete the screening process (i.e. randomised, declined, met an exclusion criterion) are required to be entered.

The screening log will include anonymous demographic information in order to monitor representativeness of the patient population. Sex, age, gender and ethnicity will be collected as well as refusals due to language.

6.1.6 Responsibility for completing and reporting the screening log

The delegation log will record the individuals responsible for the completion and reporting of screening logs.

6.2 Clinically referred participants

Potential participants will be identified from heart failure clinics, new referrals to the heart failure service, inpatient hospital admissions and referrals for invasive or CT coronary angiography. Site-specific trial teams will include dedicated heart failure specialists with links to local primary care and community heart failure teams to advertise the trial and encourage referral for screening and participation.

Potential participants will be approached by a member of their clinical team and given a basic explanation of the study. They will then be asked if they would like to speak to a member of the research team. All centres in the NIHR-funded UK HFpEF registry (NIHR301338) will be approached to identify potential participants and refer to the trial sites for participation.

The review of eligibility and initial approach to the patient must be made by a member of their direct care team. It is then dependent on the patient to contact the relevant trial site to undergo informed consent and any further study procedures.

6.2.1 Self-referred participants

Trial involvement will be advertised via posters, leaflets, the study website, NIHR Be Part of Research and community cardiac groups from which potential participants can self-refer. Participants will be

invited to contact a member of research staff at the trial site of their choosing via telephone, post or email. Consent will be sought to request clinical data to confirm trial eligibility, including echocardiographic features of HFpEF. Clinical research network-funded research nurses will retrieve clinical data from other NHS organisations to confirm eligibility and review this data with the PI.

6.3 Consent

A member of the research team will contact all eligible patients to explain the study in detail and provide a participant information sheet (PIS). The PIS will be available in a number of common non-English languages. Participant information videos will also be made available.

The research team member will answer any question from the patient, as well as their family or friends if the patient requests their support in coming to a decision.

At least 24 hours will be allowed for the patient to discuss with family and/or friends and consider their decision to participate in the study.

Consent may be taken electronically or on a paper form, depending on the patient's preference.

All participants must provide informed consent prior to any trial activities taking place.

6.3.1.1 Patients with impaired capacity

Consideration has been given to patients with impaired capacity (Appendix 1). Whilst the ambition is always to provide maximally inclusive recruitment, given the complexity of the trial intervention (an invasive procedure under conscious sedation) it would not be appropriate to enrol participants who were not able to consent.

6.4 Randomisation

Randomisation will be performed during the coronary angiography procedure, within the catheterisation laboratory, via a validated online web-based system (Sealed Envelope).

The randomised treatment allocation will be reported on the Sealed Envelope system and via e-mail to unblinded members of the research team. Treatment allocation will be concealed from all blinded team members.

The unblinded trial team will be notified of new randomisations via email.

6.4.1 Stratification

Treatment allocation will be stratified by site using randomly permuted blocks of varying size, with 1 to 1 allocation of participants between the PCI and placebo procedure arms.

6.4.2 Participant identification log

A list of all patients enrolled into the trial will be maintained by each recruiting site, containing participant identification numbers, full names, dates of birth and dates of enrolment in the trial, which could be used for unambiguous identification of each participant if required.

6.4.3 GP notification and medical records

The patient's enrolment in the trial, without treatment allocation, must be recorded in the patient's medical record. The participant's general practitioner will also be notified, unless the participant specifically asks for them not to be informed.

6.5 Intervention

6.5.1 Arranging the trial intervention

The trial intervention will be performed during a day-case hospital admission. Potential dates for the procedure will be discussed with participants in order to find a suitable date for them, including fit notes for employers and funding for relief carers where the participant is a care provider.

6.5.2 On the day of the intervention

On the day of the trial intervention, ongoing consent for the study will be confirmed and clinical consent for the invasive procedure obtained by the unblinded PI. Procedures will be performed by either the unblinded PI or an unblinded sub-investigator. Participants will receive pre-treatment with antiplatelet medication (aspirin 300mg and clopidogrel 300-600mg per local protocol). The KCCQ will be repeated to measure early changes in quality of life with medical optimisation.

Coronary angiography will be performed using standard procedure, preferentially via radial access. Following coronary angiography, a detailed physiological assessment will be performed in all target coronary arteries, including measures of fractional flow reserve (FFR), coronary flow reserve (CFR) and microvascular function. Left ventricular end diastolic pressure will be measured at rest and during handgrip exercise.

Before randomisation, patients will receive headphones playing music to ensure auditory isolation, and patients will be sedated using incremental doses of benzodiazepines and opiates to a deep level of conscious sedation.

6.5.3 Timing of randomisation

During the coronary angiography procedure, the participant will be randomised 1:1 to either PCI or placebo procedure using the online randomisation system.

6.5.4 Delivering the randomised treatment allocation

6.5.4.1 Participants randomised to PCI

In patients assigned to PCI, angioplasty and stenting will be attempted to all significant coronary stenoses as determined by the CT-FFR or FFR measurements. Contemporary best practice including the use of intracoronary imaging is mandated. The default approach will be to implant drug eluting stents, but drug coated balloon angioplasty is permitted in selected cases in accordance with the current evidence base and guidelines. Operators will achieve as much revascularisation as can safely be delivered in a timeframe which maintains blinding; if incomplete revascularisation is necessary, operators will target treatment to the most haemodynamically significant lesions subtending the largest territories. Staged procedures are not permitted, as they would invalidate blinding. Target

lesion success will be defined by a residual stenosis <10% on angiography with Thrombolysis In Myocardial Infarction (TIMI) 3 flow.

6.5.4.2 Participants randomised to placebo procedure

In the placebo procedure group, participants will undergo a placebo stent procedure that involves placement of a catheter but does not involve deployment of an actual stent. Over a period of 30 minutes, movements of the image intensifier, screen display and personnel will simulate a PCI procedure.

6.5.5 Post-intervention

At the end of the procedure the participant will be transferred to the recovery unit and observed until the effects of sedation are fully reversed and the patient is back to their baseline condition.

6.5.6 Prescription of anticoagulants

Participants who are not receiving an oral anticoagulant (OAC) will be prescribed long-term aspirin 75mg once daily from the day following the procedure. Participants who are receiving an OAC will be prescribed aspirin 75mg once daily for one week from the day following the procedure.

6.6 Prescription of clopidogrel or placebo clopidogrel

Participants randomised to PCI will receive clopidogrel at a dose of 75mg OD, to be taken for up to 6 months following PCI. Participants randomised to the placebo procedure will receive matching placebo clopidogrel tablets, to be taken for up to 6 months following PCI. The duration of clopidogrel or placebo clopidogrel will be determined by individual bleeding risk.

Clopidogrel and matching placebo clopidogrel tablets will be manufactured by Guy's and St Thomas' Pharmacy Manufacturing Unit (PMU) located on the 13th floor Tower Wing, Guy's Hospital, Great Maze Pond, London SE1 9RT.

