



REvascularisation for **I**schaemic
VEntricular **D**ysfunction
(REVIVED-BCIS2)

Trial Protocol Version 7

Sponsored by King's College London

Funded by NIHR HTA CET

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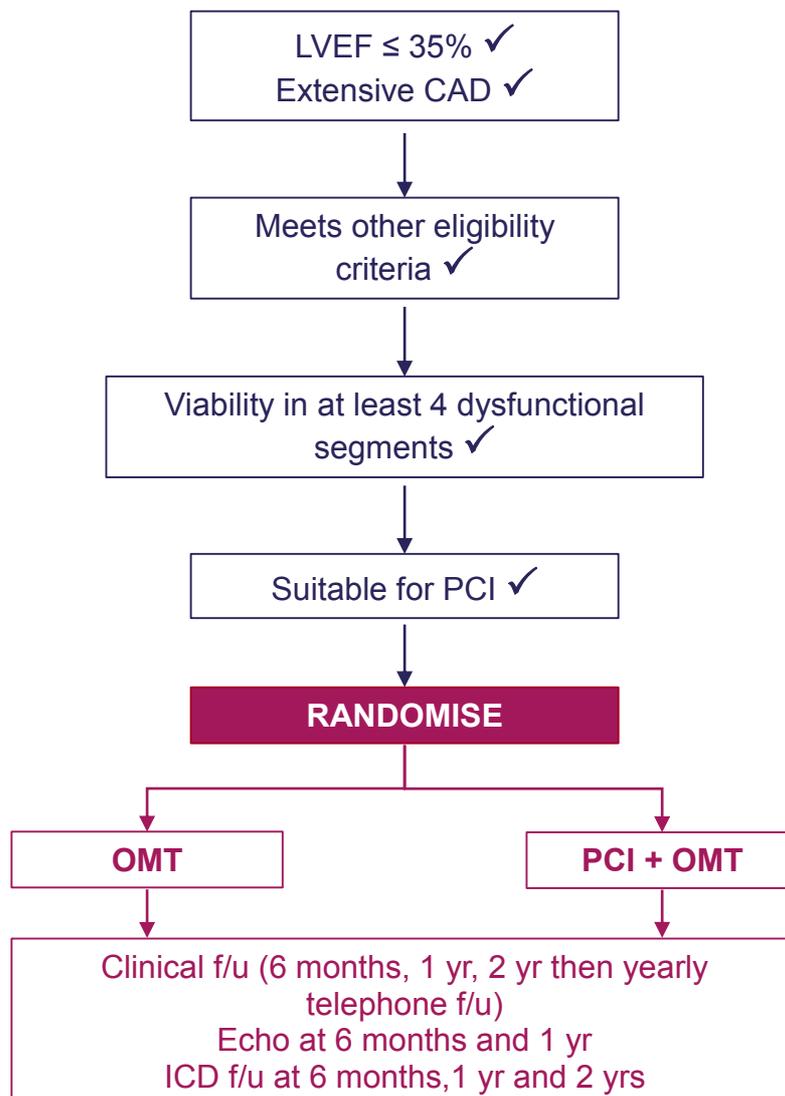
1. Trial Summary

1.1. Protocol Summary

| | |
|---------------------|---|
| Trial Title | Revascularisation for Ischaemic Ventricular Dysfunction (REVIVED-BCIS2) |
| Aim | To evaluate the efficacy and safety of percutaneous coronary intervention compared to optimal medical therapy 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 NYHA Functional Class LVEF on echocardiography at 6 months and 1 year Hospitalisation for heart failure All-cause death Cardiovascular death Acute myocardial infarction Appropriate ICD therapy Unplanned further revascularisation Canadian Cardiovascular Society (CCS) class NHS resource use Brain natriuretic peptide (BNP or NT-proBNP) level Major bleeding |
| Inclusion Criteria | LVEF \leq 35% Extensive coronary artery disease Viability in at least 4 dysfunctional myocardial segments, that can be revascularised by PCI |

| | |
|---------------------------|---|
| Major Exclusion Criteria | Acute myocardial infarction < 4 weeks prior to randomisation (clinical definition) Decompensated heart failure requiring inotropic support <72 hours prior to randomisation Any contraindication to PCI |
| Sample Size and Enrolment | n=700 Start date: 1 st June 2013 Recruitment start date: 1 st September 2013 Recruitment end date: 1 st March 2017 Follow-up end date: 1 st March 2019 Number of centres: 30-35 (listed in appendix 1) |

1.2. Trial Flowchart



1.3. Trial Organisation

1.3.1. NIHR HTA CET Grant applicants

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

Mr Tim Clayton, London School of Hygiene and 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 and Tropical Medicine

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

Dr Rod Stables, Cardiologist, Liverpool heart and Chest Hospital

Dr Divaka Perera, King's College London

Ms Liz Bestic, Consumer representative

Mrs Paula Young, Consumer representative

1.3.3. Project Management Group (PMG)

Dr Divaka Perera, King's College London

Mr Tim Clayton, London School of Hygiene and Tropical Medicine

Mrs Rosemary Knight, London School of Hygiene and Tropical Medicine

Mr Steven Robertson, London School of Hygiene and Tropical Medicine

Mr Richard Evans, London School of Hygiene and Tropical Medicine

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

Mrs Lucy Clack, Guy's and St Thomas' Hospital, London

Miss Sophie Jones, Guy's and St Thomas' Hospital, London

Miss Rebecca Matthews, London School of Hygiene and Tropical Medicine

1.3.4. Clinical Trials Unit (CTU)

London School of Hygiene and Tropical Medicine

1.3.5. Data and Safety Monitoring Committee (DSMC)

Dr Peter Ludman, Consultant Cardiologist, Birmingham (chair)

