Health Technology Assessment Programme

National Institute for Health Research

NIHR HTA Programme

19 June 2013

The NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), based at the University of Southampton, manages evaluation research programmes and activities for the NIHR

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REVascularisation for Ischaemic VEntricular Dysfunction

(REVIVED-BCIS2)

Trial Protocol Version 4

(Confidential)

Sponsored by King's College London

Funded by NIHR HTA CET

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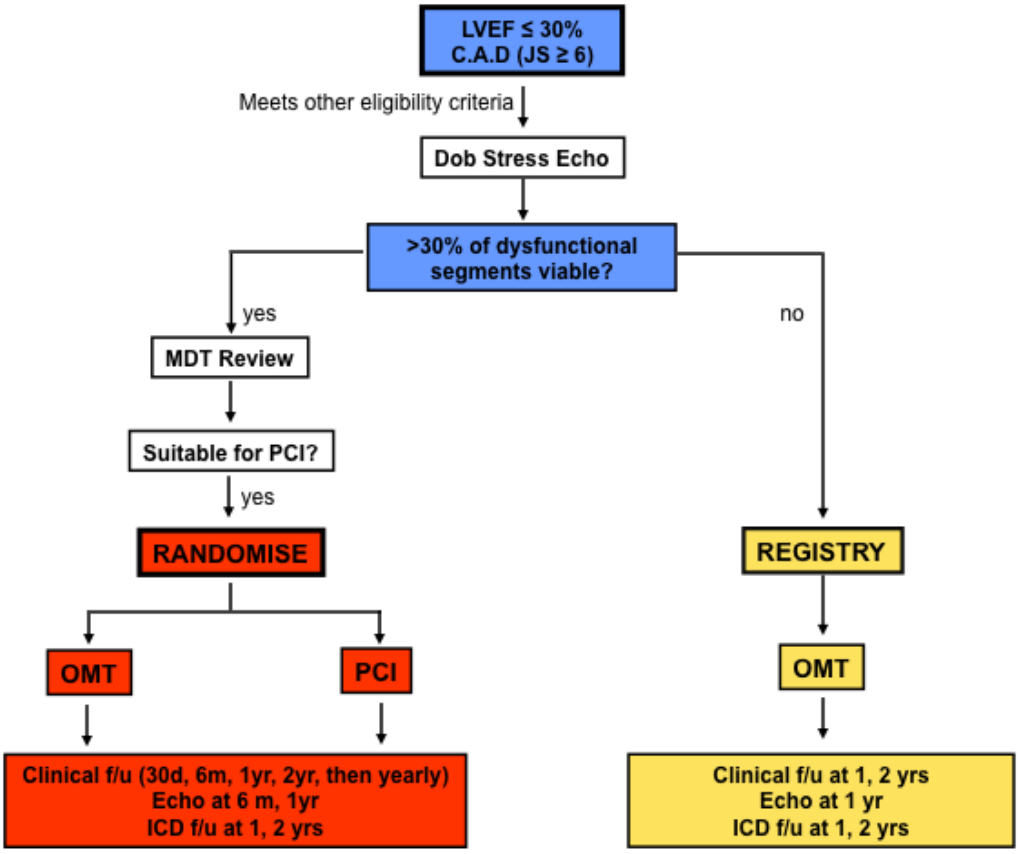
1. Trial Summary

1.1. Protocol Summary

Study 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 Seattle Angina Questionnaire NYHA Functional Class LVEF on echocardiography at 6 months and 1 year Cardiovascular Death, MI, CVA, major bleeding or unplanned revascularisation at 30 days Hospitalisation for Heart Failure 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-Pro BNP) level Major Bleeding

Inclusion Criteria	LVEF≤30% Coronary artery disease amenable to Percutaneous Coronary Intervention (PCI), BCIS-1 JS ≥ 6 Viability in >30% of Dysfunctional Segments
Major Exclusion Criteria	≥ Class 3 exertional angina Acute myocardial infarction < 6 weeks previously Haemodynamic instability (including cardiogenic shock) Any contraindication to PCI
Sample Size and Enrolment	n=700 Start date: 1st June 2013 Recruitment start date: 1st September 2013 Recruitment end date: 1st March 2017 Follow-up end date: 1st March 2019 Number of centres: 20-25 (listed in appendix 1)

1.2. Study Flowchart



* Conduct of the registry will be subject to the outcome of a separate funding bid and is likely to commence in 2014.

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, Imperial 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

TBC

1.3.3. Project Management Group

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

1.3.4. Clinical Trials Unit

London School of Hygiene and Tropical Medicine

1.3.5. Data and Safety Monitoring Committee

Dr Peter Ludman, Consultant Cardiologist, Birmingham (chair)

+ members TBC

1.3.6. Clinical Events Committee

TBC

1.3.7. Medical Therapy Committee

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

Prof. Theresa McDonagh, Professor of Heart Failure and Consultant Cardiologist, King's College London

Dr Aldo Rinaldi, 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)

Study Coordinator

Local Multi-Disciplinary Team (MDT)

A list of sites is provided in Appendix 1.