6.7 Medical therapy

All participants will receive guideline directed medical therapy for HFpEF. All participants will be prescribed a SGLT-2i unless there are specific contraindications or the participant declines treatment. Participants who are obese will be offered treatment with a GLP-1 agonist. Loop diuretics will be prescribed as dictated by fluid status. The protocol for medical therapy will be updated as further agents are adopted into clinical guidelines (e.g. finenerone). This medical therapy will be optimised at the time of enrolment and will not be adjusted by unblinded investigators after the point of randomisation.

In line with current guidelines, every effort will be made to address all relevant cardiac and non-cardiac comorbidities. Given the diverse nature of comorbidity and randomised design of REPRIEVED, specific guidelines will not be provided for the treatment of these comorbidities. Data on the prescription of relevant cardiovascular medications will be collected via the electronic case report form (eCRF).

As detailed above, no medications are currently licensed specifically for the management of ischaemia or ischaemic symptoms in patients with HFpEF. There are also concerns that many anti-ischaemic therapies may worsen symptoms or outcomes in HFpEF. The use of beta blockers has been associated with an increase in heart failure hospitalisation in observational studies. Long-acting oral nitrates

reduced patient activity and did not improve quality of life in patients with HFpEF in the NEAT-HFpEF trial. International guidelines recommend against the prescription of nondihydropyridine calcium channel blockers due to concerns about worsening heart failure outcomes. Consequently, it is not recommended that patients in REPRIEVED are prescribed these agents for their anti-ischaemic effects. Where patients have already been initiated on these medications, their use will be recorded but not adjusted by the trial team.

6.8 Blinding

Effective blinding is necessary to ensure that any observed difference between groups in quality of life is not related to placebo effect.

6.8.1 Blinded and unblinded staff at trial sites

Trial procedures will be distributed between blinded and unblinded staff at participating sites detailed in the table below. All participating sites will have an unblinded PI and a blinded PI.

Unblinded procedures	**Blinded procedures**
Jeopardy Score (eligibility)	Baseline data part 1
Eligibility criteria (inclusion and exclusion)	Baseline data part 2
Participant registration form (eCRF only)	Medical History part 1
Informed Consent Form	Medical History part 2
Randomisation	Baseline ECG and Echo
Procedure visit part 1	Baseline bloods
Procedure visit part 2	Cardiac medication at baseline
PCI report	Baseline KCCQ
PCI details	Cardiac medication pre-procedure
PCI Summary	Pre-procedure KCCQ
Post-PCI coronary anatomy	Post procedure ECG and Troponin
Post-PCI Jeopardy Score	Discharge
	3 month follow up
	Cardiac medication at 3 months
	3-month KCCQ
	6 month follow up
	Cardiac medication at 6 months
	6-month KCCQ

6.8.2 Randomisation notification emails

Randomisation notifications containing treatment allocation will only be sent to unblinded staff at each site.

Randomisation notifications not containing treatment allocation will be sent to blinded staff at each site.

6.8.3 Blinding of the procedure

Blinding will be achieved using the protocol developed and validated for placebo PCI procedures in the ORBITA and ORBITA-2 trials[39,48]. Incremental doses of benzodiazepines and opiates will be administered for sedation with auditory isolation via headphones.

A generic discharge letter will be issued stating that the patient is enrolled in the REPRIEVED double-blind trial. A generic procedure report will be kept in the patient notes; after documenting details of the diagnostic angiogram and physiology, the report should state "The patient then underwent randomisation in the REPRIEVED trial. Details of the randomised allocation and any procedure performed were recorded in the trial eCRF. In case of a need for emergency unblinding, please contact 020 7927 2885. For other queries please contact the local Principal Investigator, local research team or CTU at REPRIEVED@lshtm.ac.uk".

After the procedure, the participant will receive either clopidogrel or placebo clopidogrel, depending on treatment assignment. The unblinded PI and catheter lab team will have no further input into the care or follow up of the patient, outside of the procedures for emergency unblinding outlined below. A procedure report with the details of treatment completed will be documented in the eCRF only. At the end of the 6-month follow-up and after the participant has been unblinded, a copy of the procedure report will be stored in the patient notes.

CTU staff will be blinded to treatment assignment apart from agreed staff members such as the trial statistician and data manager. Criteria and procedures for emergency unblinding are outlined below and specified in the relevant working practice document (WPD). Unblinding will be managed via the Sealed Envelope eCRF system.

The efficacy of blinding for participants will be tested and reported using the blinding index[46] at discharge from the randomisation procedure.

6.8.4 Emergency unblinding

If a treating clinician believes they need to be unblinded to the patient's treatment arm they will contact the 24-hour unblinding telephone service to discuss the reasons for the unblinding request.

If, after discussing with the trial team, the patient's treating clinician's final decision is that the participant's safety will be compromised if they remain blinded to the treatment, then unblinding will take place. The authorised person to perform unblinding will use the eCRF system to request unblinding and will need to enter the reason for unblinding. The treating clinician will be notified of the participant's allocated treatment.

The unblinding will be recorded within the eCRF system, and an unblinding report will be produced from this for reporting unblinding to the Sponsor and the Data Monitoring Committee (DMC). All unblinding will be mentioned in the final trial report. Full unblinding procedures will be detailed in the relevant WPD.

6.9 Internal pilot study

The trial will include a 12-month internal pilot phase to confirm the feasibility of REPRIEVED. Perceived major risks to recruitment are; whether the expected proportion of screened patients have significant coronary artery disease (CAD), whether participants will consent to enrolment and whether there is a risk of emergency unblinding;

	Red	Amber	Green
Number of participants recruited	<30	30-50	>50
Blinding Index	≥0.30	≤0.30	≤0.20
Proportion of screened with significant CAD (%)	≤30	30-40	≥40
Patient consent from eligible patients (%)	<30	30-50	>50
Emergency unblinding (%)	> 10	5-10	<5

Table 3 – Criteria for progression following the 12-month internal pilot study.

During the internal pilot detailed screening data will be collected to determine whether there are inclusion or exclusion criteria which are impacting recruitment. Achievement of the green criteria will lead to direct continuation of the trial unchanged. Meeting several amber criteria will lead to discussions between the Trial Management Group, Trial Steering Committee and funder to determine what protocol amendments are needed. Meeting several red criteria will lead to discussions as to whether the trial will continue and, if so, what amendments are needed.

6.10 Schedule of assessments for each visit

6.10.1 Baseline visit

Eligible participants with HFpEF and significant coronary artery disease will attend one-stop outpatient HFpEF clinic and study visit. All investigations will be co-ordinated by the trial team to occur within this visit unless the person wishes otherwise in which case alternative arrangements will be made. Their visit will be supported by the trial research nurse, who will co-ordinate appointments and guide them through the procedures. During this visit the participant will have a clinical review by the unblinded PI, who will optimise their treatment for HFpEF and either manage or refer for optimal management of comorbidities, as per current treatment guidelines.

