REVascularisation for Ischaemic VEntricular Dysfunction

(REVIVED-BCIS2)

Trial Protocol Version 8.2

Sponsored by King's College London

Funded by NIHR HTA CET

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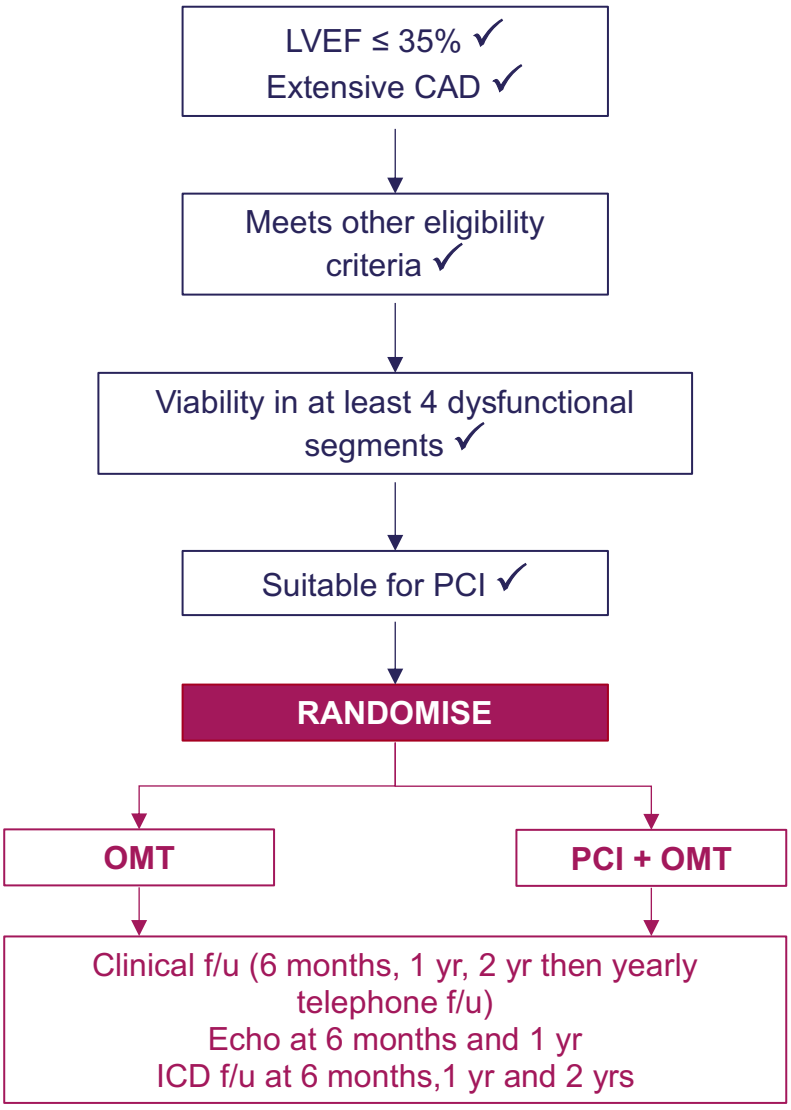
1. Trial Summary

1.1. Protocol Summary

Trial Title	Revascularisation for Ischaemic Ventricular Dysfunction (**REVIVED-BCIS2**)
Aim	To evaluate the efficacy and safety of percutaneous coronary intervention (PCI) compared to optimal medical therapy (OMT) alone for ischaemic left ventricular dysfunction
Trial Design	Multicentre prospective randomised open controlled trial
Primary Endpoint	All-cause death or hospitalisation due to heart failure
Secondary Endpoints	Quality of life score: Kansas City Cardiomyopathy Questionnaire (KCCQ) EuroQol EQ-5D-5L New York Heart Association (NYHA) Functional Class Left ventricular ejection fraction (LVEF) on echocardiography at 6 months and 1 year Hospitalisation for heart failure All-cause death Cardiovascular death Acute myocardial infarction (MI) Appropriate implantable cardioverter defibrillator (ICD) therapy Unplanned further revascularisation Canadian Cardiovascular Society (CCS) angina class Health resource use Brain natriuretic peptide (BNP or NT-proBNP) level Troponin (T or I) level Major bleeding
Inclusion Criteria	LVEF ≤35% Extensive coronary artery disease (CAD) Viability in at least 4 dysfunctional myocardial segments, that can be revascularised by PCI
Major Exclusion Criteria	Acute MI <4 weeks prior to randomisation (clinical definition) Acutely decompensated heart failure requiring treatment with inotropes/ventilation/mechanical circulatory support <72 hours prior to randomisation Any contraindication to PCI

Sample Size and Enrolment	n=700 Start date: 1st June 2013 Recruitment start date: 1st September 2013 Recruitment end date: 30th April 2020 Follow-up end date: 30th April 2022 Number of centres: 35-40 (listed on trial website)

1.2. Trial Flowchart



1.3. Trial Organisation

1.3.1. NIHR HTA CET Grant applicants

Prof Divaka Perera, King's College London (Chief Investigator)

Associate Prof Tim Clayton, London School of Hygiene & Tropical Medicine

Prof Simon Redwood, King's College London

Dr Mark De Belder, The James Cook University Hospital, Middlesbrough

Prof Tony Gershlick, Glenfield Hospital, Leicester

Prof Michael Marber, King's College London

Prof Theresa McDonagh, King's College London

Dr Gerry Carr-White, Guy's and St Thomas' Hospital, London

Prof Mark Sculpher, Centre for Health Economics, University of York

1.3.2. Trial Steering Committee (TSC)

Prof Andrew Clark, Chair of Clinical Cardiology, Castle Hill Hospital, Hull (chair)

Mrs Helen Williams, Pharmacist, NHS Southwark Clinical Commissioning Group

Dr Pablo Perel, Epidemiologist, London School of Hygiene & Tropical Medicine

Dr David Walker, Cardiologist, Conquest Hospital, St. Leonards-on-Sea

Prof Rod Stables, Cardiologist, Liverpool Heart and Chest Hospital

Prof Divaka Perera, King's College London

Ms Liz Bestic, Consumer representative

Mrs Paula Young, Consumer representative

1.3.3. Project Management Group (PMG)

Prof Divaka Perera, King's College London

Associate Prof Tim Clayton, London School of Hygiene & Tropical Medicine

Mr Steven Robertson, London School of Hygiene & Tropical Medicine

Mr Richard Evans, London School of Hygiene & Tropical Medicine

Ms Ruth Canter, London School of Hygiene & Tropical Medicine

Mrs Karen Wilson, Guy's and St Thomas' Hospital, London

Mrs Sophie Arnold, Guy's and St Thomas' Hospital, London

Dr Bhavik Modi, Guy's and St Thomas' Hospital, London

Dr Natalia Briceno, Guy's and St Thomas' Hospital, London

Dr Matthew Ryan, Guy's and St Thomas' Hospital, London

1.3.4. Clinical Trials Unit (CTU)

The trial is managed by the UKCRC accredited CTU at London School of Hygiene & Tropical Medicine (Registration ID 44).

1.3.5. Data and Safety Monitoring Committee (DSMC)

Dr Peter Ludman, Consultant Cardiologist, Birmingham (chair)

Dr Suzanna Hardman, Consultant Cardiologist, Whittington Hospital, London

Dr Louise Brown, Senior Statistician, MRC Clinical Trials Unit at University College London

The DSMC is supported by Mr Matt Dodd, Statistician at the London School of Hygiene & Tropical Medicine CTU

1.3.6. Clinical Events Committee (CEC)

Prof Roxy Senior, Professor of Clinical Cardiology, Royal Brompton Hospital, London (chair)

Dr Zaheer Yousef, Consultant Cardiologist, University Hospital of Wales

Dr Rajan Sharma, Consultant Cardiologist, St George's Hospital, London

1.3.7. Medical Therapy Committee

Prof Michael Marber, Professor of Cardiology, King's College London

Prof Aldo Rinaldi, Consultant Cardiologist, St Thomas' Hospital, London

Dr Stam Kapetanakis, Consultant Cardiologist, St Thomas' Hospital, London

Prof Mark Petrie, Consultant Cardiologist, Golden Jubilee Hospital, Glasgow

1.3.8. Recruiting Centres

At each site;

- Heart Failure lead
- PCI lead

  (One of which will be designated as the Principal Investigator and the other as a co-investigator)
- Trial Coordinator

A current list of sites is provided on the trial website http://revived.lshtm.ac.uk/