2. Background

2.1. Epidemiology

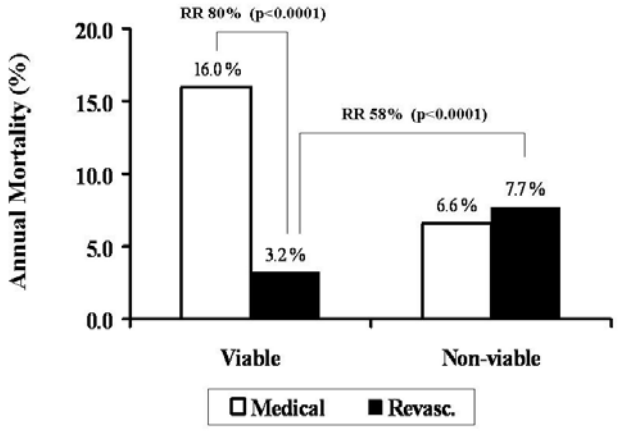
In 2002, it was estimated that approximately 900,000 individuals in the United Kingdom had a diagnosis of heart failure and at least 5% of all deaths in the country were related to this condition. At that time, one million in-hospital bed-days per year were estimated to be due to heart failure, with 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 echocardiography (DSE) or cine-MRI. While MRI allows scar imaging as well as assessment of contractile reserve, at present it is contra-indicated 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 randomised 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 (≥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 study. 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 metanalysis 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

Independent personnel who are blinded to treatment assignment will centrally adjudicate all major endpoints. Composite endpoints will be hierarchically assessed.

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 (range 1 – 60 months)

4.2. Major 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

4.3. Other Secondary Endpoints

Cardiovascular Death, MI, CVA, major bleeding or unplanned revascularisation at 30 days
Cardiovascular Death
Acute Myocardial Infarction
Appropriate ICD therapy
Unplanned further revascularisation
Seattle Angina Questionnaire
Canadian Cardiovascular Society (CCS) class
NHS Resource use
Brain natriuretic peptide (BNP or NT-Pro BNP) level
Major Bleeding

4.4. Endpoint Definitions

Acute Myocardial Infarction (34-37)	1. Spontaneous MI (>48 hrs after PCI/CABG) Detection of a rise and/or fall of cardiac biomarkers (preferably Troponin T or I, with at least one value higher than the 99th percentile upper reference limit*) 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) 2. Peri-procedural MI (<48 hrs after PCI/CABG) 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 3. Sudden death Cardiac arrest accompanied by new ST elevation/LBBB on ECG and/or evidence of fresh coronary thrombus at autopsy/angiography *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.
Hospitalisation for heart failure (38)	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. 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.
Cerebrovascular Accident	New focal neurological deficit persisting >24 hours with a neurological imaging study that does not indicate a different aetiology
Unplanned revascularisation	PCI group: any unplanned target vessel or non-target vessel revascularisation by PCI or CABG following index PCI, excluding provisional staged PCI (with plan documented at the index procedure). OMT group: any revascularisation by PCI or CABG
Appropriate ICD therapy	At least one ICD shock or episode of anti-tachycardia pacing for documented ventricular

	tachycardia (VT) or ventricular fibrillation (VF)
Cardiovascular death	All deaths where there is no clinical or post-mortem evidence of a non cardiovascular aetiology
Major Bleeding	Major bleeding will be defined using the Bleeding Academic Research Consortium (BARC) categories below: **Type 3** Type 3a • Overt bleeding plus haemoglobin drop of 3 to <5g/dL (provided haemoglobin drop is related to bleed) • Any transfusion with overt bleeding Type 3b • Overt bleeding plus haemoglobin drop ≥ 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 Type 3c • 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 **Type 4: CABG-related bleeding** • Perioperative intracranial bleeding within 48 hours • Reoperation following closure of sternotomy for the purpose of controlling bleeding • Transfusion of ≥ 5 units of whole blood or packed red blood cells within a 48 period • Chest tube output ≥ 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' **Type 5: fatal bleeding**

	Type 5a • Probable fatal bleeding: no autopsy or imaging confirmation, but clinically suspicious Type 5b • Definite fatal bleeding: overt bleeding or autopsy or imaging confirmation

5. Safety Reporting

5.1. Definition

Unexpected events that have not been defined as endpoints (section 4) or expected complications of the PCI procedure listed in PCI definitions (section 13.4) should be reported as either 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). The Chief Investigator will be responsible for the prompt notification of findings that could adversely affect the health of subjects or impact on the conduct of the trial. Notification of confirmed unexpected SAEs will be to the Sponsor, the Research Ethics Committee and the Data and Safety Monitoring Committee (DSMC).

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. As appropriate these will be reported to the sponsor, the DSMC and the Ethics Committee.

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 subject is aware of the event or symptom, but the event or symptom is easily tolerated.

Moderate: The subject experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.

Severe: Significant impairment of functioning; the subject is unable to carry out usual activities and/or the subject'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.

6. Study Population

6.1. Inclusion Criteria

ALL of the following:

1. Poor left ventricular function (EF≤30%)
2. Extensive coronary disease (BCIS-1 Jeopardy Score ≥6)(39) AND
3. Viable myocardium in ≥30% of dysfunctional segments

A LVEF threshold of 30% has been chosen, rather than 35%, as the lower threshold would identify patients who have the highest risk of cardiovascular events. Interestingly, while the overall cohort in the STICH trial (EF<35%) did not appear to benefit from revascularisation, there was a trend to benefit in the subgroup with poorest LV function (EF<27%, the median)(16). The coronary artery disease (CAD) severity threshold has been included for two main reasons – firstly, the CAD disease burden correlates with the risk of major cardiac events and mortality and secondly, this threshold will reduce the possibility of enrolling patients with non-ischaemic cardiomyopathy who have coexistent (incidental) CAD; the latter group would not benefit from revascularisation and would dilute any beneficial effects of PCI in the overall cohort. The rationale behind the myocardial viability threshold has been explained in detail in section 2.2 above. In a recently published substudy of the STICH trial, 81% of patients with ischaemic cardiomyopathy who were enrolled were found to have viable myocardium((40).