Dr Suzanna Hardman, Consultant Cardiologist, The Whittington Hospital, London

Dr Louise Brown, Senior Statistician, MRC Clinical Trials Unit at UCL

The DSMC is supported by Mr Simon Newsome, Statistician at the CTU

1.3.6. Clinical Events Committee (CEC)

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

+ members TBC

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 Kapetenakis, Consultant Cardiologist, St Thomas' Hospital, London

1.3.8. Recruiting Centres

At each site;

Heart Failure lead

PCI lead

(One of which will be designated as the PI and the other as a co-investigator)

Trial Coordinator

A list of sites is provided in Appendix 1

2. Background

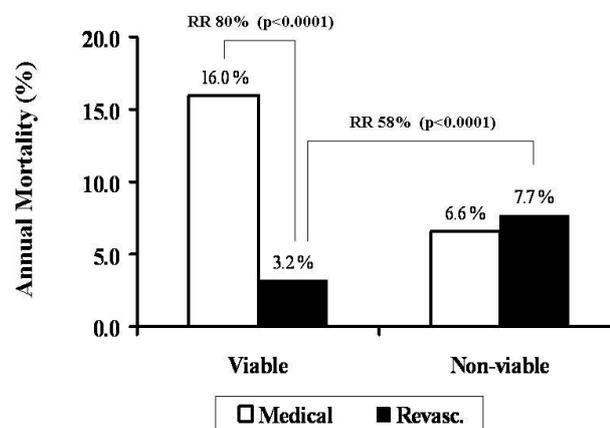
2.1. Epidemiology

In 2002, it was estimated that approximately 900,000 individuals in the United Kingdom 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 20µg/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 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 studies in this field. 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) versus optimal medical therapy 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 a class I indication for treatment of impaired LV function in the presence of significant proximal coronary disease, regardless of whether the patient has angina(13). 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 CASS registry included 651 (of a total of approximately 20,000) patients who had a 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 (EF<25%), where angina was the predominant symptom, rather than heart failure(14). 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(15). However, the results of the STICH trial, published in April 2011, may lead to reconsideration of these guidelines(16). The STICH trial (the first randomised controlled trial of any form of revascularisation in ischaemic cardiomyopathy) randomised 1212 patients with left ventricular impairment (EF<35%) to either CABG surgery (with medical therapy) or to medical therapy alone; patients with left main coronary disease were excluded, as were those with significant angina (\geq class III). CABG failed to reduce all-cause mortality (the primary endpoint) compared to medical therapy alone, at a mean follow-up duration of 4.7 years (36% vs. 41% respectively; HR 0.86, 95% CI 0.72-1.04, $p = 0.12$). The major composite secondary endpoints were significantly lower in the CABG group compared to medical therapy alone: a) all-cause mortality or hospitalisation for heart failure (48% vs. 54%; HR 0.84, 95% CI 0.71–0.98, $p=0.03$), b) all-cause mortality or hospitalisation for cardiovascular causes (58% vs. 68%; HR 0.74, 95%CI 0.64–0.85, $p<0.001$), c) all-cause mortality or further revascularisation (39% vs. 55%; HR 0.60, 95% CI 0.51 – 0.71, $p<0.001$). These results indicate that mortality and morbidity from heart failure remain unacceptably high, despite optimal medical therapy, but that CABG surgery failed to have a significant impact on mortality, in the setting of this trial.

There are several possible explanations for the lack of mortality benefit with CABG surgery in STICH(17). Firstly, the surgical procedure itself was associated with increased mortality (30-day mortality was 4% in the CABG group, compared to 1% in the medical therapy group; HR 3.2; 95% CI 1.4-7.5, $p=0.008$), with the number of deaths in this group outnumbering that of the medical therapy group for two years from randomisation. 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%, the risk increasing with age, comorbidities and degree of LV impairment(18). 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(19, 20). It is conceivable that the increased mortality associated with surgery may have ameliorated the benefits of revascularisation in STICH. Although untested in a randomised setting as yet, it is possible that PCI may allow the benefits of revascularisation to be realised without incurring the added mortality cost (see below). Secondly, the eligibility criteria used in STICH may not have identified the subset of patients with ischaemic cardiomyopathy who were most likely to gain benefit. Viability testing is routinely used in clinical practice to distinguish patients with potential for

myocardial recovery with irreversible myocardial scarring but testing for viability was not mandated in the STICH protocol; various modalities of viability testing were used by clinicians in only approximately 50% of all cases. 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 PCI and CABG surgery for patients with symptomatic coronary disease or evidence of significant reversible ischaemia, but most of the large randomised trials excluded patients with impaired left ventricular function (EF<30%)(21-23). Less than 2% of all patients included in the largest and most recent randomised controlled trial, SYNTAX, had significant LV impairment (EF<30%) at baseline(24). A metaanalysis 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(25). 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 (BCIS-1 Jeopardy Score 10/12)(26). 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%(27). 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 BCIS1 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(28).

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, 29). The 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(30). 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(31). 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(32). 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 randomised controlled trial. 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) versus optimal medical therapy alone in patients with heart failure and viable myocardium, and is expected to definitively resolve the role of this treatment.

3. Hypothesis

Compared to optimal medical therapy (OMT) alone, PCI improves event free survival in patients with ischaemic cardiomyopathy and viable myocardium.