2. Background

2.1. Epidemiology

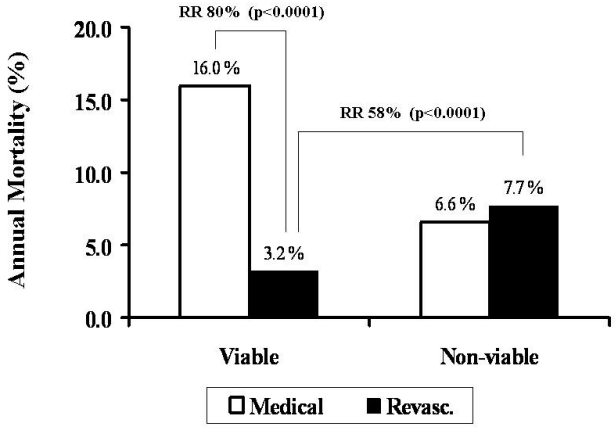
In 2002, it was estimated that approximately 900,000 individuals in the UK had a diagnosis of heart failure and at least 5% of all deaths in the country were related to this condition. At that time, one million in-hospital bed-days per year were estimated to be due to heart failure, with an annual cost to the NHS in excess of £625 million. Furthermore, there is evidence of a rising prevalence of heart failure in the population, with the number of associated hospital admissions expected to increase by around 50% in the next 25 years(1). This emerging epidemic is the likely consequence of a progressively aging population and improved survival from acute coronary syndromes, partly due to more efficient and timely revascularisation techniques. The Framingham Heart Study suggests that the most common cause of chronic heart failure is no longer hypertension or valvular heart disease, as it was in previous decades, but rather coronary artery disease(2). Recent meta-analyses of heart failure trials and large registries have shown that coronary disease is the underlying cause of heart failure in 65% of cases(3, 4), although this may have been an underestimation, given that few of these studies mandated systematic exploration of aetiology.

2.2. Hibernating Myocardium

The concept of viable but dysfunctional myocardium emerged approximately three decades ago, when it was observed that patients undergoing coronary artery bypass surgery for chronic stable angina had improvement or normalisation of left ventricular function following revascularisation(5). The energy utilized during myocyte contraction far exceeds the requirement for sustaining viability and, as such, myocardial tissue may survive in a hypocontractile state in the presence of reduced coronary blood flow or decreased coronary flow reserve, known as hibernation(6). Improvement of blood flow by revascularisation of hibernating myocardium can lead to restoration of regional and global left ventricular function and reversal of adverse remodelling(7-9), provided this is achieved before the onset of irreversible cellular and ultrastructural alterations(10). Potentially reversible, dysfunctional myocardium is characterised by preserved cellular integrity and a degree of contractile reserve, whereas scarring and absence of inducible contraction tend to reflect irreversible myocardial damage. Each of these distinguishing features can be used to predict myocardial viability or the likelihood of functional recovery following revascularisation. The parameter most widely used to determine viability is contractile reserve, which is assessed by measuring the augmentation of function of hypocontractile myocardium, in response to inotropic stimulation. The most commonly used agent is Dobutamine (at doses up to 20 µg/kg/min) while the change in regional and global contractility could be imaged by dobutamine stress echocardiography (DSE) or cine-magnetic resonance imaging (MRI). While MRI allows scar imaging as well as assessment of contractile reserve, at present it is contraindicated in patients with implantable cardioverter defibrillators or pacemakers in situ, which can limit its use in a heart failure population.

Despite variation in the sensitivity and specificity of MRI, DSE, positron emission tomography (PET) and Nuclear Medicine techniques, patients found to have viable myocardium (by any modality) have been shown to have a strong survival advantage following revascularisation compared to medical therapy alone. A meta-analysis of more than 3000 patients in 24 observational studies (in which viability was assessed by single photon emission computed tomography (SPECT), PET or DSE) showed an impressive 80% relative reduction (and 12.8% absolute reduction) in mortality with revascularisation compared to medical therapy in patients found to have significant viable myocardium(8). In contrast, no survival benefit was seen in the absence of viability and even a trend to worse outcome with revascularisation. These data also argue against a strategy of revascularising all patients with heart failure and

coronary disease, regardless of viability; mortality following coronary artery bypass graft (CABG) surgery in patients without viability was more than double that observed in those who did have viable myocardium.



A more recent analysis of 14 non-randomised studies suggests that the findings of the Allman meta-analysis have not changed despite changes in revascularisation techniques and medical therapy(11). It has traditionally been held that completeness of revascularisation (in relation to the angiographic findings) is a major determinant of outcome in ischaemic cardiomyopathy(12); whether regional viability can be used to guide the extent (and hence the mode) of revascularisation in a given patient, remains untested to date.

Notwithstanding the compelling nature of these small studies, there is a lack of consensus on the role of revascularisation in patients with heart failure owing to the absence of adequately powered randomised controlled trials (RCTs) in this field(13-15). Furthermore, there have been major advances in medical therapy for heart failure during the last decade and the incremental benefit of revascularisation in contemporary practice is unknown. REVIVED-BCIS2 will be the largest contemporary randomised comparison of percutaneous revascularisation (with optimal medical therapy (OMT)) versus OMT alone in patients with heart failure and viable myocardium, and is expected to definitively resolve the role of this treatment.

2.3. CABG surgery for ischaemic cardiomyopathy

CABG surgery is considered an appropriate treatment for impaired left ventricle (LV) function in the presence of significant proximal coronary disease, regardless of whether the patient has angina(13-16). These recommendations were based on data from registries and cohort studies that were carried out more than 20 years ago, before the routine use of medical therapies that have been shown to improve survival and symptoms in this group of patients. The Coronary Artery Surgery Study (CASS) registry included 651 (of a total of approximately 20,000) patients who had a left ventricular ejection fraction (LVEF) <50%, 231 of whom received CABG surgery. CABG provided a mortality benefit over medical therapy only in the subgroup of patients with severe LV dysfunction (ejection fraction (EF) <25%), where angina was the predominant symptom, rather than heart failure(17). The Duke registry of 1391 patients with ischaemic cardiomyopathy (EF <40%), treated over a period of 25 years, demonstrated a sustained survival benefit in the group receiving CABG surgery (339 patients) compared to those treated with medical therapy alone(18).

The landmark Surgical Treatment for Ischemic Heart Failure (STICH) trial is the only completed RCT to date that addressed this question(19). This was an international multicentre, open-

labelled RCT that enrolled 1212 patients with LV dysfunction (EF <35%) with follow up for an average of 4.7 years. The main hypothesis was that a strategy of coronary artery bypass grafting and OMT compared with OMT alone would reduce the primary outcome of all-cause mortality. The primary outcome was not found to be significantly different between groups (41% OMT versus 36% CABG, p=0.12). There was a trend for a reduction in the secondary outcome of cardiovascular mortality in the CABG treated group, which did not quite make statistical significance (p=0.05). The Surgical Treatment for Ischaemic Heart Failure Extension Study (STICHES) reported longer-term mortality data from the STICH trial; 98% of the study cohort was followed up for a median of 9.8 years, during which time 59% of patients assigned to CABG died versus 66% in the medical therapy group (hazard ratio 0.84; 95% confidence interval, 0.73-0.97; p=0.02)(20). Death from cardiovascular causes and several pre-specified composite secondary endpoints also occurred less often in the CABG group. Patients with more severe coronary artery disease, a left ventricular aneurysm suitable for surgical reconstruction, who were classified as being Hispanic/Latino/non-white or were younger than 60 years had the greatest survival benefit with revascularisation (p values for interaction 0.04, 0.03, 0.02 and 0.18 respectively)[60].

Several considerations should be taken into account when interpreting the above data. Firstly, although the trial at its onset mandated the presence of viability for enrolment, due to slow recruitment this was removed from the protocol; as a result, a patient population with both non-viable and viable myocardium were enrolled. Secondly, on average 2 patients were enrolled per centre per year, reflecting the fact that this was a difficult trial to recruit to, and may indicate selection bias. Importantly, the CABG procedure itself conferred a higher 30-day mortality than with medical therapy, which may have ameliorated any benefit seen with revascularisation, an effect which lasted for more than 2 years. This finding is in keeping with registry data on CABG surgery: perioperative mortality rates in patients with LV dysfunction have been shown to be between 5% and 30%; and the risk increasing with age, comorbidities and degree of LV impairment(21). The relative risk of early death following CABG surgery in patients with severe LV dysfunction is 3- to 4-fold higher than in those with mild dysfunction or preserved systolic function(22-24). However for patients who survive this early mortality hazard, there may be a long-term mortality benefit from CABG. Another consideration is the age of the population enrolled in STICH(ES) and whether this relatively young population are representative of the average heart failure patient. In STICHES, the reduction in mortality was about 25% for those aged <60 years (slightly more than half of all patients) but only 9% in those aged >60 years.