6.2. Exclusion Criteria

6.2.1. Specific Exclusions

ANY of

1. Significant angina (≥CCS class 3)

2. Myocardial infarction < 6 weeks previously

6.2.2. General Exclusions

1. Decompensated heart failure requiring inotropic support, invasive or non-invasive ventilation or IABP/left ventricular assist device (LVAD) therapy <72 hours prior to randomisation
2. Sustained VT/VF or appropriate ICD discharges <72 hours prior to randomisation
3. More than mild aortic stenosis or mild aortic regurgitation on echocardiography
4. Contra-indications to PCI, including contra-indications to Aspirin or Clopidogrel or Heparin
5. Age <18 yrs
6. Bleeding diathesis or Warfarin therapy with INR>3.5
7. Active internal bleeding (except menstruation)
8. Platelet count < 100,000 cells/mm3) at randomisation
9. Haemoglobin < 9 g/dl at randomisation
10. eGFR < 25 ml/min, unless established on dialysis
11. Women who are pregnant
12. Previously enrolled in REVIVED-BCIS2 or current enrolment in other study that may affect REVIVED-BCIS2 outcome data
13. Life expectancy < 1 yr due to non-cardiac pathology

7. Ethical Considerations

7.1. Consent

All patients will freely give their informed consent to participate in the study. A patient may decide to withdraw from the study at any time without prejudice to their future care. 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 study. The patient should be given sufficient time to consider the trial, recommended to be 24 hours, following which informed consent will be taken.

7.2. Declaration of Helsinki and Good Clinical Practice

The study 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 60 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 (range 24-60 months).

The above predicted event rates are conservative in relation to the existing literature (8, 16, 26, 41), 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 study 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 study is expected to have very good power to detect differences in Quality of Life (one of the major secondary outcomes).

8.2. Crossover

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. Crossover will only be allowed in the protocol if patients meet class I indications for PCI, namely Acute Coronary Syndromes or the development of limiting (CCS class 3 or 4) angina, which will simultaneously result in accrual of a primary (if myocardial infarction) or secondary endpoint (if revascularisation for unstable angina) respectively. 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 at 30 days and from 30 days to the end of follow-up. 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

Recruitment and pooled event rates will be evaluated one year after the first patient is recruited, which will inform the feasibility of completing the trial within the initially projected period. As no analysis is intended at this stage by randomised treatment, this feasibility analysis will not impact upon the power calculation above.

An independent Data and Safety Monitoring Committee (DSMC) will be established and a separate DSMC charter developed which will include details of the meeting schedule and stopping guidelines. A DSMC meeting will be convened prior to any patients being randomised and is expected to meet at least annually.

9. Screening and recruitment

The following populations of patients will be screened for eligibility:

- Patients referred to the heart failure team for optimisation of medical therapy including in-patient referrals and out-patient nurse led heart failure clinics
- Patients referred for stress echocardiography or cardiac MRI 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 who have no more than CCS class II exertional angina
- Patients referred for coronary angiography to establish the aetiology of a dilated cardiomyopathy, who are found to have coronary artery disease.

The majority of patients will have undergone coronary angiography prior to screening for this study but in cases where a stress echocardiogram has been carried out prior to angiography, the original stress echo will be reviewed for suitability for assessing viability.

A comprehensive screening log will be maintained by each centre, with an entry for every patient screened. In those considered ineligible, the reasons should be systematically documented, including inclusion criteria not met, and/or applicable exclusion criteria. The log will also include details of eligible patients who were not enrolled, including the following categories: patient declined consent, referring physician did not approve, declined by MDT or other specified reason. Patients who are ineligible for the randomised trial should be considered for the stress-echo negative registry elaborated in section 15 below.

10. Assessment of Viability

10.1. Resting trans-thoracic echocardiography (TTE)

In the event of a recent acute coronary syndrome, the qualifying echocardiogram will need to have been carried out at least 6 weeks following the event. The TTE can be performed as part of the stress echocardiogram or as a separate study.

Resting LV end diastolic and end systolic volumes and ejection fraction (EF) will be calculated from the two and four chamber views by the biplane Simpson's rule. LV volumes will be normalised for body surface area (LV volume index).

The TTE must be performed in accordance with the minimum standards set out by the British Society of Echocardiography. Eligibility for the REVIVED-BCIS2 study will be adjudicated locally, based on the resting LV EF. All images will subsequently be submitted to the echo core lab for further analysis, including quantification of mitral regurgitation and analysis of other viability parameters.

10.2. Dobutamine stress echocardiography (DSE)

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)(42). The wall motion score index (WMSI) at rest will be calculated by dividing the summed wall motion score at each step by the number of segments.

Regional wall motion (RWM) will be scored at low dose Dobutamine (5 and 10 mcg/kg/min) and high-dose Dobutamine (up to 40 mg/kg/min plus 2 mg atropine to achieve 85% predicted heart rate (PHR), if required) stimulation. Beta-blockers will be discontinued for 48 hours before DSE, unless clinically contraindicated to do so.

Assessment of viability will be based on contractile reserve during low dose dobutamine (LD-Dob) stimulation, defined as improvement by at least one grade (at least two if aneurysmal or dyskinetic at rest) compared to wall motion at rest(42, 43). **Eligibility for the study will require viability in at least 30% of dysfunctional segments**(44), which will be adjudicated locally.