4. Endpoints

An independent 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 (up to a maximum of 66 months)

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
Appropriate ICD therapy
Unplanned further revascularisation
Canadian Cardiovascular Society (CCS) class
NHS resource use
Brain natriuretic peptide (BNP or NT-proBNP) level
Major bleeding

4.4. Endpoint Definitions

| | |
|-------------------------------------|--|
| Acute Myocardial Infarction (33-36) | <p>1. Spontaneous MI (>48 hrs after PCI/CABG)</p> <p>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*) AND symptoms consistent with ischaemia OR dynamic ECG changes (including >1mm ST elevation, new Left Bundle Branch Block (LBBB) >1mm ST depression, >3mm T wave inversion)</p> <p>2. Peri-procedural MI (<48 hrs after PCI/CABG)</p> <p>Troponin (T or I) > 5 x 99th percentile upper reference limit* following PCI. Troponin (T or I) > 10 x 99th percentile upper reference limit following CABG surgery</p> <p>3. Sudden death</p> <p>Cardiac arrest accompanied by new ST elevation/LBBB on ECG and/or evidence of fresh coronary thrombus at autopsy/angiography</p> <p>*Due to improving sensitivities of Troponin assays, all results will be referenced against the 99th percentile upper reference limit. To take account of the change in the universal definition of MI in 2012 and to facilitate comparison with literature before 2012, pre-specified exploratory analyses will be carried out, of MI defined according to multiples of the 99th percentile:1-3, 3-5, 5-10 and >10.</p> |
|-------------------------------------|--|

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| Hospitalisation for heart failure (37) | <p>Hospital admission (lasting >24 hours) primarily for deteriorating symptoms of heart failure, with clinical and/or radiographic signs of heart failure, treated with at least one of the following: intravenous diuretic therapy, intravenous vasodilators, inotropic support, left ventricular assist device/ intra-aortic balloon pump (IABP) or cardiac transplantation.</p> <p>Heart failure during the PCI procedure itself is defined as prolongation of the planned admission by at least 24 hours due to acute heart failure requiring treatment with intravenous diuretic/vasodilator/inotropes or support device. Prolongation of hospital admission in patients who have prophylactic pre-PCI insertion of a support device (IABP or Impella) should not be recorded as having a heart failure hospitalisation UNLESS there are features of heart failure requiring intravenous diuretic / vasodilator / inotropes.</p> <p>Elective admission for implantation or revision of ICD/cardiac resynchronisation therapy (CRT) devices will NOT constitute an endpoint. A BNP level will be measured at hospital admission and this result (along with the baseline BNP level) will be made available to the clinical events committee who will adjudicate each potential heart failure hospitalisation event.</p> |
| Unplanned revascularisation | <p>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).</p> <p>OMT group: any revascularisation by PCI or CABG</p> |
| 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 |

| | |
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| Major Bleeding | <p>Major bleeding will be defined using the Bleeding Academic Research Consortium (BARC) categories below:</p> <p>Type 3</p> <p>Type 3a</p> <ul style="list-style-type: none"> • Overt bleeding plus haemoglobin drop of 3 to <5g/dL (provided haemoglobin drop is related to bleed) • Any transfusion with overt bleeding <p>Type 3b</p> <ul style="list-style-type: none"> • Overt bleeding plus haemoglobin drop \geq 5g/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 drugs <p>Type 3c</p> <ul style="list-style-type: none"> • Intracranial haemorrhage (does not include microbleeds or haemorrhagic transformation; does include intraspinal) • Subcategories; confirmed by autopsy or imaging or LP • Intra-ocular bleed compromising vision <p>Type 4: CABG-related bleeding</p> <ul style="list-style-type: none"> • Perioperative intracranial bleeding within 48 hours • Reoperation following closure of sternotomy for the purpose of controlling bleeding • Transfusion of \geq 5 units of whole blood or packed red blood cells within a 48 period • Chest tube output \geq 2 L within a 24 h 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' <p>Type 5: fatal bleeding</p> <p>Type 5a</p> <ul style="list-style-type: none"> • Probable fatal bleeding: no autopsy or imaging confirmation, but clinically suspicious <p>Type 5b</p> <ul style="list-style-type: none"> • 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 an SAE or NSAE depending on their severity.

5.2. Unexpected Serious Adverse Events

SAEs should be reported to the Clinical Trials Unit 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 non-serious adverse events 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 Clinical Trials Unit 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 Clinical Trials Unit, London School of Hygiene and 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 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:

Poor left ventricular function (EF≤35%)
Extensive coronary disease*

AND

Viability in at least 4 dysfunctional myocardial segments that can be revascularised by PCI

** In general, patients who do not have bypass grafts will be eligible if they have at least proximal LAD disease or at least proximal 2 vessel disease.*

For patients with patent bypass grafts, or in cases where the extent of CAD is uncertain, the BCIS Jeopardy Score (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. Myocardial infarction <4 weeks prior to randomisation (clinical definition)
2. Decompensated heart failure requiring inotropic support, invasive or non-invasive ventilation or IABP/left ventricular assist device (LVAD) therapy <72 hours prior to randomisation
3. Sustained VT/VF or appropriate ICD discharges <72 hours prior to randomisation
4. Valve disease requiring intervention
5. Contraindications to PCI
6. Age <18 yrs
7. 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 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. The primary endpoint in REVIVED-BCIS2 will be measured over the entire trial duration (i.e. up to 66 months for some patients) with a minimum follow-up duration of two years, thus increasing the number of events. A trial of 700 (350 in each group) 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 to 27% of patients with an event in the PCI group at two years. These calculations are based on patient accrual for 42 months and minimum follow-up of 24 months.

The above predicted event rates are conservative in relation to the existing literature(8, 16, 26, 39), and 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. 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.

The trial is expected to have very good power to detect differences in Quality of Life (one of the major secondary outcomes).