Furthermore, patients with left main coronary stenoses (who represent the extreme end of the spectrum of coronary disease and therefore are at highest risk of cardiovascular events) were excluded from the trial. Finally, the STICH investigators did not systematically exclude patients with non-ischaemic cardiomyopathy with co-existent coronary disease; a minimum coronary disease severity was not mandated and, as a consequence, 40% of the entire cohort had single or 2 vessel disease only. Potential inclusion of non-ischaemic cardiomyopathy patients would be expected to dilute any beneficial effects of revascularisation.

2.4. PCI for ischaemic cardiomyopathy

Numerous comparisons have been made between percutaneous coronary intervention (PCI) and CABG surgery for patients with symptomatic coronary disease or evidence of significant reversible ischaemia, but most of the large RCTs excluded patients with impaired left ventricular function (EF <30%)(26-28). Less than 2% of all patients included in the largest and most recent RCT, the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial, had significant LV impairment (EF <30%) at baseline(29). A meta-analysis of 10 such trials has found similar 5-year survival following surgery or PCI in the combined cohort, as well as in the subgroup (17% of all patients) who had modest LV dysfunction(30). We recently reported mortality rates of 1.3% and 6% at one and 6 months respectively, following PCI in 301 patients

with severely impaired LV function (EF 24%) and severe coronary disease (British Cardiovascular Interventional Society (BCIS-1) Jeopardy Score (JS) of 10/12)(31). Long-term all-cause mortality assessment in this cohort was completed in October 2011, by tracking the database of the Office for National Statistics in the UK. These data provide the best contemporary indication of the utility of PCI in ischaemic cardiomyopathy. All-cause mortality at a median of 51 months (range 28-70) was 33%(32). Notwithstanding the inherent difficulties of carrying out a non-randomised comparison, it is worth noting that mortality in the 600 medically treated patients in STICH was 46% at a median of 56 months (range 12-72), despite having better overall LV function (EF 28%) and a lower coronary disease burden than the contemporaneous BCIS-1 cohort. These results may suggest that PCI may be the preferred mode of revascularisation for patients with ischaemic cardiomyopathy who have suitable coronary anatomy. The ability to carry out surgical ventricular reconstruction has also been traditionally considered an indication for CABG surgery rather than PCI, but Hypothesis 2 of the STICH trial suggests that ventricular restoration does not offer survival or functional benefit over revascularisation alone(33).

There have been a few non-randomised comparisons of the two modalities in patients with poor LV function. In the pre-stent era, observational studies suggested better early outcomes but less complete revascularisation and more mid-term repeat revascularisation procedures following balloon angioplasty than surgery, with similar long-term survival following either treatment(12, 34). The Angina With Extremely Serious Operative Mortality Evaluation (AWESOME) investigators combined the data from randomised and registry cohorts in a pre-specified subgroup analysis and demonstrated equivalent 3-year survival following surgery or bare-metal stent PCI(35). The advent of drug-eluting stents has vastly reduced the incidence of restenosis and has facilitated a greater degree of revascularisation with PCI, which are particularly pertinent factors in the treatment of ischaemic cardiomyopathy(36). A recent observational study has confirmed these theoretical benefits by demonstrating comparable mortality at 15 months following drug-eluting stent PCI or CABG surgery, although there was a greater improvement in New York Heart Association (NYHA) functional class with surgery, possibly due to more complete revascularisation(37). However, these studies were relatively underpowered retrospective analyses that included patients who had significant angina and were not balanced in terms of baseline characteristics or completeness of revascularisation. At present, although conceptually appealing, there is no randomised evidence supporting the use of PCI for patients with ischaemic cardiomyopathy and predominant symptoms of heart failure, rather than angina. There is clearly a need for systematic evaluation of the safety and efficacy of this treatment by a RCT. Furthermore, there have been major advances in medical therapy for heart failure during the last decade and the incremental benefit of revascularisation in contemporary practice is unknown. REVIVED-BCIS2 will be the largest contemporary randomised comparison of percutaneous revascularisation (with OMT) versus OMT alone in patients with heart failure and viable myocardium, and is expected to definitively resolve the role of this treatment.

3. Hypothesis

Compared to OMT alone, PCI improves event-free survival in patients with ischaemic cardiomyopathy and viable myocardium.

4. Endpoints

An independent clinical events committee (CEC), who are blinded to treatment assignment, will centrally adjudicate and validate selected endpoints where validation is necessary.

4.1. Primary Endpoint

All-cause death or hospitalisation due to heart failure. This composite endpoint will be collected over the entire duration of follow-up in the trial.

4.2. Major Secondary Endpoints

LVEF on echocardiography at 6 months and 1 year

Quality of life score:

- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- EuroQol EQ-5D-5L

NYHA Functional Class

4.3. Other Secondary Endpoints

Cardiovascular death
All-cause death
Hospitalisation due to heart failure
Acute myocardial infarction (MI)
Appropriate implantable cardioverter defibrillator (ICD) therapy
Unplanned further revascularisation
Canadian Cardiovascular Society (CCS) angina class
Health resource use
Serial Troponin (T or I) levels
Serial brain natriuretic peptide (BNP or NT-proBNP) levels
Major bleeding

4.4. Endpoint Definitions

Acute Myocardial Infarction	**1. Spontaneous MI (>48 hrs after PCI/CABG)** Detection of a rise and/or fall of cardiac biomarkers (preferably Troponin (T or I), 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, new Left Bundle Branch Block (LBBB) >1mm ST depression, >3mm T wave inversion). **2. Peri-procedural MI (<48 hrs after PCI/CABG)*** **Following PCI**: Troponin (T or I) >5 times the 99th percentile URL (or 5 times the baseline value if this is higher than the URL) in combination with any of the following: (i) evidence of prolonged ischaemia (>20 min) as demonstrated by prolonged chest pain and/or ischaemic ST changes; (ii) new pathological Q waves; (c) angiographic evidence of a flow limiting complication, such as of loss of patency of a side branch, persistent slow-flow or no-reflow, embolisation; or (d) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. **Following CABG**: Troponin (T or I) >10 times the 99th percentile URL (or 10 times the baseline value if this is higher than the URL) in combination with any of the following: (i) new pathological Q waves; (ii) angiographically documented new graft or new native coronary artery occlusion; or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. **3. Sudden death** Cardiac arrest accompanied by new ST elevation/LBBB on ECG and/or evidence of fresh coronary thrombus at autopsy/angiography. * *In addition to classifying patients dichotomously, on the basis of the 2012 Universal Definition of MI(38), as having suffered a periprocedural MI or not, baseline and peak Troponin (T or I) levels measured within 24 hours of a procedure will be recorded. This will provide a continuous outcome measure of periprocedural myocardial injury and will also allow subsequent reclassification in the event of further revisions to the Universal Definition during the course of the trial.*

Hospitalisation for heart failure (39, 40)	Hospital admission (lasting >24 hours) for deteriorating symptoms or signs of heart failure, where there is a documented diagnosis of heart failure and the patient receives initiation or intensification of treatment for heart failure. Initiation or intensification of treatment includes at least one of the following: increase in oral diuretic dose or addition of another oral diuretic; intravenous diuretic therapy; intravenous vasoactive therapy (vasodilator, inotrope or vasopressor); mechanical circulatory support (MCS) (including intra-aortic balloon pump (IABP), Impella, extra-corporeal membrane oxygenation (ECMO)); or cardiac transplantation. Heart failure during or after the assigned PCI procedure itself is defined as prolongation of the planned admission by at least 24 hours due to acute heart failure requiring initiation or intensification of treatment as defined above. Prolongation of hospital admission in patients who have prophylactic pre-PCI insertion of a mechanical support device (IABP, Impella or ECMO) should not be recorded as having a heart failure hospitalisation UNLESS there are features of heart failure requiring initiation or intensification of treatment as defined above. Elective admission for implantation or revision of ICD/cardiac resynchronisation therapy (CRT) devices will NOT constitute an endpoint.
Unplanned revascularisation	**PCI group:** Any unplanned target vessel or non-target vessel revascularisation by PCI or CABG following index PCI, excluding provisional staged PCI (with plan documented at the index procedure). **OMT group:** Any revascularisation by PCI or CABG.
Appropriate ICD therapy	At least one ICD shock or episode of anti-tachycardia pacing for documented ventricular tachycardia (VT) or ventricular fibrillation (VF).
Cardiovascular death	All deaths where there is no clinical or post-mortem evidence of a non-cardiovascular aetiology.