Segments will be considered ischaemic if a biphasic response is noted (improvement followed by deterioration in wall motion (WM) grade when progressing from rest to LD to HD (high dose) Dob) or a worsening of WM at LD or HDDob, without initial improvement (excluding akinesia to dyskinesia) (43, 45). It should be noted that demonstration of ischaemia is not an essential criterion for eligibility for the study but this information will be captured in the trial participant's case record form (CRF). All patients who undergo HD-Dob stimulation will be included in a pre-specified comparison of responses to LD-Dob and HD-Dob stimulation (ie viability and ischaemia respectively).

Full DSE studies will be submitted to the echo core lab for further analysis.

11. Multi-Disciplinary Team Review

All patients meeting eligibility criteria for the study with be reviewed by a local multi-disciplinary cardiac team, comprising an interventional cardiologist, heart failure specialist and a cardiothoracic surgeon. The study coordinator at each site will facilitate the MDT conference and keep a log of all patients discussed and the relevant outcomes. Each patient's Syntax Score, BCIS-1 Jeopardy Score and Euroscore will be reviewed and documented at the MDT conference. The MDT will review coronary angiograms, stress echocardiograms and demographic data and all patients felt to be suitable for PCI will be invited to participate in the study.

Following MDT review, the referring physician will be informed of the outcome (if applicable) and informed consent sought from the patient for inclusion in the randomised study or registry, as decided at the conference. A log will be maintained of any patients who are not enrolled in the study or registry, due to preference of the patient or the referring physician.

12. Randomisation

Once the eligibility of a patient is confirmed by the study 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. Index PCI should be carried out as close as possible to randomisation, within two weeks, 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.

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

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

13. Percutaneous Coronary Intervention

13.1. Adjunctive therapy and devices

In the group assigned to PCI, the procedure must be within 2 weeks of randomisation. 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 Bivalidrudin) is at the discretion of the operator. In patients who have an indication for long-term formal anticoagulation (eg for LV dyskinesis or concurrent atrial fibriallation), the choice of stent type should be based on their suitability for medium-term combined antiplatelet and anticoagulation therapy.

The use of IABP therapy is at the discretion of the operator; routine elective placement of an IABP is not recommended. A standby approach should be adopted, with preparation of the contra-lateral groin (± insertion of a 5F

sheath) to allow rapid femoral access if bail-out IABP is required during the procedure.

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 when associated with a fractional flow reserve (FFR)<0.80. Planned target lesions will need to be identified by the operator and recorded by the study coordinator before the procedure. 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)(46), 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 (eg - due to unexpected high contrast volumes or procedural complications during PCI to the first vessel). Staging must be prespecified at the index procedure and cannot involve the index target vessel.

When planned, the second stage should be carried out within 14 days of the first procedure. Delay beyond this period will be considered a protocol violation but not an event unless unplanned. Urgent revascularisation before the planned 2nd stage procedure will be considered a major endpoint(47).

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

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 study (including randomised arms and registry) remains optimal and contemporary. At present, optimal medical therapy for patients with ischaemic cardiomopathy 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(48). 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/ dyskinesis 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 Resychronisation

All patients who are screened for the trial should be considered for ICD implantation, for primary prevention of sudden cardiac death from ventricular arrhythmias, in accordance with current international guidelines[40]. Patients who have evidence of LV dyssynchrony on ECG (QRS duration > 150 msec) or echocardiography (if QRS duration 120-149 msec) and ≥NYHA class 2 dyspnoea should also be considered for cardiac resynchronisation therapy(48) at the same stage.

Device implantation must be carried out BEFORE randomisation.

Implantation after randomisation will be considered a protocol violation but not necessarily a Heart Failure Hospitalisation event, unless any of the defined criteria are met (see section 4.4).

VF induction and early post-implant ICD interrogation is as per local practice but all patients will undergo ICD interrogation as per local protocol (as a minimum at 6 months, 1 year and 2 yrs in the randomised cohort and at 1 year in the registry). ICD interrogation data will be analysed by an ICD core lab.

16. Data collection and follow-up

16.1. Study Checklist – Randomised Controlled Trial Cohort

	At screening	At randomisation	<24 hrs pre-PCI ‡	8-16 hrs post-PCI ‡	48 hrs post-PCI ‡	At 30 days after randomisation	At 6 months post randomisation	At 1 year after randomisation	At 2 yrs after randomisation	Yearly follow-up	End of trial follow-up
Demographics and medical history	X					Telephone and / or Clinical follow-up					
Coro Angio	X			X							
DSE	X										
Echo	X*						X	X			
ICD check		X					X	X	X		
MDT r/v	X										
FBC	X	X	X	X							
Creatinine† & Electrolytes	X	X	X	X				X			
HbA1C		X						X			
Full Lipid Profile		X						X	X		
BNP / NT-Pro BNP		X					X	X	X		
CK			X	X							
Trop T/I			X	X							
ECG		X	X	X			X	X	X		
AKI					X						
NYHA/CCS		X					X	X	X		
EQ-5D-5L		X					X	X	X	X	X
KCCQ		X					X	X	X		
Seattle Angina Questionnaire		X					X	X	X		
Primary Endpoints				X		X	X	X	X	X	X
Secondary Endpoints				X		X	X	X	X	X	
SAEs				X		X	X	X	X		
Cardiac Medication		X		X		X	X	X	X	X	

* No later than 6 weeks after Acute Coronary Syndrome

† Urea only if routinely collected

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

At screening:

- Demographics and medical history
- Coronary angiogram
- Dobutamine stress-echo
- Echo (no later than 6 weeks after Acute Coronary Syndrome)
- MDT review
- Full blood count
- Creatinine (Urea only if routinely collected) & Electrolytes

At randomisation:

- ICD check
- Full blood count
- Creatinine (Urea only if routinely collected) & Electrolytes
- HbA1C
- Full lipid profile
- BNP / NT-Pro BNP
- ECG
- NYHA / CCS
- QOL
- Cardiac medication

Less than 24 hours before PCI (If PCI is staged please collect for each stage of the procedure):

- Full blood count
- Creatinine (Urea only if routinely collected) & Electrolytes
- CK
- Troponin T/I
- ECG

8-16 hours after PCI (If PCI is staged please collect for each stage of the procedure):

- Coronary Angiogram
- Full blood count
- Creatinine (Urea only if routinely collected) & Electrolytes
- CK
- Troponin T/I
- ECG
- Primary endpoint – death due to heart failure
- Unexpected serious adverse events
- Cardiac medication

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

- AKI

30 days after randomisation (telephone or clinical follow-up):

- Primary endpoints – death or hospitalisation due to heart failure
- Cardiovascular death
- MI
- CVA
- Major bleeding
- Unplanned further revascularisation
- Unexpected serious adverse events
- Cardiac medication
- Hospitalisation

6 months after randomisation (clinical follow-up):

- Primary endpoints – death or hospitalisation due to heart failure
- Cardiovascular death
- Acute MI
- CVA
- Major bleeding
- Unplanned further revascularisation
- LVEF on echocardiography
- ICD check
- BNP / NT-Pro BNP
- ECG
- NYHA/CCS
- EuroQol EQ-5D-5S
- Kansas City Cardiomyopathy questionnaire (KCCQ)
- Seattle Angina Questionnaire
- Hospitalisation
- Unexpected serious adverse events
- Cardiac medication

1 year after randomisation (clinical follow-up):

- Primary endpoints – death or hospitalisation due to heart failure
- Cardiovascular death
- Acute MI
- CVA
- Major bleeding
- Unplanned further revascularisation
- LVEF on echocardiography
- ICD check
- Creatinine (Urea only if routinely collected) & Electrolytes
- HbA1C
- Full lipid profile
- BNP / NT-Pro BNP
- ECG
- NYHA/CCS
- EuroQol EQ-5D-5S
- Kansas City Cardiomyopathy questionnaire (KCCQ)
- Seattle Angina Questionnaire
- Hospitalisation
- Unexpected serious adverse events
- Cardiac medication

2 years after randomisation (clinical follow-up):

- Primary endpoints – death or hospitalisation due to heart failure
- Cardiovascular death
- Acute MI
- CVA
- Major bleeding
- Unplanned further revascularisation
- ICD check
- Full lipid profile
- BNP / NT-Pro BNP
- ECG
- NYHA/CCS
- EuroQol EQ-5D-5L
- Kansas City Cardiomyopathy questionnaire (KCCQ)
- Seattle Angina Questionnaire
- Hospitalisation
- Unexpected serious adverse events
- Cardiac medication

Yearly (telephone follow-up):

- Primary endpoints – death or hospitalisation due to heart failure
- Cardiovascular death
- Acute MI
- CVA
- Major bleeding
- Unplanned further revascularisation
- Hospitalisation
- EuroQol EQ-5D-5L
- Cardiac medication

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

- Primary endpoints – death or hospitalisation due to heart failure
- EuroQol EQ-5D-5L

16.2. Data Handling

Data will be collected electronically via a web-based case record form. In addition, hard copies (paper and/or electronic records) of relevant investigations (angiograms, ECGs, echocardiograms, ICD interrogation) should be maintained at each centre in a physical CRF.

Any incidence of MACE (death or hospitalisation) should be reported to the coordinating centre by fax within 48hrs of the event and web-CRFs should be completed within 2 weeks of each study milestone (hospital discharge, 30 days, 6 months etc)**.** Adverse Events (see section 4.4 for endpoint definitions) should be reported in the CRF, regardless of causality and the following categories reported to the DSMC via the coordinating centre: serious AEs (regardless of causality), any unexpected AE causally linked to the study procedures (possible, probable or definite), any AEs resulting in the patient's withdrawal from the study.

Principal investigators at each site will be responsible for the accuracy, completeness and legibility of the data entered onto the CRF and all associated reports. In addition, a list of all patients enrolled into the study should be maintained by each centre, containing patient identification numbers, full names, dates of birth and dates of enrolment in the study, which could be used for unambiguous identification of each patient if required. The subject's enrolment in a trial must also be recorded in the subject's medical record and the general practitioner notified accordingly.

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 in-patient days in hospital, out-patient 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. The choice of resource use data collection instruments will be informed by the ongoing NIHR-funded work to develop a repository of such instruments (led by Prof Dyfrig Hughes).

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 the same intervals as the other quality of life measures in the trial 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.