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 \geq 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 prespecified in the analysis plan and are likely to include groups stratified by age, the extent of coronary disease (BCIS-1 score <12 vs. ≥12), degree of LV dysfunction (EF<20% vs. ≥20%), diabetes, NYHA class (<3 vs. ≥3) and ischaemic burden (<4 segments on DSE vs. ≥4 segments). 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 Data and Safety Monitoring Committee (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

The CTU will collect a snapshot of screening twice a year. Full detailed screening logs of all patients with extensive CAD and EF \leq 35% considered for the trial will be collected. A notification email with an electronic screening log template will be sent out in the month prior to requiring a snapshot. Only patients considered in that month are required to be entered on the screening log.

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
- The resting stage of a stress echocardiogram
- Cardiac MRI

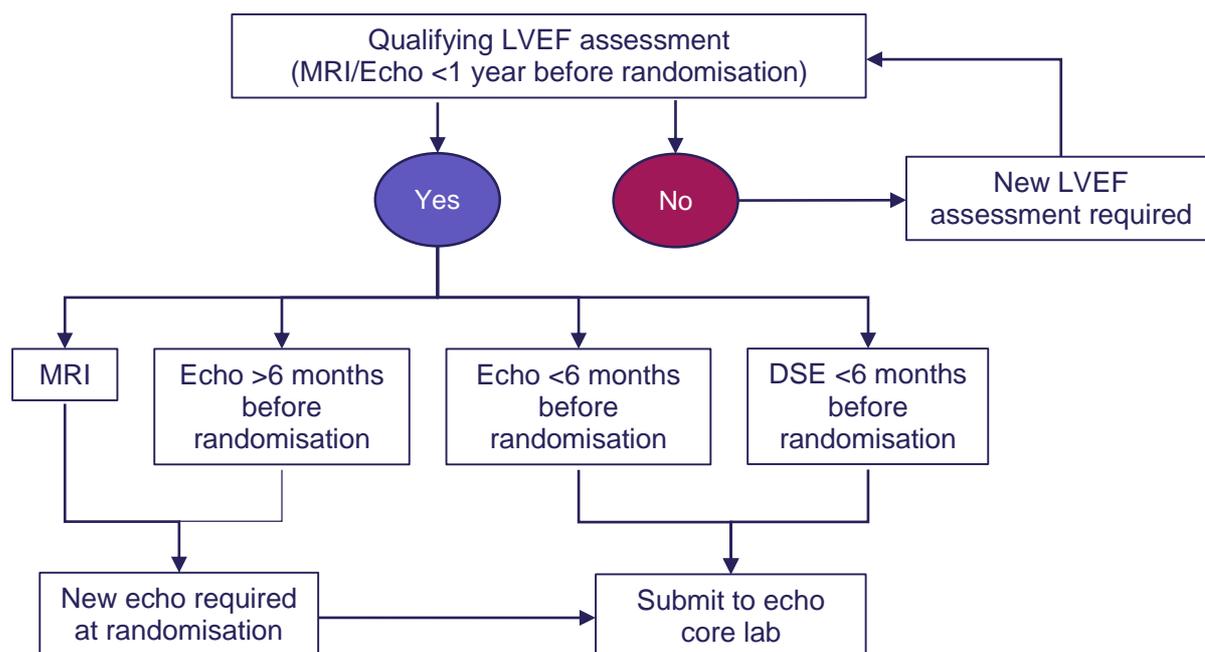
The qualifying assessment **must** have been carried out less than 1 year before randomisation. Estimation of LVEF and adjudication of eligibility for enrolment in will be done by each participating centre, using locally agreed protocols.

10.2. Baseline echocardiogram

If the qualifying echo 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 echo was done more than 6 months before randomisation, or the qualifying LVEF was assessed using MRI, a further transthoracic echocardiogram should be carried out at (or 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 echo or MRI be performed after heart failure medication has been initiated.

10.5. Echo core lab

In order to ensure that submitted studies can be used by the core lab for analysis, all study echocardiograms (baseline, 6 months and 1 year) should be performed in accordance with the minimum standard set out by the British Society of Echocardiography. 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.

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)(40). 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: $\leq 25\%$ transmural LGE. Adjudication of viability in segments with 26-50% transmural LGE should ideally be based on demonstration of contractile reserve during low-dose Dobutamine stimulation
- SPECT: tracer activity on the delayed images that is $\geq 50\%$ 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 PI 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

All patients will be pre-treated with oral Aspirin (300mg) and Clopidogrel (300mg if >12 hours before PCI, 600mg if not) or Prasugrel (60mg) unless on maintenance treatment for at least 1 week before the procedure (or newer antiplatelet regimes that become available during the trial). Bolus unfractionated Heparin will be administered intravenously (70 units/kg) at the start of the procedure, unless the patient is already receiving a continuous infusion of Heparin, with further boluses given during the procedure to maintain the Activated Clotting Time (ACT) between 200 and 250 seconds. Routine stent placement is required where feasible (drug-eluting stents are strongly recommended) but the route of access for PCI, use of additional techniques such as rotational atherectomy and use of adjunctive pharmacotherapy (e.g. GpIIb/IIIa antagonists or Bivalirudin) is at the discretion of the operator. In patients who have an indication for long-term formal anticoagulation (e.g. for concurrent atrial fibrillation or VTE), the choice of stent type should be based on their suitability for medium-term combined antiplatelet and anticoagulation therapy.

The use of circulatory assist devices (e.g. IABP or Impella) is at the discretion of the operator.

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 chronic total occlusion (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 jeopardy score (JS) and Revascularisation Index (RI)(43), 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 prespecified at the index procedure.

Urgent revascularisation before the planned 2nd stage procedure will be considered a major endpoint(44).