The participant will undergo the following baseline assessments:

- Measurement of vital signs
  - Heart rate
  - Blood pressure
  - Arterial oxygen saturations (pulse oximetry)
  - Weight
  - Height
- Medical history
  - Past medical history
  - Medication history
  - Social history
- Health status
  - Kansas City Cardiomyopathy Questionnaire
  - New York Heart Association functional class
  - Canadian Cardiac Society angina class
- Blood tests for cardiac biomarkers and pre-PCI testing
  - Full blood count
  - Full lipid profile
  - Renal function

  - Troponin
  - NT-pro-BNP
- 12-lead ECG
- Three-dimensional transthoracic echocardiogram

6.10.2 PCI procedure visit

The following assessments will be recorded in the eCRF during the PCI procedure visit

- Pre-PCI health status
  - Kansas City Cardiomyopathy Questionnaire
  - Medication history
- Pre-PCI intracoronary physiology (all target lesions)
  - Fractional flow reserve
  - Index of microvascular resistance/myocardial resistance reserve
- Left ventricular end diastolic pressure
  - At rest
  - During handgrip exercise
- Group allocation
- PCI procedure details (in PCI group)
  - As per standard NICOR dataset
- Coronary anatomy
  - BCIS Jeopardy Score
  - SYNTAX Score
- Post-PCI intracoronary physiology (all target lesions)
  - Fractional flow reserve
  - Index of microvascular resistance/myocardial resistance reserve
- Intracoronary imaging and angiography data to be anonymised and retained for core laboratory analysis
- 12-lead ECG
- Post-PCI cardiac biomarkers
  - Troponin

6.10.3 Discharge

- Procedural events and complications
- Blinding questionnaire
- Adverse events/serious adverse events

6.11 Follow-up Procedures

All follow-up procedures will be supervised by the blinded PI and research nurse.

***Three months post-randomisation*:** Participants will have the option of either attending in person or via a telephone appointment depending on their preference.

The following assessments will be recorded in the trial eCRF:

- Health status
    - Kansas City Cardiomyopathy Questionnaire
    - New York Heart Association functional class
    - Canadian Cardiovascular Society angina status
- ICHOM standard outcome set for heart failure
    - Mortality
    - Medication (including changes to prescribed clopidogrel/placebo clopidogrel)
    - Medication side effects
    - Financial burden
    - Complications of treatment
    - Number of hospital appointments
    - Number of hospital readmissions
    - Length of stay
- Adverse events/serious adverse events

***Six months post-randomisation (end of trial)*:** Participants will attend for an in-person appointment where all baseline study assessments will be repeated. Research follow-up will conclude after all six-month assessments have been completed at which point participants will be informed of their treatment assignment. The PI will discuss further treatment, including offering PCI to participants in the placebo procedure group. All participants will be offered ongoing clinical follow-up.

The following assessments will be recorded in the trial eCRF:

- Health status
    - Kansas City Cardiomyopathy Questionnaire
    - New York Heart Association functional class
    - Canadian Cardiovascular Society angina status
- ICHOM standard outcome set for heart failure
    - Mortality
    - Medication (including changes to prescribed clopidogrel/placebo clopidogrel)
    - Medication side effects
    - Financial burden
    - Complications of treatment
    - Number of hospital appointments
    - Number of hospital readmissions
    - Length of stay
- 12-lead ECG
- Biomarkers for heart failure status
    - Troponin
    - NT-pro-BNP
- Transthoracic echocardiogram
- Adverse events/serious adverse event

6.12 Trial schedule

	STUDY PERIOD					
					Follow-up	
TIMEPOINT	**Screening/ Consent**	**Baseline Visit**	**Procedural Visit**	***Discharge***	***3 months post-randomisation***	***6 months post-randomisation***
Eligibility screen	X					
Informed consent	X					
Screening CT-FFR (if required)	X					
Randomisation/allocation			X			
INTERVENTIONS:						
Angiogram and Physiology			X			
PCI Procedure			X			
Placebo Procedure			X			
ASSESSMENTS:						
KCCQ		X	X		X	X
Medical history/NYHA/CCS		X			X	X
Full blood count and U&E		X				
Troponin[#]		X	X			X
NT-pro-BNP		X				X
ECG		X	X			X
Echocardiogram		X				X
Angiography images			X			
Physiology data			X			
Procedural events and complications				X		
Blinding questionnaire				X		
NSAE/SAE				X	X	X

[#]*Post-procedural troponins should be collected at 6 hours, or immediately prior to discharge if before 6 hours*

6.13 Radiology Assessments

After consent but before randomisation, patients who have not been investigated for coronary artery disease will have a screening CT coronary angiogram to confirm their eligibility for the study. We estimate that half of these patients will not have coronary artery disease, they will exit the study and not be randomised. The other half will have coronary disease and will then be randomised.

Of the randomised population, all will have a coronary angiogram, and half will have a percutaneous coronary intervention procedure. This includes patients who have had a prior angiogram or have had a CT coronary angiogram. All procedures will be performed as per clinical standards of care and no new scanning sequences will be used.

The study does not involve radioactive substances or radiotherapy and will be reviewed via the HRA-managed radiation assurance route.

7 LABORATORIES

7.1 Central/Local Laboratories

Blood samples will be collected using standard techniques and analysed in NHS hospital laboratories for full blood count, renal function, troponin and NT-pro-BNP. No tissues will be collected.

7.2 Sample Collection

A total of 5ml of blood will be collected for full blood counts and 5ml for renal function, troponin and NT-pro-BNP. These samples will be taken for research purposes, except where they are measured clinically in which case tests will not be repeated. No samples will be stored. Results will be transcribed into the eCRF from clinical systems. Samples will be processed, stored and disposed in accordance with the information supplied in the participant consent forms and information sheets, as well as all applicable legal and regulatory requirements, including the Human Tissue Act 2004 and any amendments thereafter.

7.3 Sample Analysis Procedures

Samples will be analysed using standard analysis techniques used for clinical samples in NHS laboratories. All tests are CE marked, considered standard for diagnostic purposes and used for their intended purposes.

8 END OF STUDY DEFINITION

The study will end when the final follow-up visit has been completed, all data entered, queries resolved, and the database locked.

9 ASSESSMENT OF SAFETY

9.1 Definition

Unexpected events that have not been defined as an outcome (see section 5.2) should be reported as either a serious adverse event (SAE) or non-serious adverse event (NSAE) depending on their severity.

9.2 Unexpected Serious Adverse Events

A SAE is defined as any untoward medical occurrence(s) that is life threatening, results in death, in-patient hospitalisation or prolongation of existing hospitalisation, persistent or significant disability/incapacity congenital anomaly or birth defect. Unexpected SAEs should be reported to the Clinical Trials Unit (CTU) within 7 days of the site becoming aware of the event. The report should include an assessment of causality by the Principal Investigator at each site. The Chief Investigator will be responsible for the prompt notification of findings that could adversely affect the health of patients or impact on the conduct of the trial.

9.3 Unexpected Non-Serious Adverse Events

Unexpected NSAEs should be evaluated by the Principal Investigator. This should include an assessment of causality and intensity and reports made within 14 days. The CTU will keep detailed records of all unexpected adverse events reported. Reports will be reviewed by the Chief Investigator to consider intensity, causality and expectedness.