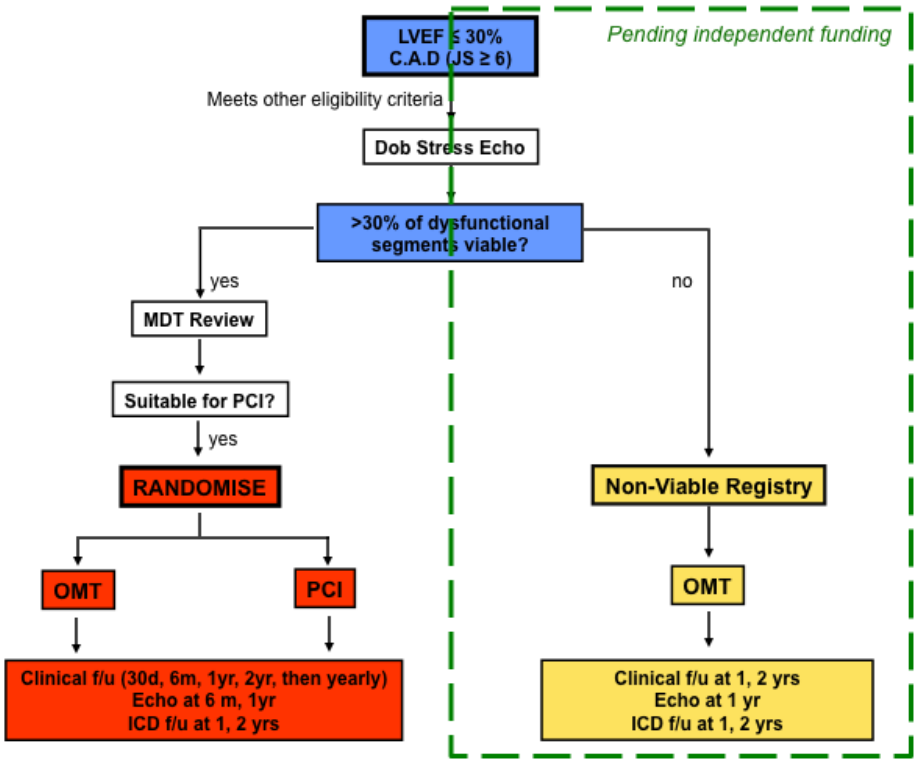
In terms of analysis, the economic evaluation will consist of a description of resource use, costs and EQ-5D-5L data collected within the trial. A formal cost effectiveness of PCI in this population will be undertaken using a decision analytic framework which is necessary for two main reasons. Firstly, 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(49, 50). 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(51). 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(52) 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. Stress-Echo Negative Registry

Conduct of the registry will be subject to an independent funding application, the outcome of which is expected by the end of 2013. Patients who fail to meet the viability criteria on DSE but fulfil *all other* eligibility criteria for the randomised trial should be considered for inclusion in the stress-echo negative registry. All patients will be offered optimal medical therapy as defined above and be considered for CRT-D as per randomised cohort. Revascularisation by PCI or CABG should only be considered for patients in this registry in the event of readmission with an acute coronary syndrome, increasing exertional angina (≥CCS class 3) or resistant/recurrent VT/VF considered ischaemic in origin. Data will be collected as per checklist below and long-term all-cause death will be assessed by national mortality database tracking and by telephone contact with the GP and/or patient if required, for up to 5 years from enrolment of the last subject.



Stress-echo negative registry check-list

	At Screening (<6 months before enrolment)	At enrolment to registry	6 months after enrollment	1 year after enrollment
Coro Angio	X			
DSE	X			
Echo	X		X	X
ICD check		X	X	X
MDT r/v	X			
FBC	X	X		
Creatinine† & Electrolytes	X	X		
HbA1C		X		X
Full lipid profile		X		X
BNP / NT-Pro BNP		X	X	X
ECG		X		
NYHA/CCS		X	X	X
QOL		X	X	X

†Urea only if routinely collected

19. MRI Substudy

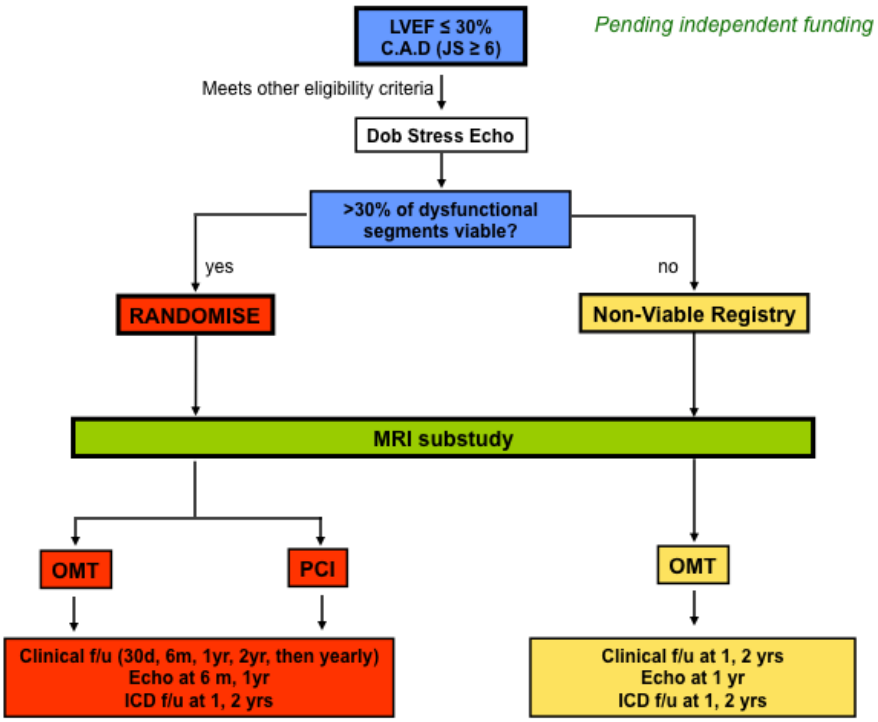
Conduct of the MRI substudy will be subject to an independent funding application, the outcome of which is expected by the end of 2013. Patients fulfilling eligibility criteria for the randomised study or the stress-echo negative registry will be considered for inclusion in the MRI substudy, excluding those with indwelling pacemakers/ICDs at enrolment or any other contra-indications to MRI.