Major Bleeding	Major bleeding will be defined using the Bleeding Academic Research Consortium (BARC) categories below: **Type 3** Type 3a • Overt bleeding plus haemoglobin drop of ≥30 to <50g/L (provided haemoglobin drop is related to bleed) • Any transfusion with overt bleeding Type 3b • Overt bleeding plus haemoglobin drop ≥50g/L (provided haemoglobin drop is related to bleed) • Cardiac tamponade • Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/haemorrhoid) • Bleeding requiring intravenous vasoactive drugs Type 3c • Intracranial haemorrhage (does not include microbleeds or haemorrhagic transformation; does include intraspinal) • Subcategories; confirmed by autopsy, imaging or lumbar puncture (LP) • Intra-ocular bleed compromising vision **Type 4: CABG-related bleeding** • Perioperative intracranial bleeding within 48 hours • Reoperation following closure of sternotomy for the purpose of controlling bleeding • Transfusion of ≥5 units of whole blood or packed red blood cells within a 48-hour period • Chest tube output ≥2L within a 24-hour period • If a CABG-related bleed is not adjudicated as at least a Type 3 severity event, it will be classified as 'Not a bleeding event' **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

5. Safety Reporting

5.1. Definition

Unexpected events that have not been defined as endpoints (section 4) or expected complications of the PCI procedure (listed in PCI definitions, section 13.4) should be reported as either a serious adverse event (SAE) or non-serious adverse event (NSAE) depending on their severity.

5.2. Unexpected Serious Adverse Events

SAEs should be reported to the Clinical Trials Unit (CTU) within 7 days. The report should include an assessment of causality by the Principal Investigator at each site (see section 5.4.2). 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.

5.3. Unexpected Non-Serious Adverse Events

Unexpected NSAEs should be evaluated by the Principal Investigator. This should include an assessment of causality (see section 5.4.2) and intensity (see section 5.4.1) 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.

5.4. 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.

5.4.1. 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 his or her 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.

5.4.2. 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 / commencement of OMT.

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 / commencement of OMT.

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.

5.5. Notification

The Sponsor, the Research Ethics Committee (REC) and the Data and Safety Monitoring Committee (DSMC) 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.

6. Trial Population

6.1. Inclusion Criteria

ALL of the following:

1. Poor left ventricular function (EF ≤35%)[#]
2. Extensive coronary disease*
3. Viability in at least 4 dysfunctional myocardial segments that can be revascularised by PCI

[#] *Biplane/3D echocardiography or MRI can be used to assess the qualifying LVEF. The imaging study should be performed at least 4 weeks after a MI, if there has been a recent clinical diagnosis of a MI.*

* *In general, patients who do not have bypass grafts will be eligible if they have at least proximal left anterior descending (LAD) disease or at least proximal 2 vessel disease. For patients with patent bypass grafts, or in cases where the extent of coronary artery disease (CAD) is uncertain, the BCIS-1 JS should be calculated. The maximum possible JS score is 12 and a score ≥6 is required to be eligible for REVIVED. N.B. The JS should be based on all coronary disease, not just the vessel subtending viable myocardium.*

6.2. Exclusion Criteria

1. MI <4 weeks prior to randomisation (clinical definition as adjudicated by recruiting centres)
2. Acutely decompensated heart failure requiring inotropic support, invasive or non-invasive ventilation or Mechanical Circulatory Assist therapy <72 hours prior to randomisation
3. Sustained VT/VF or appropriate ICD discharges <72 hours prior to randomisation
4. Valve disease deemed by the local heart team to require imminent intervention
5. Contraindications to PCI
6. Age <18 years
7. Estimated glomerular filtration rate (eGFR) <25 ml/min, unless established on dialysis
8. Women who are pregnant
9. Previously enrolled in REVIVED-BCIS2 or current enrolment in other trial that may affect REVIVED-BCIS2 outcome data
10. Life expectancy <1 year due to non-cardiac pathology

7. Ethical Considerations

7.1. Consent

Only patients that give written consent will be included in the trial. If fully informed consent is not possible, the patient will not be recruited into the trial. The patient should be given sufficient time to consider the trial, recommended to be 24 hours, following which informed consent will be taken. Consent may be taken once all requirements for inclusion have been met.

Staff at site may telephone potential patients with information about the trial before scheduled hospital appointments. If a patient is interested, then the site can post them the information sheet to read prior to their appointment and follow this up with a further telephone call within a reasonable time frame.

A patient may decide to withdraw from the trial at any time without prejudice to their future care.

7.2. Declaration of Helsinki and Good Clinical Practice

The trial will conform to the spirit and the letter of the Declaration of Helsinki, and in accordance with Good Clinical Practice Guidelines.

7.3. Ethical committee review

The National Research Ethics Service Committee London - Westminster have reviewed and approved the trial (REC reference 10/H0802/46). Copies of the letters of approval are to be filed in the trial site files at each centre.

8. Statistical Considerations

8.1. Power Calculation

The predicted occurrence of death or hospitalisation for heart failure at two years is 36% in the OMT group(8, 19, 31, 41, 42). The primary endpoint in REVIVED-BCIS2 will be measured over the entire trial duration, with a minimum follow-up duration of two years, thus increasing the number of events. A trial of 700 (350 in each group) with 300 patients experiencing an event would have over 85% power to detect a hazard ratio of 0.7 (a 30% relative reduction in the hazard) at 5% significance allowing for up to 5% losses by the end of follow-up and increasing recruitment over time. For illustrative purposes this represents a reduction in death or hospitalisation to 27% in the PCI group at two years. The hazard ratio of 0.7 used in the power calculation is pragmatic, while being clinically meaningful and is in line with the magnitude of benefit observed across other treatment modalities in this population.

For the major secondary endpoint, even half this sample size will provide 90% power to detect a minimum difference in EF of 4%, assuming a standard deviation of 11%. The trial is expected to have very good power to detect differences in Quality of Life (one of the major secondary outcomes).

The above predicted event rates take into account the possibility of patients randomised to OMT subsequently undergoing PCI (see below). If a higher event rate is found in the OMT group or patient recruitment rates exceed expectation early in the trial (thus providing a longer duration of follow-up in a larger proportion of patients), the trial would have greater

power to detect a hazard ratio of 0.7, or alternatively, provide over 85% power to detect smaller differences in treatment effect.

Although a smaller treatment effect may be clinically significant, this would have a major impact on sample size, which in turn may affect the feasibility of completing the trial within the proposed timescale and resources.

8.2. Crossover

In patients randomly assigned to receive OMT, revascularisation by PCI or CABG during the trial should only be considered in one of the following circumstances:

- Readmission with an acute coronary syndrome (ACS), including ST-elevation myocardial infarction (STEMI) and non-STE events. The diagnosis of ACS will be based on the presence of typical ischaemic symptoms as well as a rise in cardiac biomarker levels or dynamic ST deviation on ECG.
- Deterioration in exertional angina to ≥CCS class 3 level symptoms.
- Resistant ventricular arrhythmias considered to be ischaemic in aetiology.

This trial will be a comparison of strategy, rather than technique, and the projected event rates and hazard ratio allow that OMT patients may undergo subsequent revascularisation. As such, no additional adjustments have been made to the power calculation to account for unplanned revascularisation in the OMT arm.

8.3. Statistical Analysis

A detailed statistical analysis plan will be finalised before any analysis of the data by treatment group is undertaken. An unadjusted time-to-event analysis will be performed on the primary endpoint using data across all follow-up, with time to the first event (or censoring) times measured from randomisation. Hazard ratios together with associated confidence intervals will be calculated from the Cox proportional hazards model. The assumptions underlying the Cox model will be assessed. If there is clear non-proportionality, comparisons will also be made in early and later follow-up with cut-points determined based on availability of data prior to unblinding. Cumulative event rates will be calculated and presented using Kaplan-Meier time-to-event curves. As a measure of absolute treatment difference, cumulative event rates will be compared at 2 years. Secondary analyses of each individual component of the primary composite endpoint as well as other secondary time to event outcomes will be analysed using the above methods. Losses to follow-up are expected to be minimal and patients will be included up until the time they experience the event or are censored.