9.4 Reporting Unexpected Adverse Events

Investigators will make their reports of all unexpected adverse events, whether serious or not, to the CTU at the London School of Hygiene & Tropical Medicine.

9.4.1 Assessment of Intensity

Mild: The patient is aware of the event or symptom, but the event or symptom is easily tolerated.

Moderate: The patient experiences sufficient discomfort to interfere with or reduce their usual level of activity.

Severe: Significant impairment of functioning; the patient is unable to carry out usual activities and/or the patient's life is at risk from the event.

9.4.2 Assessment of Causality

Probable: A causal relationship is clinically / biologically highly plausible and there is a plausible time sequence between onset of the adverse event and the PCI procedure.

Possible: A causal relationship is clinically / biologically plausible and there is a plausible time sequence between onset of the adverse event and the PCI procedure.

Unlikely: A causal relationship is improbable, and another documented cause of the adverse event is most plausible.

Unrelated: A causal relationship can definitely be excluded and another documented cause of the adverse event is most plausible.

9.5 Ethics Safety Reporting

The Sponsor, the Research Ethics Committee (REC) and the Data Monitoring Committee will be notified by the CTU when reported SAEs have been classified by the Chief Investigator as **both** unexpected and given a causality classification of either probable or possible.

Reports of **related** and **unexpected** SAEs will be submitted to the main REC within 15 days of the Chief Investigator becoming aware of the event, using the NHS HRA (non-CTIMP) template. The form should be completed in typescript and signed by the Chief Investigator. The main REC will acknowledge receipt of safety reports within 30 days.

A copy of the SAE notification and acknowledgement receipt should be sent to gstt.RandD@nhs.net and stored in the TMF/Site file. Appendices 3 and 4 contain a flowchart and further details of the process for reporting of serious and non-serious adverse events.

10 TRIAL ORGANISATION

10.1 Trial Management Group

The trial will be managed by the accredited London School of Hygiene & Tropical Medicine CTU (UK Clinical Research Collaboration number 44). The Trial Management Group (TMG) comprising the Chief Investigator, patient Co-Applicant, trial manager and senior manager will meet at least once per month and more frequently as needed to review trial progress, recruitment and manage any issues arising.

10.2 Trial Steering Committee

The trial will be overseen by a Trial Steering Committee (TSC). The committee will comprise an independent chair and five other independent members including two representatives of patients and the public, the Chief Investigator and Trial Statistician. TSC meetings will be open to members of the public and interested parties as observers. The committee will meet prior to recruitment of the first participant and then at a frequency decided by the committee, with no more than one year permitted to elapse between meetings. The TSC will oversee the conduct of the trial, including decisions about stopping or continuing the trial, in co-ordination with the Sponsor and funder. The activities of the TSC will be governed by a charter which will be signed by all members and circulated prior to recruitment of the first participant.

10.3 Patient Advisory Committee

A Patient Advisory Committee (PAC) will be set up for the trial and consist of at least six members with lived experience of heart failure, coronary artery disease and/or involvement in interventional cardiology trials. The group will meet approximately every three months to review progress and trial matters. They will assist in the drafting and reviewing of all participant materials. Two members of the PAC will also sit as independent members of the TSC with oversight of the whole study. Activities of the PAC will be guided by a terms of reference.

10.4 Data Monitoring Committee

To ensure the safe conduct of the trial and respond to any safety concerns arising, a Data Monitoring Committee (DMC) will be convened. The DMC will comprise an independent chair, independent statistician and two further independent members who are practicing clinicians. The committee will meet prior to recruitment of the first patient and then at a frequency decided by the committee, with no more than one year permitted to elapse between meetings. A full report of the trial progress will be provided to the DMC by the unblinded statistician prior to each meeting. DMC meetings will involve an open session attended by members of the TMG, followed by a closed session for discussion of unblinded data. The DMC chair will provide a report to the TSC chair after the meeting has concluded. The activities of the DMC will be governed by a charter which will be signed by all members and circulated prior to recruitment of the first participant.

11 ETHICS & HRA APPROVALS

The study requires regulatory approval from the following bodies (NHS REC London - Riverside Favourable Opinion and HRA Approval, REF 25/LO/0277).

11.1 Required conditions before recruitment can start at trial sites

Before any site can enrol patients into the study, the Chief Investigator (CI)/Principal Investigator or designee will ensure that the appropriate regulatory approvals have been issued, and NHS Confirmations of Capacity and Capability and Sponsor green lights are in place.

11.2 Amendments

For any amendments to the study, the CI or designee, in agreement with the Sponsor, will submit information to the appropriate body in order for them to issue approval for the amendment. The CI or designee will work with sites (R&D departments as well as the study delivery team) to confirm ongoing Capacity and Capability for the study.

11.3 Correspondence

All correspondence with the Sponsor, REC and HRA will be retained. The CI will notify the Sponsor and REC of the end of the study.

12 COMPLIANCE AND WITHDRAWAL

12.1 Participant compliance

Participants will be encouraged to complete all study procedures and assessments at the appropriate timepoints or at the closest practicable timepoint. Where a participant has not attended a follow-up appointment, site teams will make every effort to contact them using all available telephone numbers and email. If a participant is uncontactable after these initial efforts, research team members will send a letter to the participant requesting them to contact the team. The clinical team and patient's general practitioner will also be contacted to ascertain if there is a reason they have not been able to contact the participant and attempt to facilitate contact.

If participants are unable to be contacted despite persistent efforts from the research team, they will be considered lost to follow-up. Local teams will use patient health records and searches of national registries will be used to confirm vital status. Completeness of follow-up for the primary endpoint will be determined from the trial eCRF and reported. As the trial allocation is to an initial intervention, details of ongoing compliance with treatment are not relevant and will not be recorded.

12.2 Withdrawal / dropout of participants

Participants are free to withdraw from the trial at any time and without having to provide a reason. Their clinical care will not be disadvantaged by their withdrawal from the study.

At the time of withdrawal, participants will be offered three options for withdrawal:

1. Participants may withdraw from active follow-up and further communication but allow the trial team to continue to access their medical records and any relevant hospital data that are recorded as part of routine standard of care; i.e., blood tests, echocardiograms and available measures of health status (e.g. NYHA class and CCS class).
2. Participants can withdraw from the study but permit data and samples obtained up until the point of withdrawal to be retained for use in the study analysis. No further data or samples would be collected after withdrawal.
3. Participants can withdraw completely from the study and withdraw the data and samples collected up until the point of withdrawal. The data and samples already collected would not be used in the final study analysis. (Any limits to this type of withdrawal where, for example analysis of their data or samples has already been integrated into interim results, should be explained in the participant information sheet).

In situations where the participant withdraws but does not specifically indicate a preference, data and samples obtained up until the point of withdrawal will be retained for use in the study analysis. No further data or samples would be collected.