13.4. PCI Definitions

| | |
|-------------------------------|--|
| Target Vessel Success | <30% residual stenosis and 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 BP ≤75 mm Hg for >10 min despite fluid resuscitation or requirement of inotropic support/IABP/LVAD to maintain augmented mean arterial BP >75 mm Hg). |
| 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 **does not necessarily need to have been optimised** before a patient can be randomised.

A Medical Therapy Committee will review available evidence annually from the start of recruitment (or in the event of relevant new data/guidelines becoming available in the interim) to ensure that drug and device therapy given to all patients in the trial remains optimal and contemporary. At present, optimal medical therapy for patients with ischaemic cardiomyopathy includes ACE-inhibitor (or Angiotensin Receptor Blocker in the event of side effects to ACE-inhibitors or as an adjunct to an ACE inhibitor), Betablocker, Aldosterone Antagonist, anti-platelet drug and statin(45). Recommended treatment targets (including lipid profile, HbA1c, resting heart rate etc.) are contained within the trial site file. Formal anticoagulation for severe left ventricular dysfunction/

dyskinesia is at the discretion of the treating physician. It is recommended that aggressive rate control or rhythm control strategies are used in patients with Atrial Fibrillation, all of whom should be considered for formal anticoagulation.

Initiation of the above treatments, dose-titration and relevant monitoring will be as per local heart failure protocols and will be supervised by a designated heart failure lead at each centre.

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 optimal medical therapy 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
- Full blood count
- Creatinine and electrolytes

Time limits for screening tests

| Eligibility criteria | Test | Time limit |
|---|-------------------------|--|
| Extensive coronary disease | Angiogram | Clinically valid |
| LVEF \leq 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 | | | | | | |
| 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 | | |

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

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

† 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
- ICD check
- HbA1C
- Full lipid profile
- BNP / NT-proBNP
- ECG
- NYHA/CCS
- EuroQol EQ-5D-5L
- Kansas City Cardiomyopathy questionnaire (KCCQ)
- Cardiac medication

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

- CK
- Troponin T/I

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

- Death
- Full blood count
- Creatinine & Electrolytes
- CK
- Troponin T/I
- 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

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

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 5 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 HSCIC for up to 5 years from enrolment of the last patient.

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 in NHS resource use including inpatient days in hospital, outpatient visits, use of primary care resources (e.g. visits to and from a GP), 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(46, 47). 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(48). 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(49) 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.

18. References

1. Peterson S RM, Wolstenholme J. Heart failure supplement. British Heart Foundation Coronary Heart Disease Statistics. 2002.
2. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D'Agostino RB, Kannel WB, et al. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation*. 2002;106(24):3068-72.
3. Gheorghide M, Sopko G, De Luca L, Velazquez EJ, Parker JD, Binkley PF, et al. Navigating the crossroads of coronary artery disease and heart failure. *Circulation*. 2006;114(11):1202-13.
4. Adams KF, Jr., Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, et al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J*. 2005;149(2):209-16.
5. Rahimtoola SH. Coronary bypass surgery for chronic angina--1981. A perspective. *Circulation*. 1982;65(2):225-41.
6. Rahimtoola SH. The hibernating myocardium. *Am Heart J*. 1989;117(1):211-21.
7. Bax JJ, Visser FC, Poldermans D, Elhendy A, Cornel JH, Boersma E, et al. Time course of functional recovery of stunned and hibernating segments after surgical revascularization. *Circulation*. 2001;104(12 Suppl 1):I314-8.
8. Allman KC, Shaw LJ, Hachamovitch R, Udelson JE. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis. *J Am Coll Cardiol*. 2002;39(7):1151-8.
9. Carluccio E, Biagioli P, Alunni G, Murrone A, Giombolini C, Ragni T, et al. Patients with hibernating myocardium show altered left ventricular volumes and shape, which revert after revascularization: evidence that dyssynergy might directly induce cardiac remodeling. *J Am Coll Cardiol*. 2006;47(5):969-77.
10. Dispersyn GD, Borgers M, Flameng W. Apoptosis in chronic hibernating myocardium: sleeping to death? *Cardiovasc Res*. 2000;45(3):696-703.
11. Camici PG, Prasad SK, Rimoldi OE. Stunning, hibernation, and assessment of myocardial viability. *Circulation*. 2008;117(1):103-14.
12. Toda K, Mackenzie K, Mehra MR, DiCorte CJ, Davis JE, McFadden PM, et al. Revascularization in severe ventricular dysfunction (15% < OR = LVEF < OR = 30%): a comparison of bypass grafting and percutaneous intervention. *Ann Thorac Surg*. 2002;74(6):2082-7; discussion 7.
13. Eagle KA, Guyton RA, Davidoff R, Edwards FH, Ewy GA, Gardner TJ, et al. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). *Circulation*. 2004;110(14):e340-437.