Scans will be carried out on 1.5T or 3T cardiac MRI scanners. LV volumes and ejection fraction will be assessed from cine data using Simpson's rule. RWM will be scored using a 16 segment -5 grade scale (as above).

Late gadolinium-enhanced (LGE) images will be reviewed to identify the presence and transmural extent of myocardial scar in each segment (transmural extent graded as 0 = 0%, 1 = 1-25%, 2 = 26-50%, 3 = 51-75%, 4 = 76-100%)

A hierarchical algorithm will be employed to define viability. LGE-MRI data will be reviewed first. Presence of grade 4 (>75%) scar on LGE-MRI will be regarded as a marker of non-viability. Grades 0 and 1 (<25% scar) will be regarded as viable. The response to LD-Dob will be used to determine viability for transmurality scores 2 and 3, with an improvement by one or more grades or systolic wall thickening on stress of >1mm regarded as markers of viability.

Adenosine stress perfusion imaging will also be carried out in these patients to assess ischaemic burden. This will be performed after acquisition of rest cine scans, before Dobutamine stress. MR first-pass perfusion will be assessed during intravenous adenosine infusion followed by an identical MRP scan at rest, 10-15mins later.



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21. Appendix 1: Provisional List of Trial Sites

1. Guys & St Thomas' Hospital, London
2. King's College Hospital, London
3. Birmingham Heartlands Hospital
4. Brighton and Sussex University Hospital
5. University Hospital of Wales, Cardiff
6. Edinburgh Royal Infirmary
7. Glenfield Hospital, Leicester
8. Golden Jubilee Hospital, Glasgow
9. James Cook University Hospital, Middlesbrough
10. Liverpool Chest and Heart Hospital
11. London Chest Hospital
12. Manchester Royal Infirmary
13. Freeman Hospital, Newcastle
14. Northern General Hospital, Sheffield
15. Nottingham University Hospital
16. Papworth Hospital, Cambridge
17. a. Poole Hospital, Poole
    b. Royal Bournemouth & Christchurch Hospitals
18. New Cross Hospital, Wolverhampton
19. Southampton General Hospital
20. University Hospital of North Staffordshire, Stoke
21. University Hospital, Bristol
22. Leeds General Infirmary
23. Norfolk and Norwich University Hospital
24. John Radcliffe Hospital, Oxford

22. 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 a 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 (e.g.Spironalactone) A diuretic used in the management of heart failure.

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.

Aortic Valve Regurgitation (AR) The leaking of the aortic valve of the heart, causing blood to flow in the reverse direction.

Aortic Valve Stenosis (AS) A disease where the opening of the aortic valve is narrowed (classed as trivial, mild, moderate, severe).

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 Responce 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.

Cardiogenic Shock Inadequate circulation of blood due to a failure of the ventricles of the heart to function properly.

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.

Cerebral Vascular Accident (CVA) (Stroke) A disturbance of the blood supply to the brain caused by a shortage of blood supply due to a blockage or a bleed.

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 Grafting (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.

Fractional Flow Reserve (FFR) A technique used during an angiogram/plasty procedure that tests the extent that a coronary vessel is blocked and whether that vessel requires treatment.

Haemodynamics The study of the blood flow or circulation. Including Blood pressure, heart rate, temperature. (***Haemodynamic instability*** refers to these values being outside their normal ranges).

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 (LV EF) Often given as a percentage*,* it is the volumetric fraction of blood pumped out of the left ventricle in the heart with each heart beat

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.

Mitral Valve Stenosis (MS) A disease where the opening of the mitral valve is narrowed (classed as trivial, mild, moderate, severe).

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.

23. Appendix 3: Questionnaires

23.1. Euroqol EQ-5D-5L

Health Questionnaire

English version for the UK

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

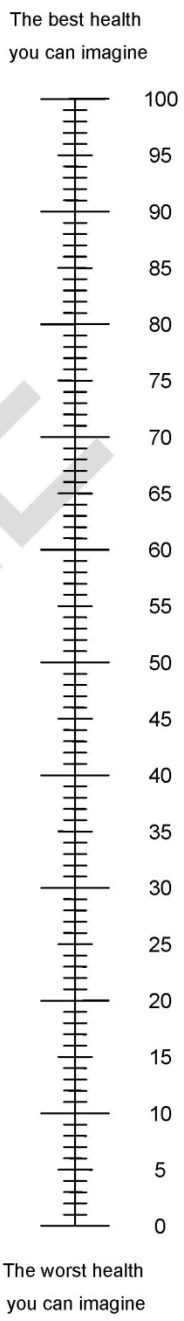
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

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 ❑

- 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 can 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 = ☐



23.2. Kansas City Cardiomyopathy questionnaire (KCCQ)

Cardiomyopathy Questionnaire (Kansas City)

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	☐	☐	☐	☐	☐	☐
Showering or having a bath	☐	☐	☐	☐	☐	☐
Walking 100 yards on level ground	☐	☐	☐	☐	☐	☐
Doing gardening, housework or carrying groceries	☐	☐	☐	☐	☐	☐
Climbing a flight of stairs without stopping	☐	☐	☐	☐	☐	☐
Jogging or hurrying (as if to catch a bus)	☐	☐	☐	☐	☐	☐

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 2 weeks
☐	☐	☐	☐	☐	☐

KCCQ - UK/English

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
☐	☐	☐	☐	☐

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**
☐	☐	☐	☐	☐	☐

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 2 weeks
☐	☐	☐	☐	☐	☐	☐

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**
☐	☐	☐	☐	☐	☐

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 2 weeks
☐	☐	☐	☐	☐	☐	☐

KCCQ - UK/English

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**
☐	☐	☐	☐	☐	☐

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
☐	☐	☐	☐	☐

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
☐	☐	☐	☐	☐

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
☐	☐	☐	☐	☐

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
☐	☐	☐	☐	☐

KCCQ - UK/English

13. If you had to spend the rest of your life with your **heart failure** the way it is right now, how would you feel about this?

Completely dissatisfied	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

14. Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your **heart failure**?

I have felt that way **all of the time**	I have felt that way **most of the time**	I have **occasionally** felt that way	I have **rarely** felt that way	I have **never** felt that way
☐	☐	☐	☐	☐

15. How much does your **heart failure** affect your lifestyle? Please indicate how your **heart failure** may have limited your participation in 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**
Hobbies, recreational activities	☐	☐	☐	☐	☐	☐
Working or doing household chores	☐	☐	☐	☐	☐	☐
Visiting family or friends	☐	☐	☐	☐	☐	☐
Intimate or sexual relationships	☐	☐	☐	☐	☐	☐

KCCQ - UK/English

23.3. Seattle Angina Questionnaire (SAQ)

The Seattle Angina Questionnaire

1. The following is a list of activities that people often do during a normal week. Although for some people with several medical problems it is difficult to determine what it is that limits them, please go over the activities listed below and indicate how much limitation you have had **due to chest pain, chest tightness, or anginal attacks over the past 4 weeks:**

Place an x in one box on each line

Activity	Extremely Limited	Quite a bit Limited	Moderately Limited	Slightly Limited	Not Limited at all	Limited for other reasons or did not do the activity
Dressing yourself	☐	☐	☐	☐	☐	☐
Walking indoors on level ground	☐	☐	☐	☐	☐	☐
Showering or bathing	☐	☐	☐	☐	☐	☐
Climbing a hill or a flight of stairs without stopping	☐	☐	☐	☐	☐	☐
Gardening, vacuuming, or carrying groceries	☐	☐	☐	☐	☐	☐
Walking more than a hundred yards at a brisk pace	☐	☐	☐	☐	☐	☐
Running or jogging	☐	☐	☐	☐	☐	☐
Lifting or moving heavy objects such as furniture, or lifting children	☐	☐	☐	☐	☐	☐
Participating in strenuous sports (e.g. swimming, tennis)	☐	☐	☐	☐	☐	☐

SAQ – UK (English)

2. Compared with 4 weeks ago, how often do you have **chest pain**, **chest tightness**, or **anginal attacks** when doing your **most strenuous** activities?

I have **chest pain**, **chest tightness**, or **anginal attacks**...

Much more often	**Slightly more** often	About **the same**	**Slightly less** often	**Much less** often	I have had **no chest pain** over the last 4 weeks
☐	☐	☐	☐	☐	☐

3. Over the past 4 weeks, on average, how many times have you had **chest pain**, **chest tightness**, or **anginal attacks**?

I have had **chest pain**, **chest tightness**, or **anginal attacks**...

4 or more times per day	1-3 times per day	3 or more times per week but not every day	1-2 times per week	Less than once a week	None over the past 4 weeks
☐	☐	☐	☐	☐	☐

4. Over the past 4 weeks, on average, how many times have you had to take GTN (nitroglycerin tablets or spray) for your **chest pain**, **chest tightness**, or **anginal attacks**?

I have taken GTN...

4 or more times per day	1-3 times per day	3 or more times per week but not every day	1-2 times per week	Less than once a week	None over the past 4 weeks
☐	☐	☐	☐	☐	☐

5. How bothersome is it for you to take your pills for **chest pain**, **chest tightness** or **anginal attacks** as prescribed?

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not** bothersome at all	My doctor has **not prescribed** pills
☐	☐	☐	☐	☐	☐

6. How satisfied are you that everything possible is being done to treat your **chest pain**, **chest tightness**, or **anginal attacks**?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

SAQ – UK (English)

7. How satisfied are you with the explanations your doctor has given you about your **chest pain**, **chest tightness**, or **anginal attacks**?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

8. Overall, how satisfied are you with the current treatment of your **chest pain**, **chest tightness**, or **anginal attacks**?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

9. Over the past 4 weeks, how much has your **chest pain**, **chest tightness**, or **anginal attacks** 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
☐	☐	☐	☐	☐

10. If you had to spend the rest of your life with your **chest pain**, **chest tightness**, or **anginal attacks** the way it is at the moment, how would you feel about this?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

11. How often do you think or worry that you may have a heart attack or die suddenly?

I think or worry about it **all the time**	I **often** think or worry about it	I **occasionally** think or worry about it	I **rarely** think or worry about it	I **never** think or worry about it
☐	☐	☐	☐	☐

SAQ – UK (English)