12.2.1 Recording participant withdrawal in the eCRF

Details of the participant withdrawal will be completed by the CTU team via the Participant Withdrawal form in the eCRF, including reasons for withdrawal where given. Immediately prior to withdrawal, participants will be asked if they consent to completing a final follow-up for completion of the primary outcome data.

12.2.2 Withdrawal due to an adverse event

If the participant is withdrawn due to an adverse event, the PI will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

12.3 Protocol Compliance

Every effort should be made to adhere to the protocol. A protocol deviation is usually an unintended departure from the expected conduct of the study protocol/WPDs, which does not need to be reported to the Sponsor. The CI will monitor protocol deviations and list them in a deviation log and include a file note in the TMF/sites file where applicable.

Significant deviations to the protocol or deviations which are found to frequently recur are not acceptable and need to be assessed by the CI to see if an amendment to the protocol is required. These will require reporting to the Sponsor and action taken through Corrective and Preventative Actions (CAPA).

A 'serious breach' is defined as a breach likely to effect to a significant degree:

- The safety or physical or mental integrity of the participants of the trial;
- The scientific value of the trial.

The CI and Sponsor must be notified immediately of a serious breach. The breach must be reported to the REC with the Sponsor in copy within **7 calendar days** of the breach being confirmed as serious.

13 TRIAL DATA

13.1 Data to be collected

Data will be collected by members of the site research team with delegated responsibility from the PI. Data will be collected as reported by patients including the use of questionnaires, from patient notes and electronic medical records, and medical images collected during clinical care or the research procedures. Data will be collected at baseline, during the admission for the PCI procedure, at subsequent follow-up visits and at the time the research team are made aware of serious or non-serious adverse events.

Data fields to be collected will follow the list of schedule of assessments detailed in section 6.10. The primary outcome will be collected via the Kansas City Cardiomyopathy Questionnaire, a validated tool for assessing health status in patients with heart failure.

13.2 Electronic Case Report Form (eCRF)

Data will be collected via an Electronic Case Report Form (eCRF), managed by Sealed Envelope Ltd. and hosted by Rackspace. In accordance with GCP, the electronic data entry system will be validated and Working Procedure Documents covering its use will be drafted and maintained. All data entered into the eCRF will be pseudonymised, and identifiable data will not leave NHS trusts.

13.2.1 eCRF access at site level

The eCRF will be accessed by users through a normal web browser. Each user will have their own individual account and secure password. Only personnel authorised by the LSHTM CTU will be granted access to the eCRF. Site staff will only be able to access data for participants recruited at their site. Direct access to the eCRF will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections. eCRFs should be completed within 2 weeks of each trial milestone where possible. Principal Investigators at each site have overall responsibility for the accuracy, completeness and legibility of the data entered onto the eCRF and associated reports.

13.3 Data security

Trial participants will be identified by a unique trial specific number and/or code in any database. The name and any other identifying detail will not be included in any trial data electronic file. Patient data will be kept confidential and managed in accordance with the Data Protection Act (2018), NHS Caldecott principles, the Research Governance Framework for Health and Social Care, and the conditions of Research Ethics Committee Approval. Personal patient data will be archived at the site after the end of trial.

13.4 Data management

The trial data manager will be responsible for checking the quality and validity of data and will raise queries with sites where statistical or qualitative monitoring identifies potential errors.

13.5 Personal Data Breaches

GDPR broadly defines personal data breaches as a security incident that has affected the confidentiality, integrity or availability of personal data. In short, there will be a personal data breach whenever any personal data are lost, destroyed, corrupted or disclosed; if someone accesses the data or passes it on without proper authorisation; or if the data are made unavailable, for example, when it has been encrypted by ransomware, or accidentally lost or destroyed.

Personal data breaches must be immediately reported to the Sponsor/data controllers and to the Data Protection Officer/IG Department of the site that incurred the breach. The following information must be provided to assess the full risk/impact of the breach: full details as to the nature of the breach, an indication as to the volume of material involved, and the sensitivity of the breach (and any timeframes that apply), steps that have been taken to mitigate the risk (trying to retrieve the data asking third parties to delete information that was sent to them in error).

Sites will additionally follow their Trust incident reporting mechanisms such as Datix and will document this within their TMF/ISFs in the form of a file note provided by the Sponsor with corrective and preventative measures addressed.

The Sponsor/data controller will determine whether the breach meets the definition of a serious breach and warrants reporting to the regulators including the ICO https://ico.org.uk/for-organisations/report-a-breach/personal-data-breach-assessment.

13.6 Data sharing

Consent will be sought from participants for data sharing via the participant consent form at the time of consenting to the trial. All data sharing will be in accordance with this consent, the Data Protection Act 2018 and UK General Data Protection Regulation (GDPR). All identifiable data will be held at NHS sites and will not be shared with anyone else or outside of the UK.

At the end of the project, the pseudonymised data will be transferred from LSHTM to King's College London (KCL) for further analysis and long-term storage in the KCL Trusted Research Environment. This transfer will be in the form of a locked excel document via encrypted and secure data transfer. The data will be stored at KCL for a period of 20 years. The flow of data leaving NHS Trusts can be found in Appendix 2.

A pseudonymised dataset will be made publicly available 1 year after the end of the study in accordance with best practices in research data sharing. This database will have all identifiers removed (including dates and study numbers) but remains pseudonymised due to the size of the sample and possibility of unique combinations of characteristics within the dataset may allow identification of a participant.

14 STUDY WITHIN A TRIAL (SWAT)

The REPRIEVED SWAT focusses on the under-representation of women and minoritised ethnic groups in interventional heart failure trials. The SWAT will take a mixed-methods approach to understanding the reasons for under-representation in these trials.

Qualitative work will include ten interviews with patients and care partners to explore their thoughts on recruitment and where hesitation or mistrust can lie. Two focus groups will also explore staff's perceptions and where they identify barriers before and after cultural safety training. The outcomes of these interviews and focus groups will be reported and will inform trial recruitment strategy.

Qualitative work during recruitment will involve analysis of ten recorded consent or information sessions to assess communication, barriers to participation and opportunities for improvement, as well as five patient reporter follow-up interviews. The learning from these interviews and recordings will be supplemented by quantitative monitoring of screening, recruitment and retention data monthly to measure the impact of interventions on the representation of under-served populations. The SWAT results will be published to share learning. The SWAT will be co-led by the one of the PPI Co-Applicants (Lynn Laidlaw) and Dr Heidi Green with the support of the CI and CTU, to facilitate the

focus groups, recordings, interviews and provide expertise in qualitative research in under-served populations.

The interviews and focus groups will support the recruitment process. These will provide insights from patients and care partners to give us an idea of the landscape in terms of mistrust, trial hesitancy, and preferred communication methods. We will also develop insights from trial staff to give us an idea of potential gate keeping before it begins, training needs, and insights from their own experience of working directly with patients.

The analysis of recruitment consultations and monitoring of recruitment/retention data will allow us to proactively evaluate the recruitment and retention process in an ongoing and proactive manner rather than a reactive manner. The SWAT should provide quantitative evidence on the current success of recruitment, and the qualitative evidence on how to act and adjust the processes if recruitment is behind target.