14. Alderman EL, Fisher LD, Litwin P, Kaiser GC, Myers WO, Maynard C, et al. Results of coronary artery surgery in patients with poor left ventricular function (CASS). *Circulation*. 1983;68(4):785-95.
15. O'Connor CM, Velazquez EJ, Gardner LH, Smith PK, Newman MF, Landolfo KP, et al. Comparison of coronary artery bypass grafting versus medical therapy on long-term outcome in patients with ischemic cardiomyopathy (a 25-year experience from the Duke Cardiovascular Disease Databank). *Am J Cardiol*. 2002;90(2):101-7.
16. Velazquez EJ, Lee KL, Deja MA, Jain A, Sopko G, Marchenko A, et al. Coronary-artery bypass surgery in patients with left ventricular dysfunction. *N Engl J Med*. 2011;364(17):1607-16.
17. Perera D, Redwood S, Marber M. CABG in patients with left ventricular dysfunction. *N Engl J Med*. 2011;365(5):468-9; author reply 70-1.
18. Baker DW, Jones R, Hodges J, Massie BM, Konstam MA, Rose EA. Management of heart failure. III. The role of revascularization in the treatment of patients with moderate or severe left ventricular systolic dysfunction. *JAMA*. 1994;272(19):1528-34.
19. Kennedy JW, Kaiser GC, Fisher LD, Fritz JK, Myers W, Mudd JG, et al. Clinical and angiographic predictors of operative mortality from the collaborative study in coronary artery surgery (CASS). *Circulation*. 1981;63(4):793-802.
20. Stahle E, Bergstrom R, Edlund B, Frostfeldt G, Lagerquist B, Sjogren I, et al. Influence of left ventricular function on survival after coronary artery bypass grafting. *Ann Thorac Surg*. 1997;64(2):437-44.
21. Serruys PW, Unger F, Sousa JE, Jatene A, Bonnier HJ, Schonberger JP, et al. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med*. 2001;344(15):1117-24.
22. Rodriguez A, Bernardi V, Navia J, Baldi J, Grinfeld L, Martinez J, et al. Argentine Randomized Study: Coronary Angioplasty with Stenting versus Coronary Bypass Surgery in patients with Multiple-Vessel Disease (ERACI II): 30-day and one-year follow-up results. ERACI II Investigators. *J Am Coll Cardiol*. 2001;37(1):51-8.
23. Hueb W, Soares PR, Gersh BJ, Cesar LA, Luz PL, Puig LB, et al. The medicine, angioplasty, or surgery study (MASS-II): a randomized, controlled clinical trial of three therapeutic strategies for multivessel coronary artery disease: one-year results. *J Am Coll Cardiol*. 2004;43(10):1743-51.
24. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med*. 2009;360(10):961-72.
25. Hlatky MA, Boothroyd DB, Bravata DM, Boersma E, Booth J, Brooks MM, et al. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. *Lancet*. 2009;373(9670):1190-7.
26. Perera D, Stables R, Thomas M, Booth J, Pitt M, Blackman D, et al. Elective intra-aortic balloon counterpulsation during high-risk percutaneous

- coronary intervention: a randomized controlled trial. *JAMA*. 2010;304(8):867-74.
27. Perera D, Stables R, Clayton T, De Silva K, Lumley M, Clack L, et al. Long-term mortality data from the balloon pump-assisted coronary intervention study (BCIS-1): a randomized, controlled trial of elective balloon counterpulsation during high-risk percutaneous coronary intervention. *Circulation*. 2013;127(2):207-12.
28. Jones RH, Velazquez EJ, Michler RE, Sopko G, Oh JK, O'Connor CM, et al. Coronary bypass surgery with or without surgical ventricular reconstruction. *N Engl J Med*. 2009;360(17):1705-17.
29. O'Keefe JH, Jr., Allan JJ, McCallister BD, McConahay DR, Vacek JL, Piehler JM, et al. Angioplasty versus bypass surgery for multivessel coronary artery disease with left ventricular ejection fraction \leq 40%. *Am J Cardiol*. 1993;71(11):897-901.
30. Sedlis SP, Ramanathan KB, Morrison DA, Sethi G, Sacks J, Henderson W, et al. Outcome of percutaneous coronary intervention versus coronary bypass grafting for patients with low left ventricular ejection fractions, unstable angina pectoris, and risk factors for adverse outcomes with bypass (the AWESOME Randomized Trial and Registry). *Am J Cardiol*. 2004;94(1):118-20.
31. Gioia G, Matthai W, Benassi A, Rana H, Levite HA, Ewing LG. Improved survival with drug-eluting stent implantation in comparison with bare metal stent in patients with severe left ventricular dysfunction. *Catheter Cardiovasc Interv*. 2006;68(3):392-8.
32. Gioia G, Matthai W, Gillin K, Dralle J, Benassi A, Gioia MF, et al. Revascularization in severe left ventricular dysfunction: outcome comparison of drug-eluting stent implantation versus coronary artery by-pass grafting. *Catheter Cardiovasc Interv*. 2007;70(1):26-33.
33. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. *Eur Heart J*. 2012;33(20):2551-67.
34. Thygesen K, Alpert JS, White HD, Joint ESCAAHAWHFTFtRoMI, Jaffe AS, Apple FS, et al. Universal definition of myocardial infarction. *Circulation*. 2007;116(22):2634-53.
35. Ellis SG, Chew D, Chan A, Whitlow PL, Schneider JP, Topol EJ. Death following creatine kinase-MB elevation after coronary intervention: identification of an early risk period: importance of creatine kinase-MB level, completeness of revascularization, ventricular function, and probable benefit of statin therapy. *Circulation*. 2002;106(10):1205-10.
36. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115(17):2344-51.
37. Zannad F, Stough WG, Pitt B, Cleland JG, Adams KF, Geller NL, et al. Heart failure as an endpoint in heart failure and non-heart failure cardiovascular clinical trials: the need for a consensus definition. *Eur Heart J*. 2008;29(3):413-21.
38. Perera D, Stables R, Booth J, Thomas M, Redwood S, Investigators B-. The balloon pump-assisted coronary intervention study (BCIS-1): rationale and design. *Am Heart J*. 2009;158(6):910-6 e2.

39. Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet*. 2003;362(9386):759-66.
40. Afridi I, Kleiman NS, Raizner AE, Zoghbi WA. Dobutamine echocardiography in myocardial hibernation. Optimal dose and accuracy in predicting recovery of ventricular function after coronary angioplasty. *Circulation*. 1995;91(3):663-70.
41. Pellikka PA, Nagueh SF, Elhendy AA, Kuehl CA, Sawada SG, American Society of E. American Society of Echocardiography recommendations for performance, interpretation, and application of stress echocardiography. *J Am Soc Echocardiogr*. 2007;20(9):1021-41.
42. Rizzello V, Poldermans D, Schinkel AF, Biagini E, Boersma E, Elhendy A, et al. Long term prognostic value of myocardial viability and ischaemia during dobutamine stress echocardiography in patients with ischaemic cardiomyopathy undergoing coronary revascularisation. *Heart*. 2006;92(2):239-44.
43. De Silva K, Morton G, Sicard P, Chong E, Indermuehle A, Clapp B, et al. Prognostic utility of BCIS myocardial jeopardy score for classification of coronary disease burden and completeness of revascularization. *Am J Cardiol*. 2013;111(2):172-7.
44. Vranckx P, Cutlip DE, Mehran R, Kint PP, Silber S, Windecker S, et al. Myocardial infarction adjudication in contemporary all-comer stent trials: balancing sensitivity and specificity. Addendum to the historical MI definitions used in stent studies. *EuroIntervention*. 2010;5(7):871-4.
45. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. *J Am Coll Cardiol*. 2009;53(15):e1-e90.
46. Briggs A, Mihaylova B, Sculpher M, Hall A, Wolstenholme J, Simoons M, et al. Cost effectiveness of perindopril in reducing cardiovascular events in patients with stable coronary artery disease using data from the EUROPA study. *Heart*. 2007;93(9):1081-6.
47. Henriksson M, Epstein DM, Palmer SJ, Sculpher MJ, Clayton TC, Pocock SJ, et al. The cost-effectiveness of an early interventional strategy in non-ST-elevation acute coronary syndrome based on the RITA 3 trial. *Heart*. 2008;94(6):717-23.
48. NICE. Guide to the methods of technology appraisal. National Institute for Health and Clinical Excellence. 2008.
49. Drummond MF, Sculpher M, Torrance G, O'Brien B, Stoddart G. Methods for the economic evaluation of health care programmes. 3rd ed: Oxford: Oxford University Press; 2005.

Appendix 1: Trial Sites

St Thomas' Hospital, London
King's College Hospital, London
Birmingham Heartlands Hospital
New Cross Hospital, Wolverhampton
Edinburgh Royal Infirmary
Liverpool Chest and Heart Hospital
Freeman Hospital, Newcastle
Royal Bournemouth & Christchurch Hospitals
Nottingham University Hospital
Southampton General Hospital
Golden Jubilee Hospital, Glasgow
Manchester Royal Infirmary
Northern General Hospital, Sheffield
University Hospital of North Staffordshire, Stoke-on-Trent
Kettering General Hospital
Glenfield Hospital, Leicester
James Cook University Hospital, Middlesbrough
Lister Hospital, Stevenage
London Chest Hospital
Papworth Hospital, Cambridge
Leeds General Infirmary
Wythenshawe Hospital, Manchester
St George's Hospital, London
Sunderland Royal Hospital
Queen Alexandra Hospital, Portsmouth
Royal Free Hospital, London
Royal Brompton Hospital, London
Hammersmith Hospital, London
Victoria Hospital, Blackpool
Harefield Hospital, Middlesex
Pinderfields Hospital, Wakefield
Royal Victoria Hospital, Belfast
Derriford Hospital, Plymouth
Worcestershire Acute Hospitals, Worcester
Sunderland Royal Hospital
Wycombe Hospital
Basingstoke and North Hampshire Hospital
Royal Blackburn Hospital
Royal Devon and Exeter Hospital
Worthing Hospital
St Bartholomew's Hospital, London

Appendix 2: Glossary

ACE (Angiotensin Converting Enzyme) 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, sweating. These symptoms usually occur as part of a heart attack.

Activating Clotting Time (ACT): 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 Implantable Cardioverter Defibrillator).

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 three dimensional 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.

Appendix 3: Questionnaires

Euroqol EQ-5D-5L



REVASCULARISATION FOR
ISCHAEMIC
VENTRICULAR
DYSFUNCTION



Health Questionnaire

English version for the UK

| | | | | | | | | |
|-----------------------|--------------------------|----------------------|--------------------------|----------------------|--------------------------|----------------------|--------------------------|--------------------------|
| REVIVED Study Number: | R | V | <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> |
| Date of Birth: | <input type="text"/> | <input type="text"/> |
| Baseline | <input type="checkbox"/> | 6 Months | <input type="checkbox"/> | 1 Year | <input type="checkbox"/> | 2 Years | <input type="checkbox"/> | <input type="checkbox"/> |
| 3 Years | <input type="checkbox"/> | 4 Years | <input type="checkbox"/> | 5 Years | <input type="checkbox"/> | Final Follow Up | <input type="checkbox"/> | <input type="checkbox"/> |

EQ-5D-5L

REVIVED Study Number:

R V



Date completed

ddmmyyyy

Under each heading, please tick the ONE box that best describes your health TODAY

Mobility

- I have no problems in walking about
- I have slight problems in walking about
- I have moderate problems in walking about
- I have severe problems in walking about
- I am unable to walk about

Self-Care

- I have no problems washing or dressing myself
- I have slight problems washing or dressing myself
- I have moderate problems washing or dressing myself
- I have severe problems washing or dressing myself
- I am unable to wash or dress myself

Usual Activities (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities
- I have slight problems doing my usual activities
- I have moderate problems doing my usual activities
- I have severe problems doing my usual activities
- I am unable to do my usual activities

Pain/Discomfort

- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort
- I have extreme pain or discomfort

Anxiety / Depression

- I am not anxious or depressed
- I am slightly anxious or depressed
- I am moderately anxious or depressed
- I am severely anxious or depressed
- I am extremely anxious or depressed