Any categorical outcome measures will be examined at specific time points using risk ratios or risk differences, confidence intervals and chi-square or Fisher's exact tests as appropriate. Continuous variables will be analysed and presented as mean treatment differences, confidence intervals and p values derived from analysis of co-variance models or unpaired t-tests as appropriate (with appropriate transformation if necessary). Analysis of endpoints in the randomised cohort will be by intention-to-treat.

A limited number of subgroups for the primary endpoint will be pre-specified in the analysis plan and are likely to include groups stratified by age, the extent of coronary disease (BCIS-1 JS <12 vs. 12), degree of LV dysfunction (EF <20% vs. ≥20%), diabetes, NYHA class (<3 vs. ≥3) and chronic total occlusion (CTO). In addition, a model will be developed and patients will be categorised according to their baseline risk of the primary outcome and this will be used to examine whether the impact of treatment depends on a person's underlying risk. Since the subgroup analyses are secondary analyses and exploratory in nature, the trial has not been powered for these. A Cox proportion hazards model incorporating tests of interaction will be used for subgroup analyses.

Other analyses such as sensitivity and per-protocol analyses will be detailed in the statistical analysis plan.

8.4. Interim Analysis

An interim analysis of recruitment and pooled event rates was performed approximately one year after the first patient was recruited to inform the feasibility of completing the trial within the initial projected period. As the number of patients randomised was still relatively small and length of follow-up short, it was felt that the expected number of events at this stage of the trial was too low for meaningful assessment. Recruitment and the pooled event rate will continue to be monitored as the trial progresses.

An independent DSMC has been established and a separate DSMC charter developed which includes details of the meeting schedule and stopping guidelines. The DSMC is expected to meet at least annually.

9. Screening

9.1. Screening population

Patients with LVEF <40% should be screened for eligibility. They may come from the following sources:

- Patients referred to the heart failure team for initiation or optimisation of medical therapy including inpatient referrals, outpatient nurse led heart failure clinics and referrals from district general hospitals.
- Patients referred for viability assessments who are known to have poor resting LV function.
- Patients referred for consideration of CRT or ICD implantation.
- Patients with poor LV function referred for consideration of revascularisation following coronary angiography.
- Patients referred for coronary angiography to establish the aetiology of a dilated cardiomyopathy, who are found to have coronary artery disease.

9.2. Screening log

Full detailed screening logs of all patients with extensive CAD and EF ≤35% considered for the trial will be completed at sites.

The CTU will collect a snapshot of screening outcomes, once a year, from all participating sites. Only patients who complete the screening process (i.e. randomised, declined, met an exclusion criterion) in that three-month period are required to be entered.

10. Assessment of LVEF

10.1. Qualifying ejection fraction

To determine eligibility for the trial, LVEF can be determined by the following modalities:

- Transthoracic echocardiogram (TTE) (Simpson's biplane on 2D or 3D echocardiography)
- The resting stage of a stress echocardiogram
- Cardiac MRI

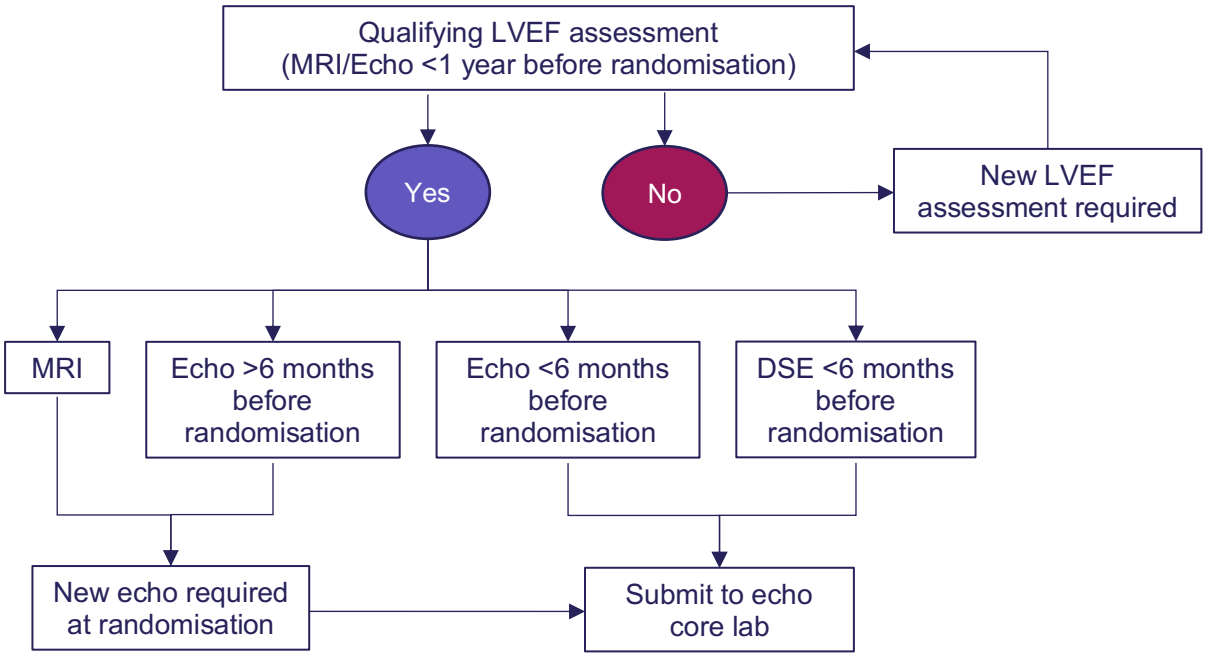
The qualifying assessment **must** have been carried out less than 1 year before randomisation. Estimation of LVEF and adjudication of eligibility for enrolment in will be done by each participating centre, using locally agreed protocols.

10.2. Baseline echocardiogram

If the qualifying echocardiogram study (TTE or resting images from a stress echo) was performed less than 6 months before randomisation, this study can also be submitted to the core lab to calculate baseline LVEF.

If the qualifying echocardiogram was done more than 6 months before randomisation, or the qualifying LVEF was assessed using MRI, a further transthoracic echocardiogram should be carried out soon after randomisation and this study submitted to the core lab to calculate baseline LVEF.

10.3. Qualifying EF flowchart:



10.4. Patients with recent MI

In the event of a recent myocardial infarction (clinical definition), assessment of qualifying LVEF should be based on a MRI or echocardiogram performed at least 4 weeks after the event.

When a completely new diagnosis is made of heart failure or ischaemic cardiomyopathy, it is recommended that the qualifying echocardiogram or MRI be performed after heart failure medication has been initiated.

10.5. Echo core lab

All trial echocardiograms should be performed in accordance with the minimum standard set out by the British Society of Echocardiography. Baseline, 6-month and 12-month echocardiograms will be anonymised and submitted to an independent echocardiography core laboratory (at Guy's and St Thomas' Hospital, London, UK), which will determine LV volumes and EF using a Simpson's biplane method, for evaluation of the major secondary outcome. The core laboratory will be blinded to treatment assignment as well as to the timing of the studies in relation to randomisation. Core laboratory analysis will also include the degree of mitral regurgitation and segmental wall motion.

In cases where endocardial definition is suboptimal, please consider using intravenous contrast to improve delineation.

Echo core lab analysis will include estimation of end diastolic and end systolic volumes, calculation of LVEF using the Simpson's biplane method and grading segmental wall motion.

10.6. Angiography core lab

At select sites, both pre-randomisation and trial procedure coronary angiogram and angioplasty images will be transferred to an angiography core laboratory (at Golden Jubilee National Hospital, Glasgow, UK) via anonymised optical media. Each participant's pre-randomisation BCIS-1 JS and PCI procedural success will be independently validated by the core laboratory. The core laboratory will calculate a number of other scores reflecting the anatomic complexity of coronary disease, the extent of effective revascularisation and the complexity of CTO lesions.

This data will be used to conduct a number of sub-analyses to identify predictors of benefit for the primary and secondary outcomes. The core laboratory will subsequently provide the relevant data to the Sponsor and CTU at the London School of Hygiene & Tropical Medicine for analysis against the data held in the eCRF.

11. Assessment of Viability

Eligibility for the trial will require demonstration of myocardial viability in at least 4 dysfunctional myocardial segments, subtended by diseased coronary arteries that can be treated by PCI.

Regional function at rest will be scored according to the American Heart Association 17 segment-5 grade scoring model (1: normal; 2: mildly hypokinetic; 3: severely hypokinetic; 4: akinetic; 5: dyskinetic)(43). Segments with resting wall motion abnormalities (grade 2-5) will be considered dysfunctional.

Segmental viability can be determined by any imaging modality. The criteria for determining viability will be based on local protocols and as determined by the local imaging specialist,

using all available information; the following are guidelines for defining segmental viability in the REVIVED trial:

- DSE: improvement in contraction by at least one wall motion grade during low-dose Dobutamine stimulation, compared to resting wall motion (improvement by at least 2 grades if aneurysmal or dyskinetic at rest).
- MRI: ≤25% transmural late gadolinium-enhanced (LGE) images. Adjudication of viability in segments with 26-50% transmurality will be at the discretion of the recruiting centres, on the basis of other available information, including of contractile reserve during low-dose Dobutamine stimulation.
- SPECT: tracer activity on the delayed images that is ≥50% of the activity in the segment with maximal activity (in rest-redistribution protocols).
- PET: perfusion – metabolism (FDG) mismatch.

Imaging and intervention specialists at each participating centre will adjudicate segmental viability and the feasibility of revascularising the relevant segments, to determine whether an individual patient will be eligible for randomisation.

12. Randomisation

Potential patients will be reviewed by the Principal Investigator before randomisation with all available tests/notes to confirm eligibility.

Once the eligibility of a patient is confirmed by the trial coordinators and written informed consent obtained, randomisation will be carried out via an online web based system. Randomisation of the treatment assignment will be stratified by centre using randomly permuted blocks of varying size, with 1:1 allocation between the PCI and OMT arms.

There is no time limit from randomisation to PCI. However, it is recommended that index PCI be carried out as close as possible to randomisation to minimise the incidence of major adverse cardiovascular events (MACE) prior to the assigned treatment. Clinical events that occur after randomisation but before planned PCI will be attributed to the assigned treatment on an intention-to-treat basis.

13. Percutaneous Coronary Intervention

13.1. Adjunctive therapy and devices

PCI will be performed according to local protocols. Dual antiplatelet therapy should be given in all cases, with pre-loading, and the post-PCI duration based on the individual's bleeding risk and local/national guidelines. In general, drug-eluting stents are recommended, but in patients who have an indication for long-term formal anticoagulation (e.g. for concurrent atrial fibrillation, LV thrombus or venous thromboembolic disease), the choice of stent type should be based on their suitability for medium-term combined antiplatelet and anticoagulation therapy.

13.2. Completeness of Revascularisation

It is strongly recommended that PCI is considered and, if feasible, attempted on all significant coronary lesions in major proximal coronary vessels (or side branches >2.5mm in diameter) subtending viable myocardium. Lesion significance is defined as >70% diameter stenosis on angiography or for lesions between 50 and 70% diameter stenosis, when accompanied by

demonstrable reversible ischaemia on invasive or non-invasive testing. Planned target lesions will need to be identified by the operator and recorded by the trial coordinator before the procedure.

Patients who meet inclusion criteria and have CTO of coronary arteries subtending viable myocardial segments *should* be considered for REVIVED, provided that the PCI operators predict a high likelihood of successfully reopening these vessels. It is recommended that dedicated CTO operators, in units that have this degree of specialisation, undertake such cases.

The coronary disease burden at baseline and the degree of final revascularisation will be characterised by the BCIS-1 JS and Revascularisation Index (RI) (44), where RI = $(JS_{pre} – JS_{post})/JS_{pre}$.

13.3. **Staged PCI**

A single stage strategy should be employed where possible. However, provisional staging could be considered in patients with renal dysfunction, complex coronary disease (including chronic total occlusions) or if it is felt during PCI that deferring intervention to one or more vessels is in the patient's best interests (e.g. due to unexpected high contrast volumes or procedural complications during PCI to the first vessel). Staging must be pre-specified at the index procedure.

Urgent revascularisation before the planned 2nd stage procedure will be considered a major endpoint(45).

13.4. **PCI Definitions**

Target Vessel Success	<30% residual stenosis and Thrombolysis in Myocardial Infarction (TIMI) III flow in target vessel.
Procedural Success	Target vessel success in ALL treated vessels.
Major Procedural Complication	VT/VF requiring defibrillation. Cardiorespiratory arrest requiring assisted ventilation. Prolonged hypotension. (Prolonged hypotension = Mean arterial pressure ≤75 mmHg for >10 min despite fluid resuscitation or requirement of inotropic support / IABP / left ventricular assist device (LVAD) to maintain augmented mean arterial pressure >75 mmHg).
Major Bleeding	≥4 g/dL decrease in haemoglobin relative to baseline (if transfusion required, 1 unit of packed cells / whole blood considered equivalent to 1 g/dL drop in haemoglobin) or intra-cranial haemorrhage.
Minor Bleeding	2-4 g/dL decrease in haemoglobin relative to baseline.
Access complication	Haematoma/limb ischaemia requiring surgical or percutaneous intervention. Documented false aneurysm / arterial occlusion.

Acute Kidney Injury (AKI)	An increase in serum creatinine to >150% of the pre-PCI level, within 48 hours of PCI.

14. Optimal Medical Therapy

It is recommended that patients are **initiated** on medical therapy prior to randomisation, however the doses **do not necessarily need to have been optimised** before a patient can be randomised.

In order to ensure that patients in both arms of the trial receive optimal medical and device therapy, there is a nominated heart failure lead at each participating centre who is actively involved in patient selection and monitoring of therapy during the course of the trial. Furthermore a trial Medical Therapy Committee has been established, which will review available evidence and guidelines at least annually and refine recommendations to ensure that drug and device therapy given to all patients in the trial remains optimal and contemporary. Each site is provided with a standard operating procedure for delivering and monitoring OMT, which sets out classes of drugs appropriate for trial patients, including heart failure therapies (such as angiotensin-converting-enzyme (ACE) inhibitor or angiotensin receptor blocker +/- neprilysin inhibitor, betablocker and mineralocorticoid receptor antagonist(13)) and secondary prevention for atherosclerosis (including statin and antiplatelet agent) as well as recommended treatment targets (including lipid profile, HbA1c, resting heart rate). Formal anticoagulation for LV thrombus detected on imaging or as prophylaxis for severe LV dysfunction / dyskinesis is at the discretion of the treating physician. Initiation of the above treatments, dose-titration and relevant monitoring is per local heart failure protocols.

15. ICDs and Cardiac Resynchronisation

ICD implantation is not a requirement for inclusion in REVIVED.

Local guidelines should be followed when deciding on device therapy but the decision to implant (or not implant) a device should be made before randomisation. This plan will be documented in the CRF at baseline.

In evaluating whether an ICD should be implanted, physicians should assume that all patients would be assigned to OMT alone, to minimise the risk of trial outcomes being affected by treatment bias.

16. Data collection and follow-up

16.1. Tests required for eligibility

The following tests are required for identifying and screening patients. These are all standard of care tests and must be performed before patient consent:

- Demographics and medical history
- Coronary angiogram
- Viability assessments
- LVEF assessment – in the case of patients with ACS, this must be done at least four weeks after the ACS
- Creatinine and electrolytes

16.1.1. Time limits for screening tests

Eligibility criteria	**Test**	**Time limit**
Extensive coronary disease	Angiogram	Clinically valid
LVEF ≤35%	Resting LVEF assessment	1 year prior to randomisation (at least 4 weeks after ACS)
Viability in at least 4 dysfunctional segments, that can be revascularised by PCI	Viability assessment	Clinically valid

16.2. **Trial Checklist**

	Tests required for eligibility	Baseline	Pre-PCI as per local protocol ‡	At discharge (up to 16 hours) post-PCI ‡	48 hrs post-PCI ‡	At 6 months post randomisation	At 1 year after randomisation	At 2 years after randomisation	Yearly follow-up	End of trial follow-up
Clinical assessments (standard of care)										
Demographics and medical history	**X**									
Coro Angio	**X**									
Viability assessment	**X**									
LVEF Assessment	**X***									
Echo		**X†**								
ICD check		**X**				**X**	**X**	**X**		
FBC	**X**			**X**						
Creatinine‡ & Electrolytes	**X**			**X**						
HbA1C		**X**								
Full Lipid Profile		**X**								
CK			**X**	**X**						
Trop T/I		**X**	**X**	**X**		**X**	**X**			
ECG		**X**		**X**						
AKI					**X**					
Trial specific assessments										
Echo						**X**	**X**			
BNP / NT-proBNP		**X**				**X**	**X**	**X**		
NYHA/CCS		**X**				**X**	**X**	**X**		
EQ-5D-5L		**X**				**X**	**X**	**X**	**X**	**X**
KCCQ		**X**				**X**	**X**	**X**		
Primary Endpoint				**X**		**X**	**X**	**X**	**X**	**X**
Secondary Endpoints						**X**	**X**	**X**	**X**	
SAEs				**X**		**X**	**X**	**X**		
Cardiac Medication		**X**		**X**		**X**	**X**	**X**		

‡ If PCI is staged, please collect for each stage of the procedure

* In the case of patients with Acute Coronary Syndrome (ACS), must be >4 weeks after ACS

† This echo is only required if there is no available echo within 6 months of randomisation and >4 weeks after ACS

Baseline (up to 6 months prior to randomisation):

- Echo
- Viability assessment report (at select sites only)
- ICD check
- HbA1C
- Full lipid profile
- BNP / NT-proBNP
- ECG
- NYHA/CCS
- EuroQol EQ-5D-5L
- Kansas City Cardiomyopathy questionnaire (KCCQ)
- Cardiac medication
- Troponin T/I (OMT arm only)

Pre-PCI as per local protocol (If PCI is staged please collect for each stage of the procedure):

- Troponin T/I or CK

At discharge (or up to 16 hours) post-PCI (If PCI is staged please collect for each stage of the procedure):

- Death
- Creatinine & Electrolytes
- Troponin T/I or CK
- ECG
- Unexpected serious adverse events
- Cardiac medication

48 hours after PCI (If PCI is staged please collect for each stage of the procedure):

- AKI

6 months after randomisation (clinical follow-up):

- Death
- Hospitalisation due to heart failure
- MI
- Major bleeding
- Unplanned further revascularisation
- LVEF on echocardiography
- ICD check
- BNP / NT-proBNP
- NYHA/CCS
- EuroQol EQ-5D-5L
- Kansas City Cardiomyopathy questionnaire (KCCQ)
- Hospitalisation (at St Thomas' only)
- Unexpected serious adverse events
- Cardiac medication
- Troponin T/I

1 year after randomisation (clinical follow-up):

- Death
- Hospitalisation due to heart failure
- MI

- Major bleeding
- Unplanned further revascularisation
- LVEF on echocardiography
- ICD check
- BNP / NT-proBNP
- NYHA/CCS
- EuroQol EQ-5D-5L
- Kansas City Cardiomyopathy questionnaire (KCCQ)
- Hospitalisation (at St Thomas' only)
- Unexpected serious adverse events
- Cardiac medication
- Troponin T/I

2 years after randomisation (clinical follow-up):

- Death
- Hospitalisation due to heart failure
- MI
- Major bleeding
- Unplanned further revascularisation
- ICD check
- BNP / NT-proBNP
- NYHA/CCS
- EuroQol EQ-5D-5L
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Hospitalisation (at St Thomas' only)
- Unexpected serious adverse events
- Cardiac medication

Years 3 to 8 after randomisation (telephone follow-up):

- Death
- Hospitalisation due to heart failure
- MI
- Unplanned further revascularisation
- Hospitalisation (at St Thomas' only)
- EuroQol EQ-5D-5L

Final follow-up at end of trial (telephone follow-up):

- Death
- Hospitalisation due to heart failure
- EuroQol EQ-5D-5L

16.3. Data Handling

16.3.1. Data Collection

Data will be collected electronically via a web-based case report form (eCRF). In addition, hard copies of ECGs should be maintained at each centre in a physical CRF.

eCRFs should be completed within 2 weeks of each trial milestone (hospital discharge, 6 months etc.), where possible.

Principal Investigators at each site have overall responsibility for the accuracy, completeness and legibility of the data entered onto the eCRF and all associated reports.

16.3.2. Adverse Events

Expected adverse events (see section 4.4 for endpoint definitions) should be reported in the eCRF. An additional SAE form is not required.

Unexpected adverse events (see section 5 for requirements) should be reported on the relevant SAE or NSAE forms and faxed to the CTU within 7 days of notification for SAE and 14 days of notification for NSAE.

16.3.3. Participant ID Log

A list of all patients enrolled into the trial should be maintained by each centre, containing patient identification numbers, full names, dates of birth and dates of enrolment in the trial, which could be used for unambiguous identification of each patient if required. The patient's enrolment in a trial must also be recorded in the patient's medical record and the general practitioner notified accordingly.

16.3.4. Mortality Tracking

In addition to telephone and hospital follow-up, mortality tracking will be carried out via NHS Digital for up to 5 years from enrolment of the last patient.

16.4. Novel coronavirus (COVID-19) outbreak

Due to the novel coronavirus (COVID-19) outbreak in the UK, some of the trial follow-up procedures may need to change or be delayed during this period.

Sites may delay follow-up appointments and telephone calls as appropriate during this time.

For sites where all non-urgent medical appointments are cancelled/ suspended, follow-up at 6 months, 1 year and 2 years will move from in person to by telephone. Any tests or procedures that need to be done in person, e.g. echocardiograms, will either be done at a later date or marked as 'not performed'. Follow-up at all other time points will continue as per protocol.

Delayed visits and tests will not be considered as protocol violations during this period.

17. Health Economic Analysis

A formal health economic analysis will be carried out under the leadership of Prof Mark Sculpher, who heads the team for the Economic Evaluation of Health Technology Assessment at the Centre for Health Economics at the University of York, UK.

REVIVED-BCIS2 will provide a vehicle to collect data to support a cost-effectiveness analysis of PCI in heart failure. Data will be collected on NHS resource use including inpatient days in hospital, use of cardiovascular medication and devices and subsequent cardiovascular procedures. These data will be collected via record forms and questionnaires to patients.

In addition, data will be collected on health-related quality of life using the EQ-5D-5L instrument, a generic, preference-based measure. This will be administered at baseline, at 6-month follow-up and at annual intervals subsequently. Resource use will be valued in

monetary terms using routine unit cost data relevant to the NHS. These will include NHS Reference Costs, British National Formulary drug prices and the Personal Social Services Research Unit (PSSRU) survey of unit costs.

In terms of analysis, the economic evaluation will consist of a description of resource use, costs and EQ-5D-5L data collected within the trial. A formal cost effectiveness of PCI in this population will be undertaken using a decision analytic framework which is necessary for two main reasons. Firstly, to extrapolate costs and benefits over a longer-term time horizon than that implied by the follow-up period of RCTs. For example, any impact of PCI on mortality will need to be expressed in terms of additional survival duration which requires a model to reflect long term all-cause mortality risks for this patient group. The second reason for using a modelling framework is that it provides a means of synthesising the evidence collected in REVIVED-BCIS2 with any other relevant evidence available in the literature. Most importantly other RCTs of PCI in heart failure will need to be systematically identified, synthesised with REVIVED-BCIS2 if appropriate and used to assess cost-effectiveness. The structure of the model will be informed by a review of recent modelling studies in the field of cardiovascular disease in general and in heart failure in particular. However, it is anticipated that it will be a cohort model with states representing death and different levels of heart failure symptoms. The modelling approach will also reflect work undertaken by the health economics team in the cardiovascular field using individual patient data from randomised trials(47, 48). The model will be extensively validated to ensure that it can replicate the results of the REVIVED-BCIS2 trial and generates longer-term estimates of survival and costs consistent with available epidemiological evidence in this area.

The cost effectiveness analysis will adhere to the reference case defined by the National Institute for Health and Clinical Excellence for technology appraisal(49). Key features will include the quantification of health benefits in terms of quality-adjusted life years (QALYs) and the use of an NHS cost perspective. Standard decision rules(50) will be used to assess cost effectiveness and extensive sensitivity analysis will be undertaken (probabilistic and deterministic) to assess the implications of uncertainty in the available evidence for cost-effectiveness. Heterogeneity in cost effectiveness between different sub-groups of patients will be assessed using methods consistent with those applied to clinical outcomes.

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Appendix 1: Glossary

***Angiotensin-Converting-Enzyme (ACE) Inhibitor*:** A drug used for the treatment of high blood pressure and sometimes heart failure.

Acute Coronary Syndrome (ACS): This refers to a group of symptoms caused by obstructed coronary arteries. The symptoms include 'crushing chest pains', nausea and sweating. These symptoms usually occur as part of a heart attack.

***Activating Clotting Time (ACT)*:** This is a coagulation test, taken after high-dose heparin has been given (i.e. during an angioplasty).

***Adenosine*:** A short acting drug used to slow down the heart, often in order to determine a fast rhythm.

Akinetic: This refers to the heart muscles inability to move.

Aldosterone Antagonist: A diuretic used in the management of heart failure (e.g. Spironalactone).

American Heart Association (AHA) 17 segment: This refers to the 17 angles/pictures of the heart that will be captured in the echocardiogram (see definition) 5 Grade Scoring Model- This will be used to grade the severity of impaired movement to the heart muscle wall in each of the 17 angles.

Angiogram Procedure: where a small tube is inserted into the groin or wrist and is passed to the heart. Pictures are then taken of the heart arteries by X-ray to show any narrowing's.

Arrhythmia/Dysrhythmia: An abnormal heart rate caused by abnormal electrical activity- it may be too fast, too slow, regular or irregular.

Atherectomy (rotational): Minimally invasive surgery to remove atherosclerosis from a blood vessel.

Atherosclerosis: An accumulation of fatty materials causing the arterial vessel wall to thicken and contributing to the blockage of blood vessels.

Atrial Fibrillation (AF): A common irregular heartbeat caused by the top chambers in the heart (the atriums) quivering (fibrillating). This rhythm is often the cause of 'palpitations'.

Beta Blocker: A group of drugs that are often used to treat high blood pressure, irregular heart rates and/or heart failure. They act to lower blood pressure and slow the heart rate.

Biphasic Response: Two separate responses that are separated in time.

Biventricular pacemaker: A treatment for heart failure using a pacemaker or ICD to stimulate the right and left side of the heart causing the lower chambers of the heart (ventricles) to beat at the same time.

Brain Natriuretic Peptide (BNP): This is a measure of amino acids (proteins) in the blood that are released in patients with heart failure.

British Cardiovascular Interventional Society (BCIS-1) Jeopardy Score (JS): A scoring system that has been developed to predict procedural risk during PCI.

Cardiac Aneurysm: This refers to a bulging or pocketing on the wall of the inside of the heart, often the left ventricle. This often occurs slowly over a long period of time or as a result of a heart attack (not the same as a vessel aneurysm).

Cardiac Re-Synchronisation Therapy Defibrillator (CRT-D): A device used in patients with heart failure that helps to enhance the blood pumped out with each time the heart beats.

Cardiomyopathy: Heart muscle disease, a measurable deterioration of the myocardium.

Cellular integrity: When the cells in the myocardium are essentially still working, that they have maintained their viability.

Contractile Reserve: This is the ability of the myocardium to increase its contractibility when under 'stress' (i.e. during physical activity or a DSE - see stress echo definition).

Coronary Artery Bypass Graft (CABG) Surgery: To improve the blood flow to the heart. Arteries or vein from elsewhere in the body are grafted to the coronary arteries to bypass the narrowings and improve the blood supply to the heart muscle.

Coronary Artery Disease (CAD): A disease that results in the accumulation of fatty material/plaques forming on the artery vessel wall and restricting the blood flow through the vessel.

Creatinine Kinase (CK): A blood test that measures the presence of cardiac enzymes. These act as markers that can assist in the diagnosis of a heart attack.

Dobutamine: A specific inotropic drug that increases blood pressure by enhancing cardiac muscle contractility. (LD - Low Dose, HD - High Dose).

Dobutamine Stress Echocardiogram' (DSE): See 'Stress Echocardiogram'.

Dyskinetic: This refers to difficulty or abnormality in the movement of the heart muscle (could include slight movement/twitches).

Electrocardiogram (ECG): A test that records the electric activity of your heart. (ST elevation/depression, T wave, QRS complex - these terms represent aspects of an ECG reading).

Estimated Glomerular Filtration Rate (eGFR): This is a test to see how well the kidneys are working. It estimates how much blood is filtered by the kidneys over a given period of time.

HbA1c (Glycated Haemoglobin): This is a form of haemoglobin (see definition) that is used to measure the average level of glucose in the blood over a period of time.

Hibernating Myocardium: A segment of the myocardium where the contraction is affected due to tissue ischemia. Significantly it is potentially reversible through revascularisation. Segments that do have this potential are referred to as 'viable'.

Hypo contractility: This refers to the reduced ability of the heart/myocardium to beat.

Hypokinetic: This refers to reduced movement in the heart muscle.

Implantable Cardioverter Defibrillator (ICD): An ICD is made up of a battery and a small computer. All of the components of the ICD are sealed inside a metal can about the size of a small pager. Additionally, an ICD monitors your heart's rhythm and can deliver therapy such as small electrical impulses and/or shocks through the lead system depending on the need of your heart. If a fast heart rhythm is detected, these small electrical impulses and/or shocks can slow down your heart. An ICD is placed under the skin in the upper chest area during an operation.

Intra-aortic Balloon Pump (IABP): A mechanical device that supports the heart and helps to increase the oxygen supply to the heart muscle and the amount of blood the heart pumps out with each beat.

Left Ventricular Assist Device (LVAD): Mechanical circulatory device that either partially or fully replaces the function of a failing heart.

Left Ventricular Ejection Fraction (LVEF): Often given as a percentage, it is the volumetric fraction of blood pumped out of the left ventricle in the heart with each heartbeat.

Magnetic Imaging Resonance (MRI): A medical imaging technique used in radiology to visualise internal structures in the body. LGE - Late gadolinium-enhanced images is a more advanced MRI, 'Cine Data' or 'Cine MRI' is a four dimensional image taken using MRI.

Magnetic Resonance Perfusion Scan (MRP): A brain scan sometimes performed following carotid endarterectomy surgery.

Major Adverse Cardiovascular Event (MACE): This comprises of a non-fatal heart attack, stroke or a cardiovascular death.

Mitral Valve Regurgitation (MR): The leaking of the mitral valve of the heart, causing blood to flow in the reverse direction.

Myocardium: The middle of the three layers forming the wall of the heart. The cardiac muscle.

Myocardial Infarction (MI) or 'Heart attack': An interruption of blood supply caused by a blockage in the blood vessels to the heart leading to cell or tissue death (infarction).

Myocyte / Myogenic Contraction: This is a contraction of the heart initiated by the cells in the myocardium.

Myocardial Remodelling: This refers to the changes in shape, size and structure to the myocardium surrounding the ventricles. This often happens as a result of a heart attack (global/regional refer to the area of myocardium that has been remodelled and cellular/ultrastructural refers to the extent of remodelling).

New York Heart Association (NYHA): A simple way of classifying the extent of heart failure using physical activity, chest pain and breathless as a measure.

Optimal Medical Therapy (OMT): This includes the best medication (tablets) that are currently available for heart failure, at doses that are individually tailored. This strategy

often also involves insertion of a special type of pacemaker (called a biventricular pacemaker, which may also function as an ICD).

Percutaneous Coronary Intervention (PCI): This procedure is used to treat the narrowed coronary arteries of the heart. A small tube is inserted in the groin or wrist and advanced to the heart. Small balloons and stents are used to open up the narrowings and improve blood flow to the heart muscle. This is sometime also known as Coronary Angioplasty.

Permanent Pace Maker (PPM): A medical device where electrodes are in contact with the heart muscle wall and send electrical impulses that cause contractions to regulate the beating of the heart.

Positron Emission Tomography (PET): An imaging technique that produces 3D images of functional processes in the body.

Proximal/Mid/Distal: These terms refer to the location within a coronary vessel - written in order from the top of the vessel (nearest the aorta) down toward the apex.

Regional Wall Motion (RWM): This refers to an abnormality in the movement of a region of the heart muscle. Scoring will be done using the wall motion scoring index.

Revascularisation: 'To restore blood supply'. This refers to a PCI or CABG.

Single Photon Emission Computed Tomography (SPECT): A type of nuclear imaging that shows how blood flows to tissues and organs.

Stress Echocardiogram (SE): A test that uses sound waves to visualise the beating of the heart when responding to 'stress' i.e. physical activity. Physical activity can be simulated using a drug called Dobutamine (see definition). This is sometimes referred to as a 'Dobutamine Stress Echocardiogram' (DSE).

Trans Thoracic Echocardiogram (TTE): A test that uses sound waves to visualise the beating of the heart using a non-invasive technique; a probe is placed on the chest and can pick up the sound waves through the chest wall.

Ventricular Fibrillation (VF): The heart is not beating effectively as the ventricles instead of contracting in a coordinated fashion are instead quivering (fibrillating). This rhythm is not compatible with life.

Ventricular Tachycardia (VT): A heart rhythm where the ventricles in the heart are beating very fast.

Wall Motion Score Index (WMSI): A score measured following an echocardiogram (see definition) used to assess the movement of the left ventricle. It will be the average of each score taken using the AHA grading scale from 17 views of the heart.