15 MONITORING AND AUDITING

The Chief Investigator will be responsible for the ongoing management of the study, with the support of the LSHTM CTU.

The Sponsor will monitor and conduct audits on a selection of studies in its clinical research portfolio. Monitoring and auditing will be conducted in accordance with the UK Policy Framework for Health and Social Care and in accordance with the Sponsor's monitoring and audit procedures.

15.1 Central statistical monitoring

The primary method of data monitoring will be via central statistical monitoring. Site monitoring visits will not routinely be conducted but may be arranged if concerns regarding the integrity and quality of research data are raised either by the site, CTU or a trial committee.

The eCRF will form the primary record for the study at site level. Paper records are not required but may be used by sites to facilitate data entry. Integrity of the eCRF may be checked against source records during monitoring visits.

15.2 Monitoring due to protocol non-compliance

A monitoring visit may be required due to concerns about protocol non-compliance, such as to prevent serious breaches from reoccurring (further details can be found in the Protocol compliance WPD).

15.3 Recording research conduct at site

Sites are required to maintain up to date and detailed records of research conduct. These include but are not limited to the site file, delegation and training logs, records of adverse events and their reporting and any other records required by relevant regulatory bodies.

16 STATISTICAL CONSIDERATIONS

A detailed statistical analysis plan will be written and signed off prior to database lock and unblinding of trial data. For the KCCQ-OSS and CFR measures, differences in mean levels of the outcome measures between treatment groups at the relevant timepoints will be calculated, together with 95% confidence intervals, using a linear mixed model with treatment group, categorical treatment by timepoint interaction and baseline outcome measures included in the model (random intercept, unstructured correlation). It may be necessary to examine the measures for transformations to adhere to the assumptions of the linear mixed model or use bootstrapping techniques if a suitable

transformation cannot be found. For the primary analysis, any patient who dies will be excluded but as a sensitivity analysis a value of 0 will be imputed. All analyses will be on an intention-to-treat basis. Key secondary outcomes include all-cause death and/or hospitalisation for heart failure which will be assessed and compared between groups with hazard ratios using a Cox proportional hazards model. In addition risk differences will also be presented together with 95% confidence intervals at 6 months. The individual components of all-cause-death and hospitalisation for heart failure will also be analysed . In addition, groups will be compared using the unpaired win ratio method with a prespecified hierarchy of all-cause death, hospitalisation for heart failure and difference in KCCQ-OSS ≥ 7 between participants at six months. Sensitivity analyses will be reported excluding any participants who underwent emergency unblinding. Whilst the sample size will not permit definitive analyses based upon subgroups, hypothesis generating subgroup analyses will be performed to assess for differential treatment response based on age, sex and baseline NT-pro-BNP.

16.1 Sample size calculations

In pilot data from our REVIVED-BCIS2 trial (which has been selected as calculations can be performed using individual participant data and represents the only randomised comparison of PCI to medical treatment in a heart failure population), the baseline KCCQ-OSS was 60.9 with a between-group difference at six months of 6.5 (95% confidence interval 3.5 to 9.5) points. There was a high degree of correlation between baseline and six-month scores (correlation coefficient: 0.67). Though the standard distributions of scores at each timepoint were non-normally and widely distributed, the distribution of change in score from baseline to follow-up was close to normally distributed. Assuming similar baseline values, a standard deviation of KCCQ-OSS of 25, correlation coefficient of 0.6 and an alpha of 0.05, a total of 350 participants are required to have in excess of 85% power to detect a minimum clinically important difference (MCID) of 7 points, allowing for 10% withdrawals or losses to follow-up. If correlation were higher (0.65) a sample size of 350 participants will achieve in excess of 90% power for a difference of 7. If the standard deviation were increased (27), we would retain in excess of 80% power for a MCID of 7. The inclusion of a three month follow-up timepoint will enable repeated measures of KCCQ-OSS which will further increase power. A review of the sample size assumptions blinded to treatment allocation will be made after 1 year of recruitment to assess the correlation between baseline and follow up measures; consideration will be given to extending the sample size at this point if recruitment permits.

17 FINANCING

The trial is funded by the NIHR Efficacy and Mechanism Evaluation Advanced Fellowship: Building Clinical Trials Experience Programme (Award ID: NIHR159715). The duration of the award is 60 months (September 2024 to September 2029). Funding was awarded on 23rd May 2024. The grant holders have no financial conflicts of interest to declare.

18 INSURANCE AND INDEMNITY

This study is co-sponsored by KCL and Guys and St Thomas' NHS Foundation Trust (GSTFT). The sponsors will, at all times, maintain adequate insurance in relation to the study: KCL through its' own professional indemnity (Clinical Trials) & no-fault compensation and GSTFT having a duty of care to patients via NHS indemnity cover, in respect of any claims arising as a result of negligence by its employees, brought by or on behalf of a study participant.

19 DATA RESPONSIBILITIES

19.1 Data controller

GSTFT and KCL are co-sponsors of this research project and have shared Data Controller responsibilities. Where personal data are disclosed by GSTFT to KCL or vice versa, directly or indirectly to satisfy the requirements of the protocol, or for the purpose of monitoring or reporting adverse events, or in relation to a claim or proceeding brought by a participant in connection with the Trial, KCL and GSTFT agree to comply with the obligations placed on a Controller by the Data Protection Legislation. This is not limited to, but includes, being responsible for and able to demonstrate compliance with the principles relating to Processing of Personal Data (Article 5 UK GDPR).

GSTFT and KCL have outlined their Data Controller to Controller arrangements in an overarching Master Data Sharing Agreement which sets out the principles of data sharing in accordance with UK GDPR, regulatory and statutory laws. GSTFT and KCL have agreed to the mutual study specific Joint Controller data sharing template which details their individual roles and responsibilities at a study level.

19.2 Data processors

LSHTM have been delegated to process trial data on behalf of GSTFT and KCL.

20 INTELLECTUAL PROPERTY (IP)

It is not anticipated that new intellectual property will be developed in the study. If unanticipated intellectual property is developed in the conduct of the study, the Sponsor will retain ownership of this property.

21 REPORTING AND DISSEMINATION

The project is expected to produce the following scientific outputs based on previous outputs from the group in recent work:

1. Coronary disease in HFpEF review article
2. Trial protocol paper
3. Main efficacy outcome paper, plus further efficacy studies on secondary outcomes
4. Main mechanistic outcome paper, plus further mechanistic studies
5. Main SWAT paper plus further papers on EDI work package.

We aim to secure a late-breaking clinical trial presentation at a major international scientific meeting, facilitating engagement with media bodies and the news media. We will establish an online presence for the trial with a webpage and social media accounts. Participants will be invited to attend a dedicated trial results webinar or receive the results from their local research teams in writing or by meeting a member of the research team, depending on their preference. If they choose to attend the webinar, their participation can remain anonymous if they prefer, and they can engage in discussion either speaking or via chat functions. Participants will be invited to contribute to public engagement activities in the dissemination of the research, including sharing their experiences via impact statements. The trial will provide the first evidence to inform both NICE and international guidelines on the management of coronary artery disease in patients with HFpEF.

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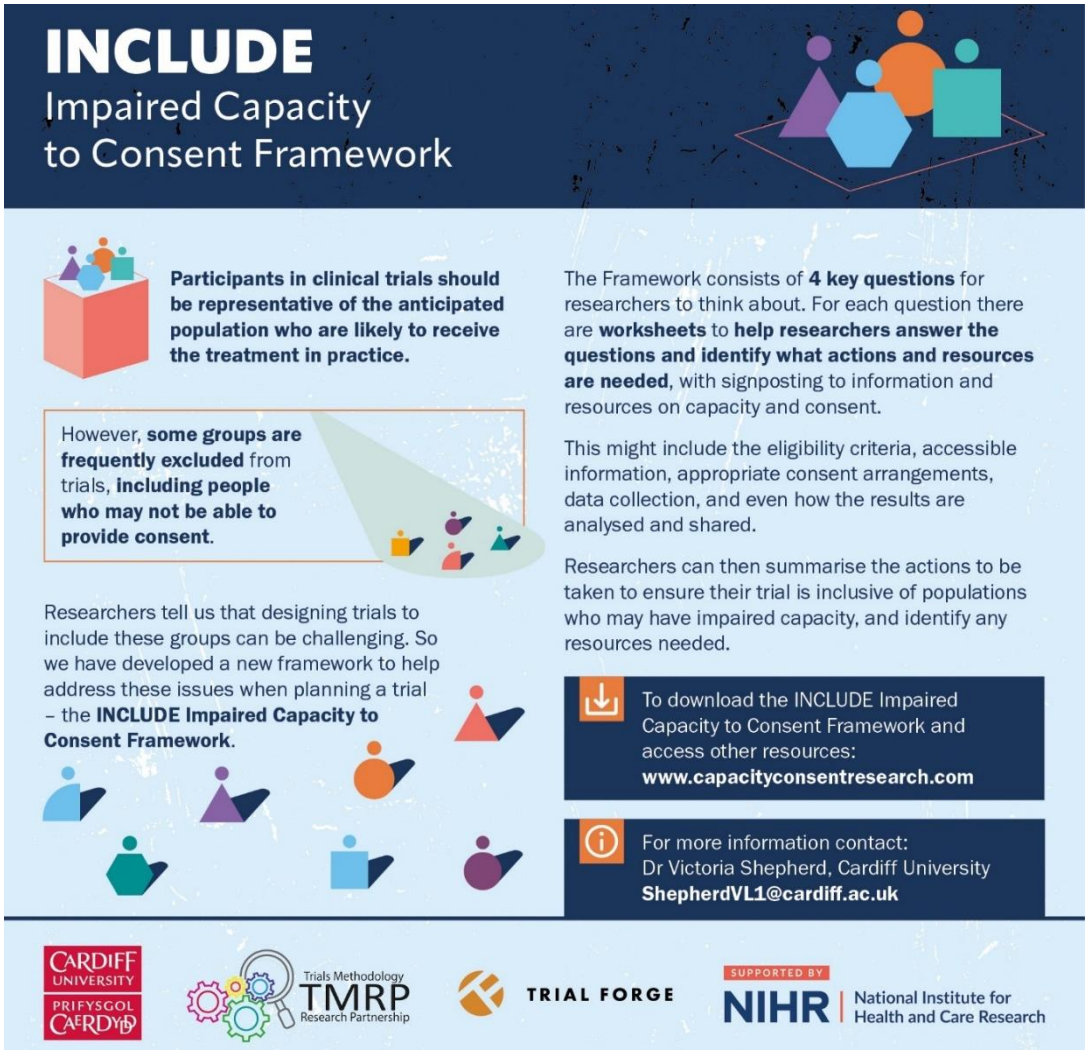
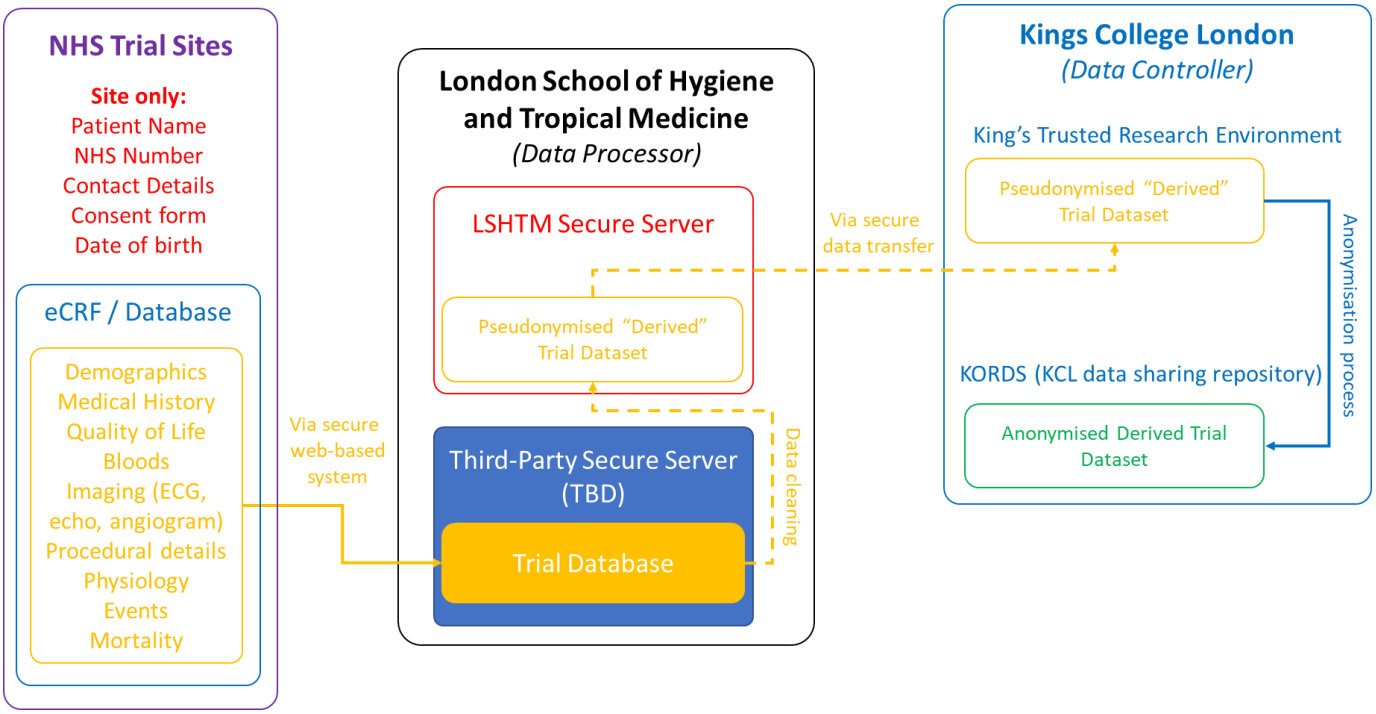
APPENDIX 1: NIHR INCLUDE IMPAIRED CAPACITY TO CONSENT FRAMEWORK

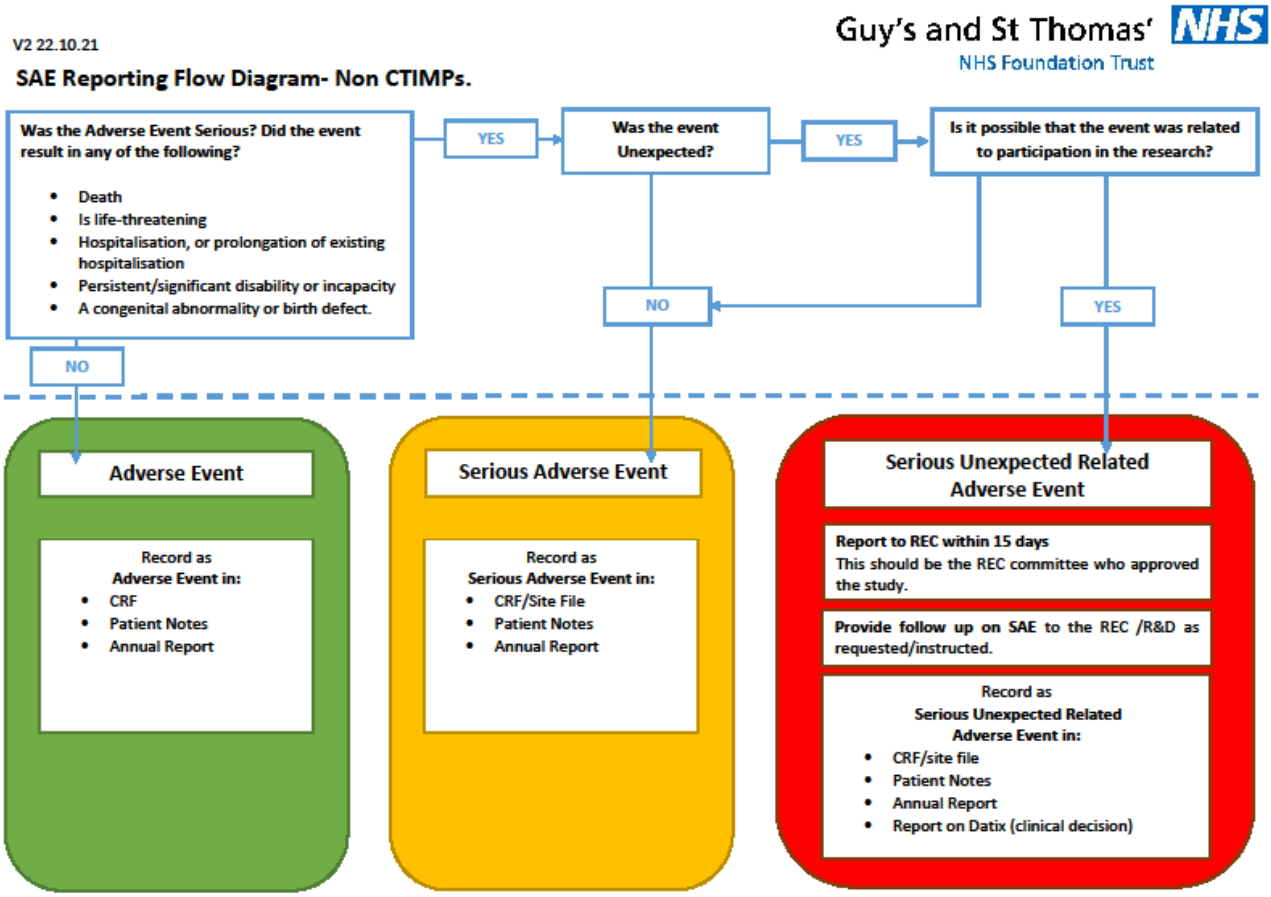


Full details of the exploration of involving patients with a reduced capacity to consent can be found at www.capacityconsentresearch.com/include-impaired-capacity-to-consent-framework.html

APPENDIX 2: DATA FLOW DIAGRAM FOR DATA LEAVING TRUST/SITE PREMISES



APPENDIX 3: SAE REPORTING FLOW DIAGRAM-NON CTIMPS



APPENDIX 4: SAFETY REPORTING IN NON-CTIMP RESEARCH

	Who	When	How	To Whom
SAE (related and unexpected)	Chief Investigator	Report to Sponsor within 24 hours of learning of the event. Report to the MREC within 15 days of learning of the event.	SAE Report form for Non-CTIMPs, available from NRES website.	Sponsor and MREC.
Urgent Safety Measures	Chief Investigator	Contact the Sponsor and MREC Immediately. Within 3 days.	By phone. Substantial amendment form giving notice in writing setting out the reasons for the urgent safety measures and the plan for future action.	Main REC and Sponsor. Main REC with a copy also sent to the Sponsor. The MREC will acknowledge this within 30 days of receipt.
Progress Reports	Chief Investigator	Annually (starting 12 months after the date of favourable opinion).	Annual Progress Report Form (non-CTIMPs) available from the NRES website.	Main REC with a copy to be sent to the Sponsor.
Declaration of the conclusion *or* early termination of the study	Chief Investigator	Within 90 days (conclusion). Within 15 days (early termination). *The end of study should be defined in the protocol.*	End of Study Declaration form available from the NRES website.	Main REC with a copy to be sent to the Sponsor.
Summary of final Report	Chief Investigator	Within one year of conclusion of the Research.	No Standard Format However, the following Information should be included: Where the study has met its objectives, the main findings and arrangements for publication or dissemination including feedback to participants.	Main REC with a copy to be sent to the Sponsor.

APPENDIX 5: PROTOCOL AMENDMENT HISTORY

Version Stage	Version No	Version Date	Protocol updated & finalised by	Details the key protocol updates
Superseded	1.0	17/03/2025	Dr Matthew Ryan, Chief Investigator	N/A

Current	2.0	22/08/2025	Matthew Ryan and Matthew Kwok	• Added ISRCTN registry number
				• Updates to key study contacts and added emergency unblinding phone number (pg 2)
				• Updates to outcome definitions (section 5.2) including:
				  • Clarification to MI definition to include index procedure and subsequent unplanned revascularisation
				  • Change to atrial fibrillation definition to include new onset AF
				• Update to trial flowchart (section 5.3) and inclusion criteria (section 5.5) to include non-hyperaemic pressure ratio
				• Update to screening logs (section 6.1.5) to include sex, age, gender, ethnicity and refusals due to language
				• Addition of participant identification log (section 6.4.2)
				• Updates to blinding (section 6.8) to include table of unblinded and blinded procedures and clarifications to blinding procedures
				• Updates and corrections to schedule of assessments (section 6.10) and trial schedule (section 6.12)
				• General clarifications to text including updates to headings, layout, and formatting