EQ-5D-5L

REVIVED Study Number:

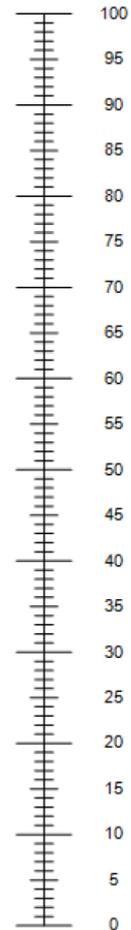
R V



- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the **best** health you can imagine.
- 0 means the **worst** health you could imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

The best health
you can imagine



The worst health
you can imagine

Kansas City Cardiomyopathy questionnaire (KCCQ)



REVASCULARISATION FOR
ISCHAEMIC
VENTRICULAR
DYSFUNCTION

REVIVED-BCIS2

Kansas City Cardiomyopathy Questionnaire (KCCQ)

| | | | | | | | |
|-----------------------|--------------------------|----------------------|--------------------------|----------------------|--------------------------|----------------------|--------------------------|
| REVIVED Study Number: | R | V | <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> |
| Date of Birth: | <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> |
| Baseline | <input type="checkbox"/> | 6 Months | <input type="checkbox"/> | 1 Year | <input type="checkbox"/> | 2 Years | <input type="checkbox"/> |

KCCQ

REVIVED Study Number:

R V



Date completed

The following questions refer to your **heart failure** and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. **Heart failure** affects different people in different ways. Some may mainly feel shortness of breath while others mainly fatigue. Please indicate how limited you have been by **heart failure** (for example, shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Please put an X in one box on each line

| Activity | Extremely limited | Quite a bit limited | Moderately limited | Slightly limited | Not at all limited | Limited for other reasons or did not do the activity |
|--|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--|
| Dressing yourself | <input type="checkbox"/> |
| Showering or having a bath | <input type="checkbox"/> |
| Walking 100 yards on level ground | <input type="checkbox"/> |
| Doing gardening, housework or carrying groceries | <input type="checkbox"/> |
| Climbing a flight of stairs without stopping | <input type="checkbox"/> |
| Jogging or hurrying (as if to catch a bus) | <input type="checkbox"/> |

2. Compared with 2 weeks ago, have your symptoms of heart failure (for example, shortness of breath, fatigue, or ankle swelling) changed?

My symptoms of heart failure are now...

| | | | | | |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--|
| Much worse | Slightly worse | Not changed | Slightly better | Much better | I've had no symptoms over the last two weeks |
| <input type="checkbox"/> |

3. Over the past 2 weeks, how many times have you had **swelling** in your feet, ankles or legs when you woke up in the morning?

| | | | | |
|--------------------------|---|--------------------------|--------------------------|-----------------------------|
| Every morning | 3 or more times a week, but not every day | 1-2 times a week | Less than once a week | Never over the past 2 weeks |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

4. Over the past 2 weeks, how much has **swelling** in your feet, ankles or legs bothered you?

| | | | | | |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Extremely bothersome | Quite a bit bothersome | Moderately bothersome | Slightly bothersome | Not at all bothersome | I've had no swelling |
| <input type="checkbox"/> |

5. Over the past 2 weeks, on average, how many times has **fatigue** limited your ability to do what you wanted?

| | | | | | | |
|--------------------------|--------------------------|--------------------------|--|--------------------------|--------------------------|-------------------------------|
| All of the time | Several times a day | At least once a day | 3 or more times a week but not every day | 1-2 times a week | Less than once a week | Never over the past two weeks |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

6. Over the past 2 weeks, how much has your **fatigue** bothered you?

| | | | | | |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Extremely bothersome | Quite a bit bothersome | Moderately bothersome | Slightly bothersome | Not at all bothersome | I've had no fatigue |
| <input type="checkbox"/> |

7. Over the past 2 weeks, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

| | | | | | | |
|--------------------------|--------------------------|--------------------------|--|--------------------------|--------------------------|-------------------------------|
| All of the time | Several times a day | At least once a day | 3 or more times a week but not every day | 1-2 times a week | Less than once a week | Never over the past two weeks |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

8. Over the past 2 weeks, how much has your **shortness of breath** bothered you?

| | | | | | |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|---------------------------------|
| Extremely bothersome | Quite a bit bothersome | Moderately bothersome | Slightly bothersome | Not at all bothersome | I've had no shortness of breath |
| <input type="checkbox"/> |

9. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of **shortness of breath**?

| | | | | |
|--------------------------|---|--------------------------|--------------------------|-----------------------------|
| Every night | 3 or more times a week, but not every night | 1-2 times a week | Less than once a week | Never over the past 2 weeks |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

10. **Heart failure** symptoms can worsen for a number of reasons. How sure are you that you know what to do, or whom to call, if your **heart failure** gets worse?

| | | | | |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Not at all sure | Not very sure | Somewhat sure | Mostly sure | Completely sure |
| <input type="checkbox"/> |

11. How well do you understand what things you are able to do to keep your **heart failure** symptoms from getting worse (for example, regularly weighing yourself, eating a low salt diet etc.)?

| | | | | |
|--------------------------|-----------------------------|--------------------------|--------------------------|--------------------------|
| Do not understand at all | Do not understand very well | Somewhat understand | Mostly understand | Completely understand |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

12. Over the past 2 weeks, how much has your **heart failure** limited your enjoyment of life?

| | | | | |
|--|--|---|---|---|
| It has extremely limited my enjoyment of life | It has limited my enjoyment of life quite a bit | It has moderately limited my enjoyment of life | It has slightly limited my enjoyment of life | It has not limited my enjoyment of life at all |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |