A multi-centre randomised trial of surgical versus percutaneous revascularisation of ischaemic left ventricular dysfunction in the United Kingdom, with embedded internal pilot and health economic analysis (STICH3-BCIS-4)

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SIGNATURE PAGE

The undersigned confirm that this protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent modifications of the clinical trial regulations, ICH-GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given. Any discrepancies and serious breaches of ICH-GCP from the trial as planned in this protocol will be explained.

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LIST OF ABBREVIATIONS

ACE-I	Angiotensin-Converting Enzyme Inhibitors
ACS	Acute Coronary Syndrome
AE	Adverse Event
AESI	Adverse Events of Special Interest
AHA	American Heart Association
AIC	Akaike
AKI	Acute Kidney Injury
API	Application Programme Interface
ARB	Angiotensin Receptor Blockers
ATE	Adjusted Treatment Effect
BCIS-JS	British Cardiovascular Intervention Society Jeopardy Score
BHF	British Heart Foundation
BIC	Bayesian
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
C&C	Confirmation of Capacity and Capability
CCGs	Clinical Commissioning Groups
CCS	Chronic Coronary Syndromes
CI	Chief Investigator
CKD	Chronic Kidney Disease
CMR	Cardiac Magnetic Resonance
CPB	Cardiopulmonary Bypass
CRF	Case Report Form
CRN	Clinical Research Network
CRT	Cardiac Resynchronisation Therapy
CTIMP	Clinical Trial of an Investigational Medicinal Product
CONSORT	Consolidated Standards of Reporting Trials
CTO-PCI	Chronic Total Occlusion Percutaneous Coronary Intervention
CV	Cardiovascular
DMC	Data Monitoring Committee

EACTS	European Association of Cardiothoracic Surgery
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
ESC	European Society of Cardiology
EQ-5D-5L	European Quality of Life 5 Dimensions 5 Level Version
EuroSCORE II	The European System for Cardiac Operative Risk Evaluation
EC	Executive Committee
FFR	Fractional Flow Reserve
GDPR	General Data Protection Regulation
GLM	Generalised Linear Model
GP	General Practitioner
HCRW	Health and Care Research Wales
HES	Hospital Episode Statistics
HF	Heart Failure
HFrEF	Heart Failure with reduced Ejection Fraction
HRA	Health Research Authority
HR	Hazard Ratio
IABP	Intra-Aortic Balloon Pump
IAS	Information Assurance Services
ICD-10	International Classification of Diseases, Tenth Revision
ICD	Implantable Cardioverter Defibrillators
ICER	Incremental Cost-Effectiveness Ratio
ICF	Informed Consent Form
ICH-GCP	International Committee on Harmonisation of Good Clinical Practice
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive Care Unit
iLVSD	Ischaemic Left Ventricular Dysfunction
iPCQ	Productivity Cost Questionnaire
IRAS	Integrated Research Application System
IRB	Institutional Review Board
ISF	Investigator Site File

ISRCTN	International Standard Randomised Controlled Trial Number Registry
ITT	Intention to Treat
IVUS	Intravascular Ultrasound
KCCQ	Kansas City Cardiomyopathy Questionnaire
LAD	Left Anterior Descending Artery
LCEHR	Leicester Centre for Ethnic Health Research
LCTU	Leicester Clinical Trials Unit
LPLV	Last Patient Last Visit
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
MDT	Multidisciplinary Team
MI	Myocardial Infarction
MRA	Mineralocorticoid Receptor Agonists
MSA	Minimum Stent Area
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research Health Technology Assessment
NMB	Net Monetary Benefit
NYHA	New York Heart Association
OCT	Optical Coherence Tomography
ONS	Office for National Statistics
PIC	Participant Identification Centre
PCI	Percutaneous Coronary Intervention
PeRSEVERE	Principles for Handling end-of-participation Events in Clinical Trials Research
PI	Principal Investigator
PIS	Participant Information Sheet
POC	Polygon of Confluence
POT	Proximal Optimisation Technique Procedure
PP	Per Protocol
PPI&E	Patient and Public Involvement and Engagement

PROMS	Patient Reported Outcome Measures
QALYs	Quality-Adjusted Life Years
RCT	Randomised Controlled Trial
R&D	Research and Development
REB	Research Ethics Board
REC	Research Ethics Committee
RFS	Research Filestore
RGO	Research Governance Office
R&I	Research and Innovation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAQ-7	Seattle Angina Questionnaire-7
SGLT2	Sodium-Glucose Co-Transporter-2 Inhibitors
SIV	Site Initiation Visit
SOP	Standard Operating Procedures
STEMI	ST Elevation Myocardial Infarction
STICH-1	Surgical Treatment for Ischemic Heart Failure Trial
STICH-3	The Canadian CABG or PCI in Patients with Ischaemic Cardiomyopathy Trial
STICH3-BCIS4	A multi-centre randomised trial of surgical versus percutaneous revascularisation of ischaemic left ventricular dysfunction in the United Kingdom, with embedded internal pilot and health economic analysis
SWEDEHEART	The Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies
SYNTAX SCORE	Synergy Between PCI With Taxus and Cardiac Surgery
TSC	Trial Steering Committee
TMF	Trial Master File
UK	United Kingdom
UKCRC	The UK Clinical Research Collaboration
UoL	University of Leicester
VA ECMO	Venoarterial Extra Corporeal Membrane Oxygenation

KEY WORDS

Ischaemic left ventricular dysfunction, revascularisation, coronary artery bypass grafts, percutaneous coronary intervention.

STUDY SUMMARY

Study Title	A multicentre randomised trial of surgical versus percutaneous revascularisation of ischaemic left ventricular dyfunction (iLVSD) in the United Kingdom, with embedded internal pilot and health economic analysis
Internal ref. no (or short title)	CABG or PCI in Patients with Ischaemic Left Ventricular Dysfunction (STICH3-BCIS4)
Study Design	Multicentre, open label, parallel group, RCT of two common revascularisation strategies in people with iLVSD. An internal pilot including built in progression criteria, to assess whether the target number of UK centres within 9 months of green light, and recruitment rate of one participant per location per month, can be achieved. A health economic evaluation will assess the cost-effectiveness of the intervention from an NHS and English societal perspective.
Hypothesis	CABG is superior to PCI in people with iLVSD
Research Question/Aims	1. STICH3-BCIS4 will compare PCI versus CABG for the revascularization of patients with iLVSD (defined as LV ejection fraction (LVEF) ≤ 40% and multi-vessel coronary artery disease) who are deemed to derive clinical benefit from revascularization 2. Hospitalisation with a minimum follow-up of 4 years post randomisation. 3. An internal pilot will test design assumptions around recruitment at 12 months. 4. A health economic analysis will determine cost-effectiveness. 5. A PPI Researcher led work package will improve recruitment in underserved groups. 6. The trial will contribute data to the international STICH 3 analysis that will evaluate the comparative effectiveness of CABG versus PCI in iLVSD for the outcome all-cause mortality.
Study Participants	**Setting:** At least 28 tertiary cardiac centres in the UK. **Target Population:** Patients with multi-vessel disease, a documented indication for revascularisation, and where it is deemed appropriate and suitable for revascularisation with both PCI and CABG by the local Heart Team, are eligible for randomisation if they meet all the inclusion criteria and no exclusion criteria.

	Inclusion Criteria: 1. Age ≥ 18 years. **2.** LVEF ≤ 40% quantified by any recognised assessment of LVEF within the last 12 months. If the patient has had an MI within the last 12 months post-MI imaging is required with LVEF ≤ 40%. **3.** Significant amount of myocardium at risk defined as coronary artery disease with BCIS myocardial jeopardy score ≥ 6 on recent (< 6 months) coronary angiogram. **4.** Signed informed consent. **Exclusion Criteria: 5.** Decompensated heart failure requiring inotropic support, invasive or non-invasive ventilation or mechanical circulatory support less than 48 hours prior to randomisation. **6.** ST Elevation Myocardial infarction (STEMI) < 72 hours. **7.** Valvular heart disease indicating the need for mechanical repair/replacement or any other structural cardiac surgery (e.g. LV aneurysm resection) **8.** Pregnancy. **9.** Individuals who have declined access to Hospital Episode Statistics for research purposes. **10.** An inability to understand the languages in which the trial materials are provided.
Randomisation	Randomisation with allocation concealment will utilise a centralised, web-based system (Sealed Envelope Ltd, London, UK). Participants will be randomised on the day of consent in a 1:1 ratio stratified by centre, and presentation (acute versus chronic coronary syndrome).
Trial Interventions	Study participants will be randomised in a 1:1 manner to either **Revascularisation by PCI** or **Revascularisation by CABG**
Outcomes	**Primary Outcome:** Survival time from all-cause mortality and cardiovascular hospitalisation. **Secondary Outcomes: 1.** Overall survival time (all-cause). **2.** Cardiovascular survival time **3.** Time to first cardiovascular hospitalisation. **4.** Time to first heart failure hospitalisation. **5.** Time to first non-procedural myocardial infarction **6.** Time to first revascularisation following assigned treatment with PCI or CABG. **7.** Time to stroke. **8.** Days Alive and Out of Hospital at 90-and 365-days. **9.** The number of total (first and recurrent) cardiovascular hospitalisations and heart failure hospitalisations. **10.** Kansas City Cardiomyopathy Questionnaire (KCCQ) at baseline, discharge, 3 months, 6 months and then every 6 months until end of trial follow-up. **11.** Seattle Angina Questionnaire-7 (SAQ-7) at baseline, discharge, 3 months, 6 months, and then every 6 months until end of trial follow-up. **12.** Quality of life measured by the EQ-5D-5L questionnaire at baseline, 3 months, 6 months and annually until end of trial follow-up. **Serious Adverse events within 30 days of PCI or CABG: 1.** Stroke **2.** New onset end-stage renal failure defined as requiring renal replacement therapy. **3.** Unplanned mechanical circulatory support (IABP, Impella, VA ECMO). **4.** Major bleeding requiring reoperation or re-hospitalisation. **5.** Major vascular complication requiring interventional radiology or surgical intervention. **6.** All-cause mortality.

	7.Infection defined a septic shock. 8.Pneumonia defined as autopsy diagnosis or roentgenographic infiltrate and a least two of the follow criteria (fever, leukocytosis and positive septum culture; and or deep sternal or leg wound infection requiring intravenous antibiotics and/or surgical debridement).
Planned Size of Sample (if applicable)	Using a time-to-event analysis to detect a Hazard Ratio of 0.7 for the primary outcome with a 1:1 allocation ratio, 90% power, and a 2-sided alpha value of 0.05, a total of 414 events will be required, enrolling 630 participants (n=315 in each arm).
Cardiac MRI sub-study	202 patients from the main trial will be recruited to an imaging sub-study, involving a baseline and follow up cardiac MRI scan at 4 months. The primary outcome is change in ischaemic burden.
Follow up duration	A median follow-up of up to 5 years (and minimum 4 years follow-up) post randomisation.
Planned Study Period	101 months starting from 1st October 2023.
Recruitment Period	41 months with a built in 9-month internal pilot (based on 0.7 participants per location per month). As a contingency, slower recruitment at 0.5 participants per location per month would require 35 locations and 48 months to complete recruitment.
Analysis	The primary analysis of the primary outcome will be performed in the intention to treat population using survival analysis methods and compare groups using a log-rank test calculating the hazard ratio with a cox regression model. All analysis methods will be pre-specified fully in the statistical analysis plan before data lock. Health Economic Evaluation will determine the cost-effectiveness of CABG, compared with PCI, from the perspectives of the UK, NHS, personal social services, and the wider societal perspective. We will conduct the evaluation alongside the clinical trial over a minimum 4-year time horizon and a model-based evaluation over a lifetime horizon. The trial data will be shared with International STICH3 consortium for an individual patient data analysis of multiple similar trials that will test whether CABG is superior to PCI for the outcome All-cause Mortality at 5 years.

ROLE OF TRIAL SPONSOR AND FUNDER

The trial has been funded by a grant from the National Institute for Health and Care Research Health Technology Assessment (NIHR HTA) Programme (ref: NIHR155123). Additional support and resources for the trial will be provided by the participating Trusts and their corresponding Clinical Research Networks (CRN). The sub-study has been funded by a project grant from the British Heart Foundation.

The funder will be responsible for funding the trial but will not be part of the trial conduct, data analysis and interpretation, manuscript writing, and dissemination of results. The Sponsor, the University of Leicester, will be responsible for all aspects of the trial. The University of Leicester is registered as a research Sponsor with the Department of Health and routinely takes responsibility as Sponsor for research activities within the NHS. The Sponsor will delegate duties to other parties, including Leicester Clinical Trials Unit (LCTU), this delegation will be formally documented. However, like the funder, the Sponsor will not be part of the trial conduct, data analysis and interpretation, manuscript writing, and dissemination of results.

TRIAL FLOW CHART

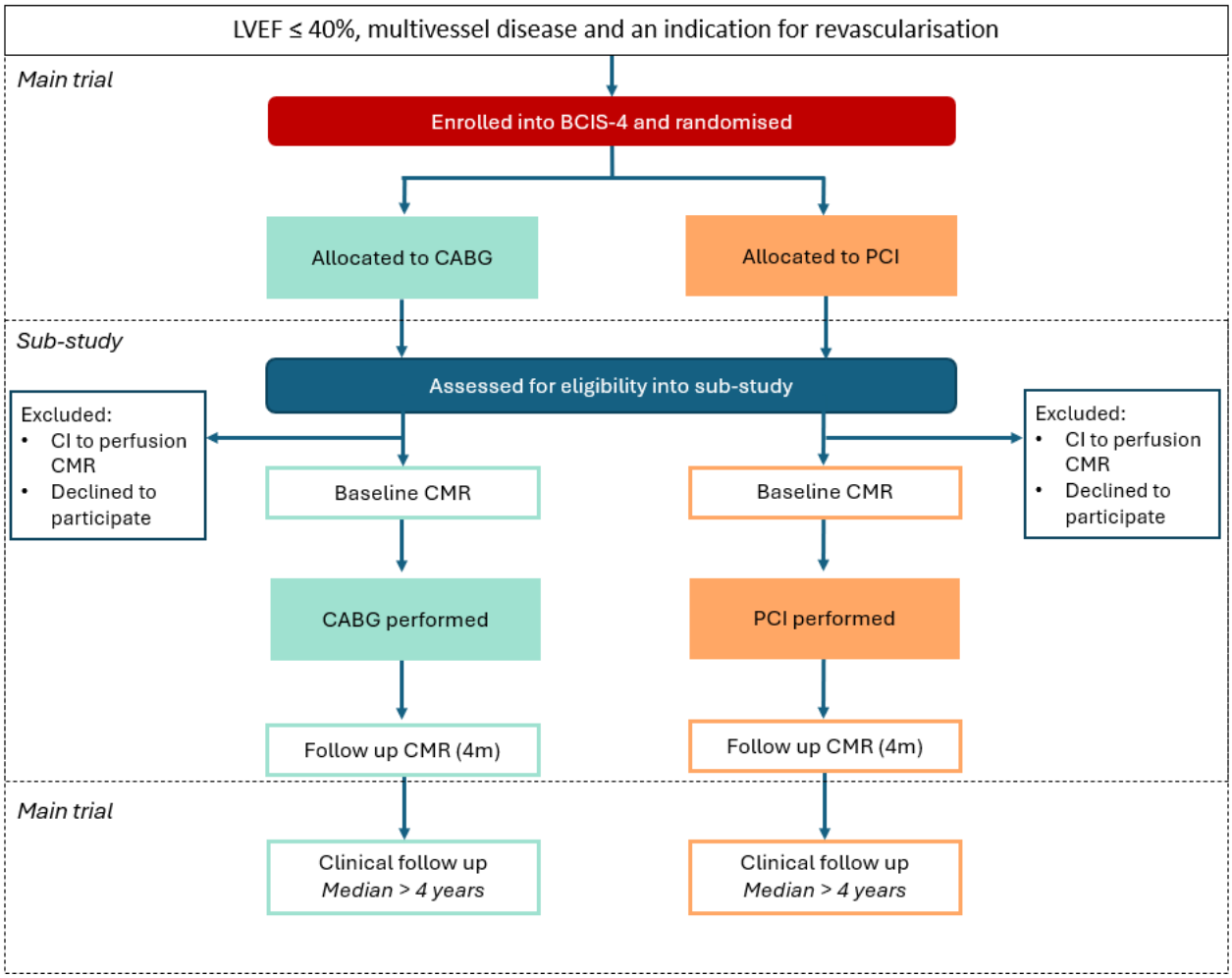


Figure 1 Trial Flow Chart

TITLE

A multicentre randomised trial of surgical versus percutaneous revascularisation of ischaemic left ventricular dysfunction in the United Kingdom, with embedded internal pilot and health economic analysis (STICH3-BCIS4)

BACKGROUND

1.1 THE HEALTH PROBLEM BEING ADDRESSED

Heart failure (HF) affects 1-2% of the population and is increasing in prevalence due to a growing, ageing, more sedentary population, and improved management of acute myocardial infarction (MI) (2, 3). HF causes severe, debilitating symptoms, high rates of mortality, frequent long hospitalisations, and costs the NHS £2 billion per year (2% of the total NHS budget) (4). Coronary artery disease (CAD) is the most common cause of HF, responsible for 52% of cases in patients under 75 years of age, and is the primary cause of HF with reduced ejection fraction (HFrEF) (5, 6).

In the UK, over 20,000 people per year with ischaemic left ventricular dysfunction (iLVSD) and CAD undergo revascularisation with coronary artery bypass grafting (CABG) or percutaneous angioplasty and stents (PCI). However, the choice of revascularisation strategy in HF is not guided by high quality evidence because most randomised controlled trials (RCTs) comparing the effectiveness of CABG versus PCI included small numbers (1%-7%) of people with iLVSD (7, 8). The evidence from these trials may not be generalisable to people with HF; observational analyses suggest that the risks and benefits for CABG (1) and PCI are different in people with – versus people without HF (9). No RCT has compared the effectiveness of PCI and CABG in people with iLVSD. This represents an important unmet need in a high-risk population that experiences all-cause mortality rates of up to 30% at 5 years (1).

1.2 THE CLINICAL IMPACT OF THE HEALTH PROBLEM

In the UK, this knowledge gap is associated with significant and unwarranted variation in care. The proportion of people with HF undergoing multi-vessel revascularisation who undergo CABG ranges from 30% to 100% across Clinical Commissioning Groups (CCGs) in England. This variation is not attributable to differences in measured cofounders and is associated with significant variation in clinical outcomes; 5-year all-cause mortality in the quartile of CCGs with the lowest CABG: complex (multivessel) PCI rates were 34%, whereas in the quartile with the highest CABG: PCI rates it was 29%.

1.3 A REVIEW OF EXISTING EVIDENCE

The 2018 European Society of Cardiology / European Association of Cardiothoracic Surgery (ESC / EACTS) Guidelines on Revascularisation (10) state that coronary revascularisation is superior to medical therapy alone in improving survival in patients with iLVSD, however they conclude that the optimal revascularisation strategy is unclear. ESC / EACTS make a Class I, Level of Evidence A, recommendation for CABG in patients with left main stem or multivessel CAD and higher (>22) Synergy between PCI with TAXUS and Cardiac Surgery (SYNTAX Scores), or in patients with diabetes. They make weaker recommendations for PCI (Class Iia, Iib or III) in these settings. These recommendations are based on the results of multiple head-to-head RCTs comparing PCI versus CABG (reviewed in (7, 8)). Only 1%-7% of people enrolled in these trials had iLVSD.

ESC / EACTS provide a Class I, Level B recommendation for CABG in people with iLVSD, multivessel disease, and acceptable surgical risk. The recommendation is based on the Surgical Treatment for Ischemic Heart Failure (STICH-1) trial, which showed no difference in terms of its primary analysis of the primary outcome all-cause mortality; Hazard ratio (HR) 0.86 (95% Confidence Interval, 0.72 to 1.04; P = 0.12), but demonstrated a survival benefit with extended follow-up; HR 0.84 (95% Confidence Interval, to 0.73 to 0.97; P = 0.02) over 9.8 years in favour of CABG (11, 12). In contrast, PCI receives a Class Iia, Level C recommendation for people with iLVSD where other clinical factors increase surgical risk, in the absence of RCT evidence (10).

The recently reported Percutaneous Revascularization for Ischemic Left Ventricular Dysfunction trial, (13) demonstrated that PCI was not superior to best medical care for the primary outcome all-cause death or heart failure hospitalisation in people with ischaemic left ventricular dysfunction. Patients with recent acute coronary syndromes were excluded a priori and the population enrolled had little or no angina. Furthermore, a proportion of eligible patients who were screened were not subsequently randomised, as they underwent CABG surgery. Hence, the REVIVED findings are unlikely to affect the target cohort for STICH3-BCIS4 (which will include patients with angina and/or a recent Acute Coronary Syndrome (ACS)). Whilst it is difficult to compare the two trials head-to-head, as they enrolled different cohorts of patients and were conducted in different eras of prognostic HF medication, the headline findings of REVIVED and STICH contrast sharply; the first showing no beneficial impact of PCI and the second showing a benefit of CABG surgery on both mortality and hospitalisation, underscoring the importance of a head-to-head trial, which is the rationale of STICH3-BCIS4.

To address this uncertainty, and to assess the feasibility of a RCT of CABG versus PCI in iLVSD, we emulated the STICH3-BCIS4 trial *in-silico* using routinely collected Hospital Episode Statistics (HES) in England. Using regional variation in CABG: complex PCI as a statistical instrument and instrumental

variables analysis to adjust for unmeasured confounders, we estimated that CABG was associated with a 16% absolute reduction in all-cause mortality or cardiovascular hospitalisation at 5 years compared to complex PCI (1). Moreover, to assess the effects of potential selection bias of younger, fitter patients to such a trial we also performed the analysis in a HES cohort matched to individual patient data from STICH. This analysis showed that the treatment effects, even in a highly selected cohort were generalisable to the overall population. The analysis concluded that a pragmatic clinical trial is needed to test this hypothesis and this trial would be feasible in UK centres (1).

RATIONALE

In trials of PCI versus CABG that have enrolled patients with preserved left ventricular (LV) systolic function, early outcomes typically favour PCI because it is much less invasive, results in substantially less organ injury, and allows much more rapid recovery. In contrast, the superior patency of coronary grafts over stents in conditions that increase the likelihood of stent failure; extensive multivessel or left main stem disease, or diabetes, favour CABG in the long-term. In patients with long-term conditions or frailty, the point at which the balance of early risk outweighs the later benefits for CABG is often a matter of judgement. These situations require multidisciplinary team (MDT) Heart Team discussion that includes assessment of surgical risk. In the UK, this is provided by EuroSCORE II. However, multiple additional considerations are included in these discussions for which there is no high-quality evidence:

First, as many patients with iLVSD are elderly, clinicians and patients are often unwilling to accept increased short-term risk even if they might eventually achieve long-term benefit given that they have substantially higher rates of adverse events and early mortality post CABG compared to people without iLVSD. **Second,** the completeness and durability of revascularisation will have a greater relative effect on long-term outcome in iLVSD given the severity of disease and resulting higher mortality rate in the longer term versus those without iLVSD (9). A **third** consideration is the duration of follow-up required to derive benefit. In STICH-1, the survival benefit from CABG versus medical therapy was only evident at 10 years (11, 12). **Fourth,** in STICH-1, although the reduction in cardiovascular (CV) mortality was consistent across all age groups, a convincing reduction in all-cause mortality was only evident in patients less than 60 years of age. In the *in-silico* study, sub-group analysis did not demonstrate a significant interaction between the overall treatment effect and age. However, in patients with chronic kidney disease (CKD) or previous stroke the treatment benefit for CABG was not significant, further highlighting the knowledge gap (1). **Fifth,** quality of life is commonly ranked as more important than survival in patients with HF (14, 15). To our knowledge, no study has evaluated this in the context of PCI versus CABG in iLVSD. **Sixth,** contemporary state-of-the-art PCI is associated with improved outcomes compared to historical practices. The STICH-1 trial is over 15 years old, and contemporary PCI approaches have yet to be compared to CABG in patients with iLVSD. **Finally,** there is a current lack of high-quality evidence to evaluate the cost-effectiveness of PCI, compared with CABG, in patients with iLVSD. Given that HF costs the NHS £2 billion per year (2% of the total NHS budget), and that this cost is likely to increase due to an ageing population and lifestyle factors, it is important that such data be generated to ensure the efficient use of scarce NHS resources. Together, these knowledge gaps highlight the unmet need for a high-quality trial of CABG versus PCI in a representative cohort of UK patients with iLVSD.

1.4 EVIDENCE EXPLAINING WHY THIS RESEARCH IS NEEDED NOW

As concluded by the ESC / EACTS Guidelines, there is no modern high-quality randomised evidence addressing which mode of revascularisation is most effective in patients with iLVSD (10). Therefore, this high-risk group, with all-cause mortality rates as high as 30% at 5 years, are currently managed by Heart MDTs in the absence of evidence. There is wide variation in care, an objective indicator of clinical uncertainty. This is in turn associated with variation in clinical outcomes (1).

1.5 THE STICH-3 INTERNATIONAL CONSORTIUM

The STICH-3 International Trial Consortium has been established to address the research question. The Consortium, which previously delivered the STICH-1 trial, are undertaking nation specific trials comparing revascularisation by CABG vs. PCI in people with iLVSD in nine countries. In each country, the trial addresses research questions prioritised by local funders with a country specific protocol, but all protocols are aligned with the international STICH-3 protocol, with common eligibility criteria and a core case report form (CRF) and outcome set. The international STICH-3 study, a prospective individual patient data meta-analysis that will use a Bayesian Poisson regression model that allows Bayesian predictions at fixed follow-up time points, aims to recruit at least 2,000 participants and is designed to determine whether CABG is superior to PCI in reducing all-cause death. This analysis, led by Professor Mark Petrie, will be co-ordinated and analysed by the SWEDEHEART team, see Figure 4 (Data Flow Diagram). Trials in Sweden and Canada are funded and recruiting. The UK trial, STICH3-BCIS4, will recruit between 20 and 30% of total participants.

THEORETICAL FRAMEWORK

1.6 WHAT THE TRIAL WILL ADD AND HOW IS IT NOVEL?

BCIS-4 represents a collaboration between UK trialists in HF, interventional cardiology and cardiac surgery. It builds on the success of the BCIS-1, 2 and 3 trials (led by Professor Divaka Perera with over 1000 people with iLVSD randomised to date (13, 16, 17)), the new British Heart Foundation Clinical Research Collaborative networking platform, and the National Cardiac Surgery Clinical Trials Initiative that is co-led by the National Cardiac Surgery Patient and Public Involvement and Engagement (PPI&E) group (18, 19). The applicants have used novel *in-silico* trial modelling techniques to underpin the rationale and provide evidence of feasibility and generalisability for STICH3-BCIS4 (1). This will directly inform the analysis plan of routinely collected healthcare data for ascertainment of the primary and key secondary outcomes in the trial. BCIS-4 uses a pragmatic and efficient design, and for the first time evaluates patient reported outcome measures (PROMS) and health economic outcomes in people with iLVSD undergoing CABG or PCI. A work package designed to increase recruitment from underserved groups is integrated within the trial. Finally, the results of STICH3-BCIS4 will provide insights into the validity of the *in-silico* trial modelling approach.

1.7 HOW THE TRIAL MIGHT IMPACT ON CLINICAL PRACTICE

The trial results will inform patients, clinicians, international practice guidelines, and payers as to the pros and cons of CABG vs. PCI in patients with iLVSD requiring coronary revascularisation. Results from this trial will be generalisable to a large proportion of patients with advanced iLVSD and will inform Heart Team discussions and appropriateness of care. If CABG has a survival advantage over PCI, it will remain the preferred strategy for revascularisation in Heart Team discussions and reduce the number of non-evidence-based PCIs. If CABG is not superior to PCI, the results have the potential to minimise the early mortality and mortality hazards associated with CABG and to facilitate the access to revascularisation in a growing population of patients with HfrEF.

RESEARCH QUESTION/AIM(S)

1.8 HYPOTHESIS

CABG is superior to PCI in terms of primary and secondary clinical and cost-effectiveness outcomes in people with iLVSD.

1.9 OBJECTIVES

1. STICH3-BCIS4 will compare PCI versus CABG for the revascularisation of patients with iLVSD, defined as left ventricular ejection fraction (LVEF) ≤ 40% and multivessel coronary artery disease.
2. An internal pilot will test design assumptions around recruitment at 12 months.
3. A health economic analysis will determine cost-effectiveness.
4. A PPI researcher led work package will improve recruitment in underserved groups.
5. The trial will contribute data to the international STICH-3 analysis that will evaluate the comparative effectiveness of CABG versus PCI in iLVSD for the outcome all-cause mortality.

1.10 OUTCOME

The trial will be considered positive if the time-to first event for the primary outcome of all-cause mortality or cardiovascular hospitalisation is superior (longer) in the CABG arm (intervention) versus the PCI (control) arm at the 5% (two-sided) statistical significance level with a HR of less than or equal to 0.7.

TRIAL DESIGN

1.11 TRIAL DESIGN

Multicentre, open label, parallel group, RCT of two common revascularisation strategies in people with iLVSD, using a superiority design, with embedded internal pilot, and health economic analysis.

1.12 TRIAL SETTING

At least 28 tertiary cardiac centres in the UK will recruit to STICH3-BCIS4. Over 100 international locations will recruit to STICH-3.

1.13 PARTICIPANTS

1.13.1 Target Population

Patients with multivessel disease, a documented indication for revascularisation, who are deemed by the local Heart Team to be appropriate and suitable for revascularisation by either PCI or CABG and meet all the eligibility criteria.

1.14 ELIGIBILITY CRITERIA

1.14.1 Inclusion Criteria

1. Age ≥18 years
2. LVEF ≤ 40% (quantified by any recognised imaging modality) within the last 12 months. If the patient has had an MI within the last 12 months post-MI imaging is required with LVEF ≤ 40%
3. Significant amount of myocardium at risk defined as coronary artery disease with BCIS myocardial jeopardy score ≥6 on recent (<6 months) coronary angiogram
4. Signed informed consent

1.14.2 Exclusion Criteria

5. Decompensated heart failure requiring inotropic support, invasive or non-invasive ventilation or mechanical circulatory support less than 48 hours prior to randomisation
6. ST Elevation Myocardial Infarction (STEMI) <72 hours
7. Valvular heart disease indicating the need for mechanical repair/replacement or any other structural cardiac surgery (e.g. LV aneurysm resection)

8. Pregnancy
9. Individuals who have declined access to Hospital Episode Statistics for research purposes
10. An inability to understand the languages in which the trial materials are provided

1.15 SAMPLING

Eligibility will be determined by the Heart Team at individual locations. Patients will be identified in the cardiology or cardiac surgery (in person/ hybrid/ virtual) clinics, catheterisation laboratories, Heart Team meetings or wards at each hospital before the index revascularisation procedure where informed consent will be obtained. The benefits and risks of participating in the trial will be explained to the patient, and the patient will have the opportunity to read the Participant Information Sheet (PIS) and Informed Consent Form (ICF) and ask any questions they may have. Patients and carers may attend once or more times, or have subsequent telephone or video calls, to carefully consider their participation. Prior to conducting any trial-related procedures, the patient must provide informed consent to participate by signing the Institutional Review Board / Research Ethics Board (IRB/REB) approved ICF. Patients will be randomised on the day of consent. Recruitment of participants will be guided by the INCLUDE Ethnicity Framework and a STICH3-BCIS4 trial work stream that aims to increase representation from underserved communities as described above.

1.16 SIZE OF SAMPLE

STICH3-BCIS4 is a superiority trial powered for the primary outcome of survival time from cardiovascular hospitalisation and all-cause mortality. Using a time-to-event analysis to detect a HR of 0.7 with a 1:1 allocation ratio, 90% power, and a 2-sided alpha value of 0.05, a total of 414 events are required. Participants will receive a minimum of 4 years follow-up and 630 participants (n=315 in each arm) will be randomised in the UK.

The sample size is based on the following assumptions. **1.** A minimum clinically important treatment effect HR for CABG vs. PCI of 0.7 that is written within the range of treatment effects (0.63 to 0.74) observed in previous pragmatic RCTs of CABG versus PCI that have changed clinical practice (20-22). The proposed effect size was chosen as stakeholders felt that a large benefit would be required to convince clinicians of the benefits of more invasive treatment (CABG) in this high-risk population. **2.** Frequency of death or cardiovascular hospitalisation of 70% at 5 years in the PCI arm, from HES. To calibrate this outcome, we compared the frequency of death or *heart failure* hospitalisation at 5 years in the STICH-1 matched HES cohort (42%) to event rates in both REVIVED and STICH trials (see Figure 1, from reference (1)). As heart failure hospitalisation is underestimated in HES data, the expected

outcome frequencies are consistent. Coding for CV hospitalisation is more accurate and is included in the primary outcome for STICH3-BCIS4. **3.** A total study period of 89 months. **4.** An expected crossover rate of 8% typical for CABG vs. PCI trials; range 7-9%. (7, 8). **5.** Zero attrition due to the use of HES / Office for National Statistics (ONS) data for the primary outcome.

1.17 OUTCOMES

1.17.1 Primary Effectiveness Outcome

Survival time from cardiovascular hospitalisation all-cause mortality: defined in whole days measured as time from randomisation until date of first cardiovascular hospital or death from any cause, whichever happens first. Participants who withdraw or are lost to follow-up will be censored at the date last known to be alive and free from cardiovascular hospitalisation. Participants not having an event at the time of the analysis will be censored at the last date known to be alive and free from cardiovascular hospitalisation.

1.17.2 Secondary Effectiveness Outcomes

1. Overall survival time, defined in whole days measured as time from randomisation until date of death from any cause. Participants who withdraw or are lost to follow-up will be censored at the date last known to be alive. Participants not having an event at the time of the analysis will be censored at the last date known to be alive.
2. Cardiovascular survival time, defined in whole days measured as time from randomisation until date of death from cardiovascular cause. Participants who withdraw or are lost to follow-up will be censored at the date last known to be alive. Participants not having an event at the time of the analysis will be censored at the last date known to be alive. Participants who die from other causes will be censored at date of death.
3. Time until cardiovascular hospitalisation, defined in whole days measured as time from randomisation until cardiovascular hospitalisation. All other participants will be censored at last known follow-up assessment having not had a cardiovascular hospitalisation.
4. Time until heart failure hospitalisation, defined in whole days measured as time from randomisation until heart failure hospitalisation. All other participants will be censored at last known follow-up assessment having not had a heart failure hospitalisation.

5. Time until non-procedural myocardial infarction, defined in whole days measured as time from randomisation until non-procedural myocardial infarction. All other participants will be censored at last known follow-up assessment having not had a non-procedural myocardial infarction.

6. Time until revascularisation other than assigned treatment, defined in whole days measured as time from randomisation until revascularisation. All other participants will be censored at last known follow-up assessment having not had a revascularisation.

7. Time until stroke, defined in whole days measured as time from randomisation until date of stroke. All other participants will be censored at last known follow-up assessment having not had a stroke.

8. Days Alive and Out of Hospital at 90 and 365 days, defined in whole days measured as a continuous variable, calculated as last known date to be alive, minus discharge date following assigned treatment, minus all episodes of hospitalisation (discharge date minus admission date).

9. The number of total (first and recurrent) cardiovascular hospitalisations and heart failure hospitalisations, defined as a count and calculated as the sum of all episodes of hospitalisation with cardiovascular or heart failure cause.

10. Kansas City Cardiomyopathy Questionnaire (KCCQ), derived clinical summary score as a continuous measure collected at discharge and then 3 months and 6 months, and every 6 months thereafter by telephone / ResearchApp®

11. Seattle Angina Questionnaire-7 (SAQ-7), derived overall summary score as a continuous measure collected at discharge and then 3 months and 6 months, and every 6 months thereafter by telephone / ResearchApp®.

1.18 ADVERSE EVENTS OF SPECIAL INTEREST (AESI) WITHIN 30 DAYS OF PCI OR CABG

The following will be collected as AESIs within 30 days of PCI or CABG with the aim of providing reportable data to the Data Monitoring Committee (DMC) at regular meetings ahead of HES data being available.

1. Stroke. 2. New onset end-stage renal failure requiring renal replacement therapy. 3. Unplanned mechanical circulatory support (intra-aortic balloon pump (IABP), Impella, venoarterial extra corporeal membrane oxygenation (VA ECMO)). 4. Major bleeding requiring reoperation or rehospitalisation. 5. Major vascular complication requiring interventional radiology or surgical intervention. 6. All-cause mortality. 7 Infection defined a septic shock 8. Pneumonia defined as autopsy diagnosis or roentgenographic infiltrate and a least two of the follow criteria (fever, leukocytosis and positive septum culture; and or deep sternal or leg wound infection requiring intravenous antibiotics and/or surgical debridement).

1.19 HEALTH ECONOMIC OUTCOMES

1. Health-related quality of life will be captured using European Quality of Life 5 Dimensions 5 Level Version (EQ-5D-5L) questionnaire. **2.** Healthcare resource use and productivity loss will be captured using a bespoke resource questionnaire. The outcomes will be collected at baseline, 3 months, 6 months, 12 months and then annually to the end of trial follow-up.

1.20 FOLLOW-UP

Patients will be followed up during their index hospital stay (or stays for planned staged PCI). Primary and secondary outcome measurements will be collected for a minimum follow-up of 4 years and given a 41-month recruitment period will result in a median follow-up length of 5.3 years. Outcome measurements during follow-up (excluding PROMS and 30-day serious adverse events (SAEs)) will be determined through routinely collected HES/ONS data.

Quality of Life Assessments, and Health Economic Outcomes will be ascertained at baseline, and then using telephone follow-up or self-completion using the ResearchApp™ (Healthbit®) at 3 months, 6 months, 12 months and then annually post randomisation (± 28 days) until the end of trial follow-up. Please refer to **Table 1** for further details about follow up visits.

Consent for life-long trial follow-up following completion of this trial's current funded period (i.e., beyond 41 months recruitment + 48 months follow-up period) using routinely collected healthcare data will be obtained.

Consent will be sought for friend(s)/relative(s) to provide information if and when it is established that the participant is not contactable, has lost capacity or is too unwell, to ascertain what has happened to them. Where available and willing, two alternative contacts should be sought, through the means of the Friend/Relative Follow Up Consent Form. If it is subsequently determined that the participant has lost capacity or has become too unwell to respond to follow-ups, the research teams will initially attempt contact with the named friend(s)/relative(s) to seek consent using the Friend/Relative Follow Up Consent Form. We will also seek consent to notify their general practitioner (GP) of their participation of their participation in the trial.

1.21 END OF TRIAL

For an individual participant, the end of trial is defined as time of last follow-up visit (4 years post randomisation), participant withdrawal, or mortality, whichever occurs sooner.

Participants will be considered lost to follow-up if there is insufficient information or inability to gather necessary data points required for the trial, although this is expected to be anomalous as data points are routinely collected in standard practice. In the instance where it is not possible to obtain follow-up data for one particular point in time (e.g., 6-month follow-up) the participant should not be considered as lost to follow-up at this point but rather the next follow-up in sequence should be attempted at the relevant time point within the stipulated window (e.g., 12 months). This process should be followed up until the last follow-up visit at which point if no further follow-ups have been completed from timepoint X, then the participant should be considered as lost to follow-up from that timepoint. This should not prevent the performance of NHS Digital (or equivalent) extractions, unless an explicit withdrawal from this element of the trial is communicated.

The length of time covered by routinely collected data extractions will depend on the point at which the participant consented to participation in the trial. For example, a participant recruited early on in the recruitment phase (months 5 – 45) will have more routinely collected data collected until last patient last visit (LPLV) (month 93) than a participant recruited later on in the trial.

On the whole, the definition of end of the trial is the final data lock following any data query resolutions (months 94 – 97, or approximately 8 years). Following this, participants will be informed of the trial study result should they have explicitly requested this by way of informed consent, thus being reflected on the ICF. This will be performed by each recruiting location.

TRIAL PROCEDURES

1.22 SCREENING

Locationss will be responsible for ensuring that participants have provided informed consent and that this is recorded in a data secure manner. Before revascularisation, non-identifiable, non-personal data will be collected electronically by the research staff at each location on screening forms recording trial eligibility and consent rates. Specific screening requirements, including laboratory or diagnostic testing, are not required. Details of all participants approached for the trial and reasons for non-participation (e.g., reasons for being ineligible or refusal where provided) will be documented.

1.23 PLANNED RECRUITMENT RATE

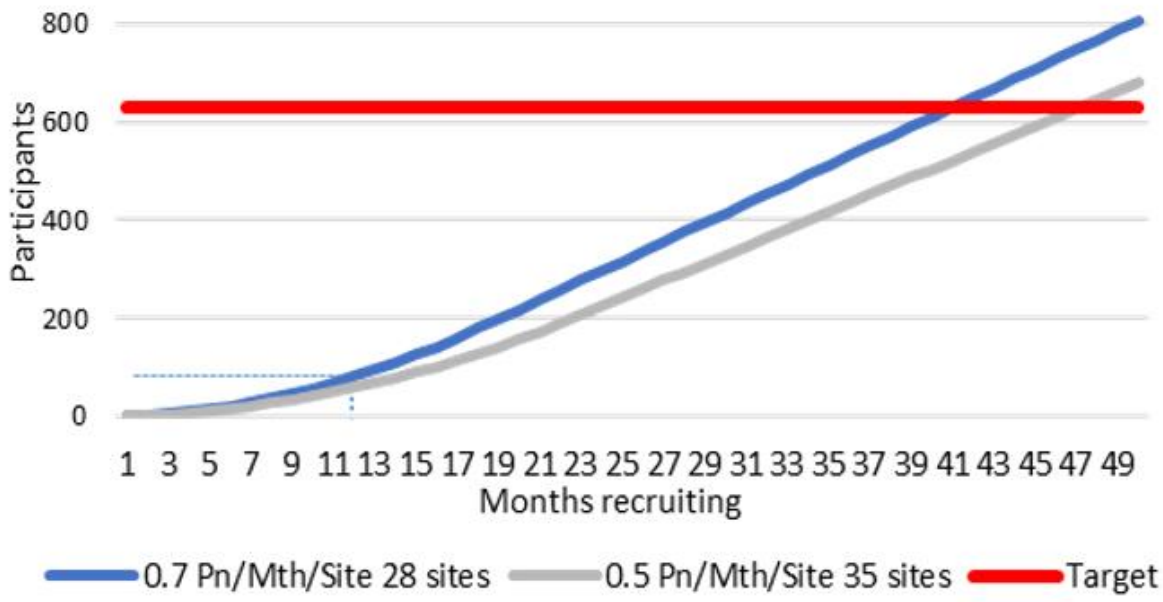


Figure 2 Target Recruitment Rates

With at least 28 centres, set up over 18 months at a rate of 1.5 centres per month, and a recruitment rate of 0.7 pts/location/month, the target sample size of 630 patients will be achieved in 41 months. As a contingency, slower recruitment at 0.5 pts/location/month would require 35 locations and 48 months to complete recruitment (above Figure 2).

The timetable is: Start Date 1st October 2023. Months 1 – 4 set-up, months 5 – 45 recruitment, months 46 – 93 follow-up to last patient last visit (LPLV), months 94 – 97 data cleaning, data lock, months 97 – 101 analysis, location closedown, dissemination.

1.24 PARTICIPANT IDENTIFICATION

All eligible patients will be identified by the clinical care team and provided with a Participant Information Sheet (PIS). This will be followed up with further telephone or face-to-face discussion by a clinician and/or clinician researcher should the patient be agreeable.

1.24.1 In the Elective Setting

Potentially eligible patients will be identified from clinic lists or Heart Team meetings, and contacted by a clinician and/or clinician researcher either during clinic attendance or by post, should they have been spoken to about research at the hospital prior to the posting of this information. All eligible patients who are approached will be given the PIS. The patient will then be offered an opportunity for face-to-face discussion of the PIS and informed consent, if appropriate, at a scheduled clinic visit. Alternatively, the patient may choose to speak to a local research team member via telephone having received the PIS to discuss it at a later date. Written or electronic consent will be obtained in the latter scenario to protect the participant from burden from additional research visits. Patients and their carers may take more than one visit to decide upon participation. Subsequent visits can be over the telephone or via a Microsoft Teams call (or similar platform) to again protect the participant from additional burden.

1.24.2 In the Urgent Setting

Potentially eligible patients will be given the PIS as soon as possible after the Heart Team has determined suitability for both PCI and CABG. The patient will speak to a clinician and/or local clinician research team member (face-to-face) who will discuss the PIS and seek consent if the patient is agreeable and able to provide consent. There will be no requirement that a patient has the PIS for a minimum duration (please see section 1.25). Despite the short notice, it is important to include these patients for the applicability of the trial findings since about 40% of patients having coronary artery bypass, and 70-80% of patients undergoing PCI are admitted as urgent cases. These patients often have left ventricular dysfunction and are an important target population for the trial. Written informed consent will be obtained during the hospital admission prior to randomisation.

1.25 CONSENT

Prior to participation in the trial, patients will be required to provide informed consent. It will be possible to do this either via written informed consent or electronic consent using the REDCap consent module. The PIS, ICF(s) and any modifications will be submitted and approved by a Research Ethics Committee (REC), the Health Research Authority (HRA), Study Sponsor and the local Trust Research and Development/Innovation (R&D/I) department prior to implementation. The process of consent by either method will require individual discussion with the patient.

There is no requirement that a patient must have the PIS for a minimum duration prior to consent in either setting and by either method, considering the often-urgent requirement for revascularisation in people presenting with ACS. However, every effort should be made to maximise the amount of time the patient has for consideration of trial enrolment.

Written or electronic versions of the PIS and ICF will be presented to the participant detailing no less than: the exact nature of the trial; the implications and constraints of the protocol; the known side effects and any risks involved with taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason and without prejudice to future care, and with no obligation to give the reason for withdrawal.

Having considered the information, the patient may give their consent straight away. Alternatively, if they wish to consider the information and have the opportunity to ask questions of the Investigator, their GP or other independent parties to aid their decision of whether they wish to participate in the trial, they will be afforded this time to make their decision (setting dependent).

The person who obtained consent must be suitably qualified and experienced, and have been authorised to do so by the Principal Investigator (PI) as delegated on the Delegation of Authority and Signature Log for the trial. In this particular trial, consent can be sought by Research Nurses (if local regulations allow), or by the participating surgeons or surgical trainee, if all appropriately delegated to do so. Eligibility must be confirmed by a delegated clinician and / or clinician researcher on ResearchApp™ (HealthBit®).

1.25.1 Written Informed Consent

Written Informed Consent will be obtained by means of participant dated signature and dated signature of the person who presented and obtained the informed consent. The original signed ICF will be

retained at the trial location within the Investigator Site File (ISF). A copy of the signed ICF will be provided to the participant and a copy retained in the participant medical notes.

Participant identifiers will be allocated using the Sealed Envelope randomisation system and recorded on the corresponding written ICFs in the space provided.

1.25.2 Electronic Consent

The trial will offer the option of electronic consent as an alternative to face-to-face methods. It is recognised that not everyone will be able to utilise this method due to technology access and so this option is only intended as an alternative to face-to-face consent. This model will however allow for minimisation of participant burden as well as a resilient option. The electronic consent process will mirror the content of the paper documents, including a localised electronic PIS, and will be supported by the REDCap electronic consent module. The ICF will reflect the same options but participants will record consent by marking a radio button for each consent option as opposed to initialling boxes as reflected by the paper method. This process will be supported by a Video/Telephone Consent Form to be completed by the researcher or delegated individual at the trial location performing consent, confirming that the participant has understood the information and consent process. The electronic consent system will only be accessible by appropriate personnel active on the trial who will only be able to view consents for the trial location with which they are associated. The system will notify of any errors in a submitted consent form which can be rectified by the participant only, as well as produce a PDF for the participant, research and medical records upon which research staff at the trial locations should record the participant identifier once the participant has been randomised using Sealed Envelope. Where appropriate, electronic consent will be supported either over the telephone or by videocall between the participant and the clinician/researcher. Trial locations wishing to utilise electronic consent should nominate one person to undertake the trial location Set-up Exercise and anyone else wishing to use the system to issue consent invitations to potential participants should read the training document. Following this, anyone wishing to be issued with a REDCap account to invite potential participants using a nominated email address should be delegated this specific activity separate to, but in addition to, that of performing consent.
Whilst the option of electronic consent will be offered to reduce participant burden, baseline assessments must still be conducted in person following consent and ahead of randomisation to allow for the required clinical measures to be performed.

1.26 METHOD OF IMPLEMENTING THE RANDOMISATION/ALLOCATION SEQUENCE

1.26.1 Randomisation

Randomisation with allocation concealment will utilise a centralised, web-based system (Sealed Envelope Ltd, London, UK). Participants will be randomised on the day of consent in a 1:1 ratio to either CABG or PCI stratified by centre and clinical presentation; acute versus chronic coronary syndrome.

The participant's initials, date of birth, and sex will be entered into the randomisation system which will generate the participant's randomised allocation (PCI or CABG) and unique participant identifier (Trial ID).

1.27 ALLOCATED TREATMENT

Revascularisation appropriateness and feasibility will be confirmed by the local Heart Team (a minimum of an interventional cardiologist and a cardiac surgeon). Revascularisation should be performed as soon as dictated by clinical urgency but no more than 18 weeks (+/- 28 days) from randomisation for elective cases or 6 weeks from randomisation for urgent/ACS cases (+/- 28 days).

Complete revascularisation of all viable myocardium is the goal for all patients. Revascularisation will be attempted on/for significant lesions in major coronary vessels/side branches as planned by the local Heart Team, with the general recommendation of stenotic/occluded vessels with diameter >1.5mm. As per contemporary ESC treatment guidelines, physiological or non-invasive functional confirmation of haemodynamic severity should be sought in any vessel that has <90% stenosis. As a measure of process, and to estimate completeness of revascularisation, the British Cardiovascular Intervention Society Jeopardy Score (BCIS-JS) will be calculated at baseline and after final stage PCI or CABG using the www.BCIS-JS.com calculator.

1.27.1 Co-enrolment

Co-enrolment is permitted in line with the inclusion and exclusion criteria of the STICH3-BCIS4 protocol as well as the corresponding trial being considered for co-enrolment with.

1.27.2 Percutaneous Coronary Intervention

For patients randomised to PCI, contemporary best practices should be used. These include:

1. Physiological assessment of stenosis severity (with invasive fractional flow reserve (FFR) and/or angio-based FFR estimation) in all coronary stenoses with a visual stenosis severity ≤ 90% and the use of intracoronary imaging (with intravascular ultrasound (IVUS) or optical coherence tomography (OCT) to document the final result, as a minimum, but to guide all aspects of the procedure). See Section 1.27.3 below regarding the collection of this data.
2. IVUS/OCT assessment post stent implantation for optimisation of stent deployment is mandated with the following goals:
   a) A relative stent expansion of > 80% (minimum stent area (MSA) divided by average reference lumen area) should be obtained in routine clinical practice.
   b) An MSA of > 5.5mm^2 by IVUS and over 4.5mm^2 by OCT should be achieved in on-left main lesions wherever possible.
3. IVUS/OCT use pre-PCI is recommended (but not mandated) with the following guidelines:
   a) Plaque preparation based on pre-procedural IVUS/OCT. Rotational atherectomy or cutting, scoring balloon, shockwave should be considered if a >270° arc of superficial calcium is evident in IVUS or OCT.
   b) Selection of stent size dimensions.
      i. In *non-bifurcation* stenosis: the chosen stent diameter should match the distal vessel diameter or area.
      ii. In *bifurcation* stenosis: stent diameter should match distal (daughter) branch, with mandatory post-dilation of the proximal (mother) segment and polygon of confluence (POC) with a larger balloon size according to IVUS/OCT imaging (Proximal Optimisation Technique procedure, POT). IVUS/OCT should also be used to guide stent length by identification of proximal and distal landing zones that have minimal or no atheroma.
      iii. Incomplete stent expansion: aim to achieve MSAs as above by post dilation.
      iv. Incomplete stent apposition. A non-compliant balloon sized IVUS/OCT to vessel luminal diameter or area will be used in segments with malposition.
4. Transradial access is strongly encouraged where there is no contraindication.
5. New-generation drug-eluting stents, atherectomy and/or intravascular lithotripsy for extensive calcification, recommended bifurcation techniques are strongly encouraged (23).
6. Where patients have one or more chronic total occlusions supplying viable myocardium, the participant should only be enrolled if the necessary expertise in CTO-PCI is available, if the Heart Team consider the risk/benefit balance favours CTO intervention.

7. Staging PCI is permitted where the cardiologist feels that this is in the patient's best interest, but the intention to stage must be documented at the first procedure.
8. Mechanical circulatory support should be reserved for bailout in case of mechanical complication of the PCI or developing cardiogenic shock, unless new evidence arises during the course of the trial to indicate benefit to routine use.

Details of physiological, intracoronary imaging, and advanced percutaneous methods will be recorded in the CRF as will mechanical circulatory support.

1.27.3 Stress perfusion CMR sub-study physiology study collection

For trial locations participating in the CMR sub-study, coronary angiography and pressure wire studies will be pseudonymised and sent to the King's College London physiology core laboratory for wire and non-wire based physiology analysis. This will include baseline diagnostic coronary procedures in all study patients, and post procedure imaging +/- physiology data from participants in the PCI arm. Information on the sub-study is detailed in section 1.33.

1.27.4 Coronary Artery Bypass Grafting

The left internal thoracic artery is the preferred graft for the LAD. The choice of performing on-pump or off-pump surgery will be at the discretion of the operator based on the local expertise. Perioperative management of cardiopulmonary bypass will follow local protocols. Minimally invasive or hybrid revascularisation is not allowed. The use of multi-arterial graft, intraoperative echocardiography, epi-aortic ultrasound, and anaesthetic technique will be tailored to the patient and the centre, with best contemporary practices encouraged. Details of the surgical procedure will be captured in the eCRF. Valvular heart disease indicating the need for mechanical repair/replacement or any other structural cardiac surgery (e.g. LV aneurysm resection). Planned major concomitant cardiac surgery is an exclusion criterion, however unplanned concomitant surgery will occur as part of normal care and will be recorded.

1.27.5 Concomitant Therapies

All participants will receive antiplatelet therapy and anticoagulation as defined by the most recent international practice guidelines (24-26). **Guideline-directed** medical therapy for HFrEF (27) may evolve during the course of BCIS-4 recruitment and follow-up but currently includes 1). Beta-blockers 2). Angiotensin-converting enzyme inhibitors (ACE-I), or angiotensin receptor blockers (ARB) or

sacubitril/valsartan 3). Mineralocorticoid receptor agonists (MRA) 4). SGLT2 inhibitors adjusted to optimally tolerated doses unless contraindicated. We will mandate that every effort be made to establish patients on optimally-tolerated medical therapy for HFrEF, however, as decisions regarding revascularisation are generally made at the time when patients undergo angiograms and after the Heart Team makes a decision that there is equipoise between PCI and CABG, in some cases optimisation of medical therapy may occur after the revascularisation procedure.

We will strongly encourage the research teams to refer patients to their local heart failure team for ongoing management. Diuretics and NHS DigiTrials use will be individualised to patient-specific indications. Implantable cardioverter defibrillators (ICD) and cardiac resynchronisation therapy will be used as per the most contemporary guidelines (28). Medical therapy for secondary prevention of CAD will also be individualised by Heart Teams as per guideline recommendations. Angina will be managed as defined by the Chronic Coronary Syndromes (CCS) practice guidelines (29). Regular heart failure medications will be captured at follow-up visits. Heart failure medications and ICDs/ cardiac resynchronisation therapy (CRT) will be recorded at baseline and follow-up in the eCRF.

1.27.6 Duration of the Intervention

Revascularisation will be completed as per institutional norms after consideration of presentation, access to care, and resources. In ACS, revascularisation should be encouraged to be undertaken during the index admission but patients may be discharged to return for PCI or CABG. If this is the case, revascularisation should be undertaken as soon as dictated by clinical urgency but no more than 6 weeks (+/- 28 days) of randomisation. For non-ACS cases, the assigned treatment should be undertaken as soon as possible after randomisation and no more than 18 weeks (+/- 28 days) later.

1.27.7 Table 1 Schedule of Processes

Assessment										
	Screening	**Baseline Assessment**	**Index Procedure**	**Post Procedure until Discharge**	**3 Months**	**6 Months[1]**	**12 Months[1]**	**6 Months and every 6 Months to 4 Years**	**Every 12 months to 4 Years[1]**	**Following LPLV**
Visit window (days) (± number of days this visit can take place ahead or after its due date)	**-120 to 0**	**-90 to 0**	**Day 0**	**Day of revascularisation procedure until hospital discharge**	**+/- 28 days after Day 0**	**+/- 28 days after Day 0**	**+/- 28 days after Day 0**	**6 months +/- 28 days after Day 0**	**+/- 28 days after Day 0**	
Informed Consent	X									
Inclusion/Exclusion	X									
Revascularisation and feasibility confirmed by local Heart Team	X									
Pregnancy Test[2]	X[2]									
Demographics, Height and Weight		X								
Medical/Cardiac History (including long term conditions and severity of cardiac diseases		X								
Risk Scores (BCIS Myocardial Jeopardy Score and EuroSCORE II		X		X						
Randomisation		X								
NYHA Class and CCS Class		X		X	X			X		
Kansas City Cardiomyopathy Questionnaire (KCCQ)		X		X	X			X		

Assessment	Screening	Baseline Assessment	Index Procedure	Post Procedure until Discharge	3 Months	6 Months[1]	12 Months[1]	6 Months and every 6 Months to 4 Years	Every 12 months to 4 Years[1]	Following LPLV
Visit window (days) (± number of days this visit can take place ahead or after its due date)	**-120 to 0**	**-90 to 0**	**Day 0**	**Day of revascularisation procedure until hospital discharge**	**+/- 28 days after Day 0**	**+/- 28 days after Day 0**	**+/- 28 days after Day 0**	**6 months +/- 28 days after Day 0**	**+/- 28 days after Day 0**	
Seattle Angina Questionnaire 7 (SAQ-7)		X		X	X			X		
EQ-5D-5L		X[1]			X[1]	X[1]	X[1]		X[1]	
Health Care Resource Use		X[1]			X[1]	X[1]	X[1]		X[1]	
Revascularisation procedures and revascularisation completeness[3]			X[3]							
Procedural Data Collection				X						
Concomitant Medications[4]		X[4]	X[4]	X[4]	X[4]			X[4]		
Clinical Events[5]			XXXXXXXXXXXXXX[5]							
Routinely collected data extraction (HES/ONS/NICOR)[6]										X[6]
Cardiac MRI sub-study		Baseline cardiac MRI			Repeat MRI (4 months post revasc)					

[1] Assessment timepoints included for purposes of Health Economics only (EQ-5D-5L and Health Care Resource Use). Health Economic timepoints, where required, match the time point requirements of the other follow-up questionnaires and should be conducted together. Where a timepoint does not require Health Economics questionnaires to be completed, all other measures should be completed in line with the schedule. [2]Women of childbearing potential. [3]May include Chest X-Ray (CABG only, location dependant). [4]Includes antiplatelet therapy and anticoagulation (defined by most recent international practice guidelines), statins, and heart failure treatment as per guideline recommendation. [5]Clinical events from the start of surgery until hospital discharge. The following clinical events will be assessed through review of the patient medical records/chart, and reported in the eCRF from the start of the index procedure until discharge. [6]Where explicit consent is provided and remains without withdrawal.

1.28 STEPS TO ADDRESS POTENTIAL INEQUITY OF SAMPLING ACROSS THE POPULATION

STICH3-BCIS4 recruitment aims to reflect the diversity of the UK population, and the team will develop tools that anticipate how health inequalities interact to create barriers to inclusion among underserved groups. A dedicated Patient Researcher will deliver this component of the research plan in partnership with the Leicester Centre for Ethnic Health Research (LCEHR), which has expertise in engagement with underserved communities, developing competencies in research staff, and mitigating the effects of health inequalities on research participation. To ensure effective engagement, the Patient Researcher will be employed by the LCTU and work alongside the trial management team. As well as the below, steps will be taken to provide patient facing documents in a variety of languages, as well ResearchApp™ (Healthbit ®) for direct participant data entry. Specific steps will include:

1.28.1 Engagement with Underserved Groups

A nominated Community Engagement Officer will ensure application of all the expertise of the LCEHR. They will work with the Patient Researcher to co-host workshops and advisory groups with ethnic minorities and other underserved groups to ensure their perspectives are heard in the development of recruitment techniques, paperwork, and other resources for engagement that can mitigate social, cultural, educational, or language barriers to participation.

1.28.2 Effective Community Engagement and Cultural Competence Training

To ensure the research team are culturally competent and confident with engaging with underserved groups during this trial, the LCEHR will offer training to the Patient Researcher who will then disseminate this throughout the wider research team. Modules include the use of an online toolkit that provides researchers with a framework to improve participation in research, making it more diverse and inclusive. These materials will be road tested in a national workshop, hosted by the Patient Researcher and the LCEHR and attended by participating investigators from all regional centres prior to implementation.

1.28.3 Impact

To ensure the research team are conducting research in an appropriate manner and making it inclusive, the LCEHR will support the team to conduct their own Equality Impact Assessments, by providing a toolkit and inviting the research team to drop-in training sessions to guide completion.

1.28.4 Dissemination

The Patient Researcher will work with LCEHR staff to develop and effective dissemination strategy to promote the importance of the research findings to underserved groups. This will involve workshops after trial completion to identify how best to share our results and ensure they reach all communities and to develop an advocacy strategy to make sure that the results each key stakeholders and decision makers, including by participating in a national stakeholder event to disseminate trial findings. In addition, to disseminate new knowledge arising from the Patient Researcher's work, they will produce outputs for investigators, researchers and participants, including a publication in a peer reviewed journal and other outputs.

1.29 WITHDRAWAL CRITERIA

The trial will adhere to the Principles for Handling end-of-participation Events in Clinical Trials Research (PeRSEVERE) (https://perseverepriciples.org) so that all patients are at the centre of the trial and their wellbeing considered at every step. If a patient chooses to withdraw their participation from the trial, they will be treated with respect, courtesy and will be offered the opportunity to provide feedback to the research team regarding the reason(s) for their withdrawal.

During recruitment, the investigator or designee will explain to participants that they are under no obligation to enter the trial and that they can withdraw at any time, without having to give a reason and without prejudicing their further treatment. If a patient states that they wish to withdraw, exactly what they mean by "withdraw" will be established, the extent of withdrawal will be documented in the patient notes and entered in the eCRF. The component parts of which any or all can be withdrawn are as follows:

- Withdrawal from trial assessments
- Withdrawal from procedure
- Withdrawal from self-completed questionnaires
- Withdrawal from performance of data linkage and therefore use of routinely collected data

Guidance on how to withdraw from further participation in the trial will be provided to patients in the PIS. Withdrawal from collection of outcomes through routinely collected data via data linkage should be a rare event.

1.30 DATA COLLECTION

Data collection will include all fields listed in the eCRF, completable by both the participant and the research staff.

1.31 OUTCOMES POST RANDOMISATION

Trained staff will use the Investigator portal in the ResearchApp™ (Healthbit®) to collect the following:

1. Baseline data will include patient demographics, such as age, sex, and ethnicity, as well as long term conditions and pre-operative investigations, severity of cardiac disease, risk scores (BCIS Jeopardy Scores. EuroSCORE II), revascularisation procedures, completeness of revascularisation, defined as change in BCIS-JS from baseline.
2. Mortality will be ascertained in UK participants through ONS data access request.
3. Outcomes until hospital discharge:
   a) Unplanned mechanical circulatory support defined as the need for IABP, ventricular assist device or ECMO postoperatively.
   b) New onset end-stage renal failure requiring renal replacement therapy (excluding dialysis during cardiopulmonary bypass (CPB)).
   c) New focal neurological deficit (stroke) lasting more than 24 hours confirmed by clinical assessment and brain imaging.
   d) Infection: defined as septic shock with positive blood cultures; pneumonia defined as autopsy diagnosis or roentgenographic infiltrate and at least two of the following three criteria: fever, leukocytosis, and positive septum culture; and/or deep sternal or leg wound infection requiring intravenous antibiotics and/or surgical debridement.
   e) Bleeding requiring surgical or percutaneous intervention.
   f) Length of stay in the Intensive Care Unit (ICU) readmissions and hospital (time to discharge from acute care after index hospitalisation; this includes time to discharge from satellite acute care units) and Days Alive and Out of Hospital at 6 months.
4. Clinical effectiveness and adverse outcomes post discharge will be ascertained using HES data obtained from NHS Digital using Primary Diagnostic International Classification of Diseases, Tenth Revision (ICD10) codes as previously described (1). ONS data will be used for ascertainment of mortality. NHS numbers will be used to submit ONS/NHS Digital data access requests by the LCTU after last participant/last visit in the UK arm.

For the primary outcome, the following HES codes will be used:

a) All-cause mortality (ICD10): (dismeth = 4) OR (a linked record in ONS death registry). Follow-up begins the day after operation date.

b) Cardiovascular hospitalisation and hospitalisation admission after the index admission with ICD10: I00 to I99 (which encompass all the cardiovascular diagnoses) as the *primary* diagnostic code.

HES codes for all pre-specified clinical outcomes, severe adverse events of interest will be specified in the Statistical Analysis Plan (SAP).

5. Disease-specific PROMS, including the clinical summary scores of the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the overall summary scores of the Seattle Angina Questionnaire-7 (SAQ-7) will be ascertained at baseline and discharge, and then at follow-ups at 3 months, 6 months, and every 6 months thereafter using telephone / ResearchApp™ (Healthbit®). Where related to baseline, relevant measures will be performed after consent and prior to randomisation.
6. Resource use data, productivity loss, and EQ-5D-5L will be captured at baseline, and thereafter at 3, 6 and 12 months and then annually thereafter. Participants will have the option of either remote data capture using the Participant Portal to ResearchApp™ (Healthbit®), or if preferred, the Investigator Portal with research staff in person during enrolment and hospital stay, or by post or telephone follow-up post discharge in survivors identified from NHS SPINE.

1.32 OUTCOME ADJUDICATION

Given the pragmatic and objective nature of this trial, coding accuracy (>96%) (30) of the primary outcome, and given the limited added value of adjudication beyond high quality prospectively, independently coded events (31), no outcome adjudication is planned for the trial.

STRESS PERFUSION CMR SUB-STUDY

Researchers will be undertaking a nested observational study (enrolling 202 of the 634 patients randomised in the main trial) to compare the effect of CABG versus PCI on ischaemia, scar and remodelling. This sub-study will provide novel insights into the relative efficacy of PCI and CABG at reducing ischaemia and the correlation between residual ischaemia and clinical outcomes.

1.33 RATIONALE

Retrospective observational series have shown that the burden of ischemia is inversely related to the likelihood of survival in patients with preserved or impaired LV function (32) (33). Hence, it has long been assumed that relieving the ischaemic substrate by revascularisation of coronary artery disease will reverse reduce mortality. However, there are multiple sources of bias that limit interpretation of such observational data and it remains unclear whether ischaemia is merely a marker of risk or is a mechanistic determinant, the modulation of which might lead to improvement in survival.

A limitation common to many published ischaemia analyses is that the effect of revascularisation on ischaemic burden is unclear because patients did not undergo ischaemia testing during follow-up. There is however a body of evidence that the amount of residual ischaemia following revascularisation is both greater than expected and heterogenous. The nuclear sub-study of the COURAGE trial included a subgroup who underwent myocardial perfusion scintigraphy at baseline and post revascularisation. At 12 months follow up, 16% of the PCI arm had >10% residual ischaemia; a survival benefit was only seen in those with ischaemia reduction, amplified by the extent of ischaemia at baseline (33). Our pilot data also identified significant residual ischaemia post revascularisation in patients with impaired LV function. Therefore, the efficacy of different modalities of revascularisation on reducing ischaemic burden, and how this modulation relates to clinical outcomes, remains unclear. The stress perfusion CMR sub-study aims are:

1. To compare the efficacy of CABG and PCI at reducing ischaemia, and

2. To assess the relationship between baseline ischaemia, residual ischaemia after revascularisation and clinical outcomes.

1.34 SUB-STUDY DESIGN

Study Population.

1.34.1 Inclusion criteria:

1. Enrolled in BCIS-4 trial.

2. Enrolled at a centre that provides (or has access to) a perfusion cardiac magnetic resonance (CMR) service.
3. Consents to participate in the sub-study.

1.34.1 Exclusion criteria:

Unable to undergo CMR for any reason (including indwelling non-conditional cardiac device or patient factors such as prohibitive claustrophobia or the inability to lie flat or remain still for the scan duration).Intervention: Stress perfusion CMR will be performed before (up to 3 months prior) and 4 months (+/- 1 month) post revascularisation.

1.35 OUTCOMES AND ANALYSIS

Primary outcome: Change in ischaemic burden at 4 months on CMR (baseline minus follow up).

Secondary outcomes: Change in segmental wall motion and global LV volumes/ejection fraction and scar burden.

Analysis*:* Scans will be pseudonymised and transferred to the King's College London core laboratory for analysis. Primary analysis of inducible ischaemia will be undertaken by visual consensus of expert readers, blinded to trial-group assignment, the temporal sequence of scans (baseline versus follow-up) and all clinical and outcome data. Each American Heart Association (AHA) segment will be visually assessed and marked as ischaemic or not ischaemic. The volume of ischaemia will be expressed as a percentage of total LV mass ([number of ischaemic segments]/16*100). Secondary analysis of inducible ischaemia will utilise quantitative perfusion via automated software developed at KCL.

Data collection and storage: pseudonymised scans will be transferred securely to King's College London. These will be stored on a secure electronic research database at KCL, only accessible by members of the research team. Data will be kept for a minimum of six years from the end of the study, in accordance with UoL records retention policy (this may be longer if consent has been provided for long term follow up). For further information on data storage, see section 1.41.

The trial is a comparison of two accepted management pathways which involve routine clinical care; neither intervention is a research procedure, as such, a pragmatic approach to safety reporting has been applied. The complications of both PCI and CABG are well known and dependent on the age and existing comorbidities of the patient. All of the participants in the trial will, in the opinion of the multidisciplinary Heart Team, be eligible for both treatments. Trial participants are also typically younger and fitter than the overall target population and therefore at lower risk for adverse events. For example, **Figure 3** shows freedom from death or cardiovascular hospitalisation in people with HF following PCI or CABG in the general English population (the target population) and also in the population matched to individual participant data from the STICH trial of CABG versus no treatment in iLVSD. The data demonstrates that the typical trial population is at lower risk of death or cardiovascular hospitalisation, particularly in the long term.

1.36 EXPECTED SERIOUS ADVERSE EVENTS

The risk of intervention is not negligible. In the STICH trial, participants with ischaemic left ventricular dysfunction undergoing CABG had 5% mortality at 30 days post-surgery. In contrast, the peri-procedural risk of death following PCI should be less, although the overall burden of SAEs may be similar. In the SYNTAX trial (22) for example, the rate of Major Adverse Events at 30 days was the same in both CABG and PCI groups (only 7% of participant in this trial had iLVSD). However, with time, recurrent symptoms and repeat revascularisation are typically higher in the PCI treated patients, meaning that freedom from death or revascularisation is lower. This is evident in the Kaplan Meier curves in **Figure 3,** where the CABG curve (blue) is initially lower, but then crosses the PCI curve (red) after 3-6 months.

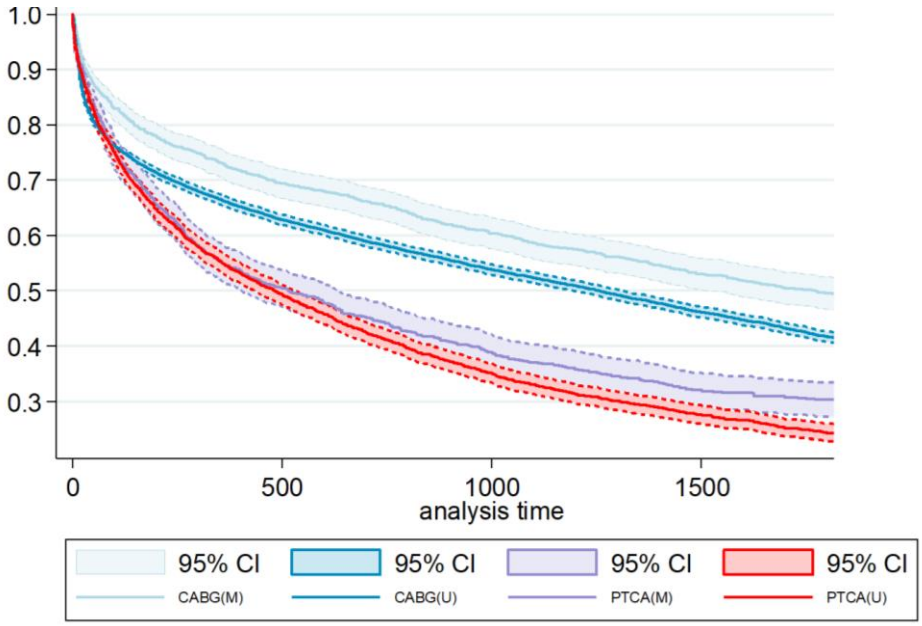


Figure 3 Freedom from death or cardiovascular hospitalisation in people with heart failure undergoing CABG or complex PCI in England 2013-2018, or matched to the STICH cohort (1)

However, other trials have identified important differences in early expected adverse events following both PCI or CABG (34). These include the risk of stroke, severe acute kidney injury (AKI), unplanned mechanical circulatory support for low cardiac output, major bleeding requiring intervention, or vascular complications requiring intervention. Along with early deaths, this information may be important for future patients with iLVSD who are deciding whether to undergo PCI or CABG. These early events may also be used by governance committees to establish whether there are any clinical differences in the number of these events versus expected event rates in normal practice. For this reason, we propose to collect the following SAEs occurring within 30 days of the date of surgery or the date of the first index PCI procedure, for review by governance committees.

1. Stroke
2. New onset end-stage renal failure defined as requiring renal replacement therapy
3. Unplanned mechanical circulatory support (IABP, Impella, VA ECMO)
4. Major bleeding requiring reoperation or re-hospitalisation
5. Major vascular complication requiring interventional radiology or surgical intervention
6. All-cause mortality
7. Infection defined a septic shock
8. Pneumonia defined as autopsy diagnosis or roentgenographic infiltrate and a least two of the follow criteria (fever, leukocytosis and positive septum culture; and or deep sternal or leg wound infection requiring intravenous antibiotics and/or surgical debridement).

1.37 SAE REPORTING / CLINICAL OUTCOMES

SAEs that are deemed related to the trial, meet the criteria for seriousness, and are identified as expected in Section 1.36 - occurring within 30 days of the date of surgery or the first index PCI procedure, must be reported to the Sponsor and the STICH3-BCIS-4 trial management team immediately, and within 24 hours of becoming aware of the event. SAEs must be reported using the Sponsor's SAE reporting form and according to the Sponsor SOP for reporting serious adverse events (S-1009). For clarity, only the expected SAEs listed in Section 1.36 should be reported to the Sponsor; any other SAEs that fall outside this definition do not require reporting.

All occurring SAEs should be documented in the Serious Adverse Events Log, the Post-Procedure Case Report Form and the Health bit IQ database as outlined.

Any other adverse events must be reviewed and if the event leads or results in an AESI listed in section 1.36, this should be recorded in the Serious Adverse Events Log under the AESI that has occurred.

DATA PROTECTION AND PATIENT CONFIDENTIALITY

The LCTU will be the Data Co-ordinating Centre for the BCIS4 trial (UK arm of the STICH-3 Consortium).The Data Controller is UoL. All data handling and record keeping will be kept in adherence to University of Leicester's (UoL) and NHS Organisation(s) policies. The SWEDEHEART team, Sahlgrenska University Hospital Sweden, will act as the Data Controller for the STICH-3 data worldwide and Data Processor for the STICH-3 Consortium inclusive of UK data.

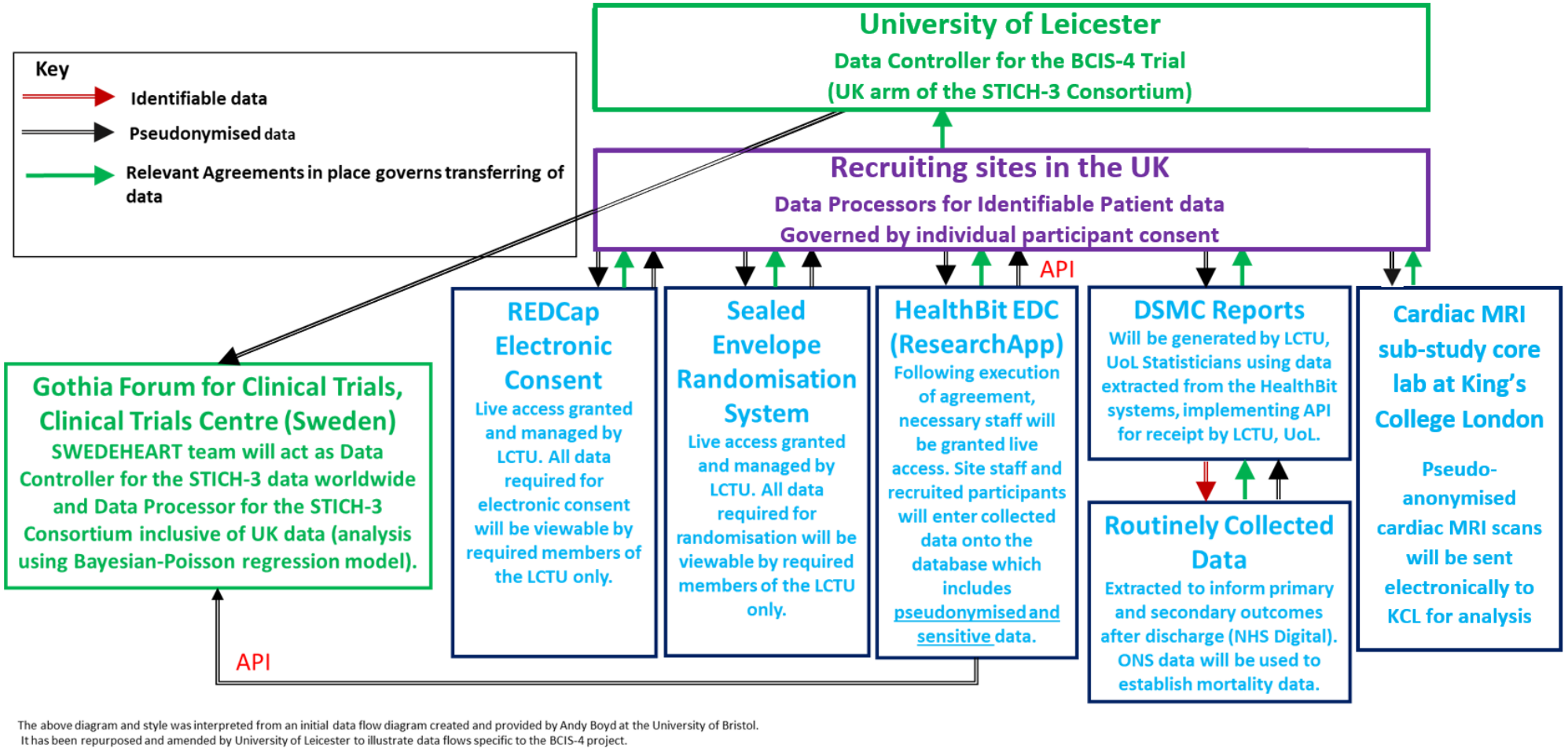
1.38 QUALITY ASSURANCE

Data quality will be optimised through several established strategies. The LCTU has trained and certified study personnel who monitor data quality and follow the necessary Standard Operating Procedures (SOPs). There will be periodic internal database quality-control checks performed, and data audits will be performed during and at the conclusion of the trial.

Numerous checks for consistency of data, including range and limit checks, checks for missing data, and logical consistency checks will be implemented in the ResearchApp™ (Healthbit®) electronic data management software and performed automatically at the time of data entry. Discrepant or inconsistent data will be flagged immediately, queries generated, and the trial location can respond promptly with corrections while the participant records are immediately available. This is viewable by a 'support dashboard' at both a location and trial management level. Where participants are completing responses to questionnaires via ResearchApp™ (Healthbit®) research staff will be able to manage missing data and incorrect data via this dashboard. Research staff will also be able to send broadcast messages (via push notifications) to remind participants that their follow-up is due. Trial management staff will also be able to view the 'support dashboard' to manage data queries directly with research staff and for where research staff are entering follow-up data on behalf of participants. After a data analysis set has been created from the data collected on the eCRF for analysis, data are further cross-checked, with discrepant observations being flagged and appropriately resolved through a data query system.

There are other processes in place to assure that timely, complete, and high-quality data are obtained. Prior to the start of enrolment, research staff at the trial location (e.g., investigators, study coordinators) will undergo thorough training regarding the clinical protocol and all data collection procedures, including how to use the ResearchApp™ (Healthbit®) and complete the eCRF data, which will be part of the Site Initiation Visit (SIV). Initial training will occur in an investigators' / coordinators' training virtual meeting with hands-on database interaction. Follow-up additional sessions will be conducted as needed or requested.

1.39 DATA FLOW DIAGRAM



The above diagram and style was interpreted from an initial data flow diagram created and provided by Andy Boyd at the University of Bristol. It has been repurposed and amended by University of Leicester to illustrate data flows specific to the BCIS-4 project.

Figure 4 Data Flow Diagram

1.40 DATA COLLECTION TOOLS AND SOURCE DOCUMENT IDENTIFICATION

NHS Digital will be used as the primary data source to ascertain the primary and secondary outcomes after hospital discharge. Permission will be sought from all participants to access centrally held NHS records and the Office for National Statistics (ONS) as part of the eligibility process. This will also allow for collection and confirmation of clinical events as well as participant deaths where consent remains. Consent for NHS number, date of birth, and sex to be used in order to obtain data linkage for NHS Digital will be specifically requested. Data extracts will be received by the LCTU, UoL and stored in the Research Filestore (RFS). This data will be archived and destroyed in line with agreements with NHS Digital and equivalent services.

Other source data documents will be hospital and primary care health records, and, as data will be entered into Healtbit® directly, the mobile application will also be considered as source data. Healthbit® will be designed to ensure that it collects data adequately, and audit trails will be available to demonstrate validity both during and after the trial. Where research staff at the trial location prefer, paper CRFs will also be provided as a data recording tool, althoughresearch staff at the trial locations will be encouraged to enter data directly onto ResearchApp™ (Healthbit®). Where this option is utilised, data collected on paper CRFs outside of that sitting in patient records will also be considered as source data.

Baseline and follow-up data on quality of life surveys can be completed by participants using the mobile app ResearchApp™ (Healthbit®); attendance at GP Practice or hospitalisation following discharge can also be self-reported by participants on the same mobile app. Participants will receive reminders prompting them to complete the surveys at 4 weeks post-operation and at the relevant timepoints for the follow-ups if not already completed. Where a participant is unable to complete the surveys electronically, a designated research team member will arrange either a face-to-face, telephone, or video interview with the participant pre-operatively and at 6 weeks post-operation, coinciding with participant's pre-operative consent and post-operative clinic follow-up if appropriate. This process will continue for all required follow-ups required as part of the trial. All data collection will be undertaken locally and pseudonymised results reviewed centrally using the related platform Heathbit IQ™ (Healthbit®).

All data collected for the PROM and Quality of Life assessments will be via standardised and validated questionnaires. Data collected for purposes of Health Economic analysis will be collected on bespoke designed questionnaires, designed by the Health Economist. To maximise completeness of data,

researcher staff can complete these with the participant and enter this data on their behalf, for example in the event of technical difficulties using ResearchApp™ (Healthbit®), and this can be done remotely to reduced participant burden.

All personal data will be stored for up to 3 years after the end of the trial to ensure participants can be contacted by research staff at trial locations in the instance where the participant has provided consent to receive the results of the trial. After this, only select electronic pseudonymised data will be stored on the UoL RFS for use in potential future ethically approved research. Where consent has been provided for future research, signed ICFs along with the select data will be kept indefinitely as evidence of this and to support any of this potential research. The PIS and ICF will comply with this.

1.41 DATA STORAGE

The primary trial database is provided by ResearchApp™ (Healthbit®, London UK). This is a flexible modular, data capture and storage platform that combines Investigator and Participant user-friendly mobile apps (iOS and Android) for bedside and remote data capture by research staff and participants, with built in quality assurance tools that promote efficient data capture. ResearchApp™ (Healthbit®) is also multilingual, facilitating remote data capture from diverse communities (35).

Trial data collected via ResearchApp™ and Healthbit IQ ™ and stored on MS Azure Cloud will be transferred securely via Healthbit's® Application Programme Interface (API) and stored on secure servers (e.g., RFS) hosted by the LCTU, UoL, throughout the duration of the trial and for 6 years after the trial is complete in the UK at UoL, in accordance with the UoL record retention policy. Data transferred to Sweden as part of the SWEDEHEART co-ordination will be stored for 25 years in line with the country's legal requirements. All data entered into the eCRF and any process derived from the eCRF (source data verification, adverse event reporting) will be pseudonymised. Participants will therefore be solely identified by their participant ID, which is assigned in the randomisation system, Sealed Envelope. Pseudonymised source data will be made available to the Executive Committee (EC) (see section 1.54) and/or LCTU Coordinating Centre for SAE reporting.

Local site files will be archived by research staff at the trial location as per local requirements or for 6 years after publication of the trial.

Pseudonymised substudy data will be stored at King's College London as described in Section 1.35.

Participants will be asked to consent to the sharing of pseudonymised medical data with the Coordinating Centre in Sweden, that their medical records may be inspected for purposes of monitoring, that their medical data relevant to this trial will be stored and analysed while maintaining confidentiality in accordance with local data protection laws, and may be subject to audits by authorised representatives of the Coordinating Centre or the Sponsor.

Consent will be sought for life-long trial follow-up beyond the scope of the follow-up schedule currently planned in this protocol using HES / ONS.

1.42 DATA PROTECTION

Participants' personal data shall be treated in confidence and in compliance with International Committee on Harmonisation of Good Clinical Practice (ICH-GCP), the UK Policy Framework for Health and Social Care and the UK GDPR. When processing or archiving personal data, the Sponsor or its representative shall take all appropriate measures to safeguard and prevent access to this data by any unauthorised third party.

The CI will have access to the trial documentation and will be the data custodian for the BCIS-4 UK arm of the trial.

Each participant will be assigned a unique identification number upon randomisation. All personalised information for participants will be kept confidentially at the recruiting location unless there is a specific need for transfer of a copy of a participant consent form to another location for trial-related purposes, i.e., proof of consent where a location different to that of the consenting location is performing the PCI or CABG.

All electronic patient identifiable information will be held on a secure, password-protected database accessible only to essential personnel. Each person (both the field-based data collectors and LCTU) will be assigned access to only the portions of the database they need. Access is provided under "hard" password protection that are changed at 6-month intervals. All data are encrypted. The required dataset for receipt by the SWEDEHEART team for consortium analysis will be defined and transferred securely via Healthbit's® Application Programme Interface (API). Depending on the required data items, this may mean that whole surveys (forms) may be transferred, however this data will always be pseudonymised at point of transfer and receipt.

Paper documentation will be stored in a locked filing cabinet in the relevant research office. Neither hard copies nor electronic files containing personal information will be removed from the research office or stored in a non-secure manner electronically. The study research team will comply with local NHS Trust data protection policies. Direct access to source data/documents may be required for trial-related monitoring.

1.43 ACCESS TO DATA

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections in line with participant consent.

1.44 DATA SHARING WITH THE INTERNATIONAL STICH-3 CONSORTIUM

Participants of STICH3-BCIS4 will be asked to provide a specific informed consent for their data to be included in the STICH-3 analysis described in this protocol at the time of providing their consent to the UK trial. A national PIS and ICF will contain clear wording that allows pseudonymised data to leave each country and to be received by the SWEDEHEART team. The ICF will also explain that for verification of data, authorised representatives of the Sponsor, as well as any relevant authorities, may require access to parts of medical or trial records that are relevant to the trial, including the participant's medical history. Any data collected solely for the Stress Perfusion CMR Sub study will not be shared with the international STICH-3 consortium.

1.45 ARCHIVING

All paper data will be retained for 6 years after completion of the trial, in accordance with UoL SOPs. The data will be stored at a UoL approved archiving facility which will ensure that it is stored securely and accessed only by authorised individuals. Trial locations will be required to archive their own paper data in line with their local Trust SOPs.

Electronic data will be transferred securely and stored on secure servers hosted by the LCTU (e.g., RFS), UoL, throughout the duration of the trial, and 6 years after the study is complete, in accordance with GDPR and IAS standards. Healthbit ® will retain data whilst the LCTU, UoL utilises its platform for the duration of the trial and for the agreed retention period. Once LCTU, UoL requests all records to be deleted, data will be removed from the back-ups within 3 months. Pseudonymised imaging data

collected as part of the sub-study will be stored on a secure electronic database at King's College London as per Section 1.35,

As above, research data containing personal data will be stored for up to 6 years, with signed ICFs being kept indefinitely. Storage will comply with the University of Leicester archiving Standard Operating Procedure. Details can be found at: https://le.ac.uk/research/regi/standard-operating-procedures.

STATISTICAL ANALYSIS

Researchers at the LCTU will perform the trial statistical analyses for BCIS-4. A detailed SAP will be finalised before any analysis of the data by treatment group is undertaken.

1.46 ANALYSIS POPULATION

The primary analysis will be based on ITT principles with the analysis population consisting of all participants who are randomised and compared in the groups to which they were allocated regardless of treatment being received. The per-protocol (PP) population will consist of all participants who underwent revascularisation as randomised, excluding patients who had a major protocol deviation e.g., patients who crossed over, had their allocated treatment changed or discontinued by the treating physician at any time, or withdrew consent.

1.47 BASELINE CHARACTERISTICS

The baseline characteristics of the patients will be summarised by group. Continuous variables will be summarised by mean and standard deviation, or median and inter-quartile range if data do not have a symmetric distribution. Categorical variables will be summarised with counts and percentages. No statistical comparisons of participant characteristics at baseline will be performed between groups.

1.48 INTERNAL PILOT

Key assumptions about recruitment, inclusivity, and adherence will be tested in an internal pilot with pre-specified stop / go criteria at 12 months. The primary progression criteria will be recruitment; target 0.7 pts/location/month with 1.5 new trial locationss set up per month to 18 locationswithin 12 months of

green light. Using the thresholds of 100% and 75% of these targets, we can specify the following traffic light system: Green: Procced, Amber: Amend, consult and Red: Discuss with funder, as shown below. The TSC in consultation with the funder will determine progression. As contingency, recruitment in the range 0.5 pts/location/month would require an increase in the number of centres to 35 to achieve the recruitment target within 48 months. The internal pilot will be used to refine and amend recruitment strategies where needed, to ensure the sample is representative of the UK population.

Table 2 Red, Amber, Green Progression Criteria

Progression criteria	Red	Amber	Green
	≤74%	75-99%	100%
1. Recruitment rate (n/location/month)	<0.53	≥0.53 - <0.7	≥0.7
2. Number of trial locations opened	<13	13-17	≥18
Total number of participants recruited (12 m pilot)	*42*	*43-81*	*82*

1.49 PRIMARY OUTCOME ANALYSES

The primary outcome (all-cause mortality or cardiovascular hospitalization) will be calculated by measuring time from randomisation until first event or last known event-free observation during the follow-up period as defined in 1.17.1. The primary analysis of the primary outcome will compare the randomised groups using a log-rank test statistic. Survival estimates will be presented using methods by Kaplan and Meier and the adjusted hazard ratio and 95% confidence interval presented using a cox proportional hazards model (or appropriate alternative where assumptions are not met). Superiority of CABG over PCI will be declared with a two-sided p-value <0.05 on the log-rank test. A secondary analysis of the primary outcome will follow the same methodology on the per protocol (PP) population.

1.50 SECONDARY AND TERTIARY OUTCOMES AND SAFETY ANALYSES

Details of the analysis of the secondary outcome measures will be written in the SAP as described above and will follow the same principles as the primary outcome analysis with the exception of outcomes with potentially missing follow-up observations (e.g., PROMS) where a complete case analysis approach will be followed. Secondary outcomes will be reported similarly to the primary outcome using appropriate methodology, point estimates and confidence intervals to compare randomised groups; time to event outcomes using log-rank Kaplan-Meier and proportional hazards models, binary outcomes using logistic regression, continuous outcomes using linear regression or where not normally distributed using appropriate nonparametric methods.

Serious adverse event reporting is described in earlier sections and is largely for safety and ethics monitoring during the trial accrual and follow-up periods prior to statistical analysis taking place. AEs that meet the criteria for reporting as described above will be reported descriptively and summarised between groups based on the safety population (e.g., assigned to groups only if treated and according to treatment received).

1.51 INTERIM ANALYSES

No formal efficiency interim analyses are planned for this trial; no formal statistical rule for early termination of the trial is defined. One final efficacy analyses will be planned when all participants reach a minimum of 4 years follow-up. The independent DMC may observe the control arm event rate in the case it is substantially lower than expected, to allow recommendations to increase trial size and maintain adequate statistical power or advise futility. This observation will be blinded i.e., only control group or data overall to be presented and no outcome data will be presented that compares randomised groups.

1.52 SUBGROUP ANALYSES

A limited number of subgroups for the primary outcome measure will be pre-specified in the analysis plan and are likely to include sex (male versus female), age (<65 and >=65 years), acute versus chronic coronary syndrome, the extent of coronary disease (BCIS-1 JS <12 vs. ≥12), degree of LV dysfunction (EF <30% vs. ≥30%), diabetes, New York Heart Association (NYHA) class (<3 vs. ≥3), and estimated glomerular filtration rate (eGFR) (<30 vs. ≥30 ml/min/1.78m^2). A Cox proportion hazards model (or appropriate alternative where assumptions are not met) incorporating tests of interaction will be used for subgroup analyses. The subgroup analyses will be exploratory.

1.53 MISSING VALUES

The primary outcome measures time until first event or censors at last follow-up therefore by definition there will not be any missing data. Other data adjusted for in the primary outcome analysis is a requirement of randomisation and therefore will not be missing. The use of routine and ONS data ensures we will have good long-term follow-up rates and early censoring due to loss to follow-up should be minimal at most and not expected at all. Analysis of non-time-to-event secondary outcomes like PROMs will be by complete case, the extent of missing data will be described.

HEALTH ECONOMIC EVALUATION

Evidence has shown that coronary heart disease cost £1.7 billion to the UK healthcare service, £2.4 billion in informal care, and £2.9 billion in productivity loss (36). The health economic evaluation will determine cost-effectiveness of CABG, compared with PCI, from the perspective of the UK NHS and personal social services, and the patient in line with the National Institute for Health and Care Excellence (NICE) guidance for health technology evaluation (37).

We will conduct the evaluation alongside the clinical trial over a minimum 4-year time horizon and a model-based evaluation over a lifetime horizon. We will capture all healthcare resource use utilised in both treatment groups over the duration of the trial. This will include resource use relating to treatment received (CABG and PCI), hospitalisations, cardiac outpatient visits and both paid and unpaid care received by the patient during follow-up. Hospitalisation data will be obtained from HES (as detailed in section 1.35). We will take key components of the iPCQ questionnaire relating to productivity and include these in the bespoke health resource use questionnaire. A focus group of National Cardiac Surgery PPI group members, led by our PPI co-applicants, identified the impact that HF can have on formal and informal carers as highly important. Therefore, the burden on formal and informal carers needs to be measured and incorporated in the health economic evaluation. Healthcare resource usage that is not captured by HES will be collected via a bespoke questionnaire, completed at baseline, three, six and twelve months and then annually thereafter until year four. For the within-trials analysis, mean total patient cost by trial arm will be estimated by applying national unit costs to healthcare resource use data.

Health-related quality of life will be captured using the EQ-5D-5L questionnaire. EQ-5D-5L results will be mapped on to the EQ-5D-3L system using a “crosswalk” algorithm (38). Quality-adjusted life years (QALYs) gained will be estimated using the baseline-adjusted area under the curve approach (39). Where missing data are encountered, we will explore the assumptions regarding the missing data mechanism and decide upon an imputation method based on best practice (40). The mean total cost and mean total QALY gain per patient, according to randomisation group, will be estimated using a generalised linear model (GLM) and adjusting for trial minimisation factors and potential confounding factors. The appropriate family for GLM will be selected based on the results of the modified Park’s test. Cost-effectiveness at year four will be expressed as the incremental cost-effectiveness ratio

(ICER) and net monetary benefit (NMB). We will assume a willingness-to-pay for QALY gains of £20,000. We will undertake probabilistic sensitivity analysis to explore the uncertainty in our results and plot the probability of cost-effectiveness on the cost-effectiveness acceptability curve (41). We will also undertake sensitivity analysis to explore the impact of our assumptions made regarding missing data by including a complete case analysis only. The impact of decision maker perspective will also be explored in sensitivity analysis, by including productivity costs within an analysis from a societal perspective.

A lifetime health economic model will be informed by the existing literature in this area. An initial scoping review did not identify any lifetime cost-effectiveness analyses of CABG, compared with PCI, in patients with HF. We identified multiple studies that compared either CABG, PCI or medical therapy, in patients with coronary heart disease (42-45). Methods used ranged from within-trial only analyses, to lifetime models. Lifetime models typically extrapolated from the trial data using either parametric survival modelling or observational data. Resource use was obtained from clinical trial data, and where necessary for a lifetime analysis, from the literature or national cost records. The lifetime health economic model in this trial will capture disease progression using health states that represent the natural history of people living with HF. Based on the existing literature, it is likely to be a decision-analytic model with multiple health states in which a patient with HF experiences a monthly transition probability of experiencing further complications or death. We will apply a multivariable parametric survival model to the individual participant-level data to extrapolate the relevant clinical outcomes beyond the five-year trial period.

The choice of parametric model will be based on visual inspection, Akaike (AIC) and Bayesian (BIC) information criteria goodness-of-fit statistics (46). Other relevant model parameters will be informed by a targeted literature review. We will undertake a probabilistic sensitivity analysis using a 10,000-iteration Monte Carlo simulation. To reflect uncertainty in our model's parameter values, each parameter will be characterised as a probability distribution, in oppose to a point estimate, allowing us to explore the extent to which uncertainty in model parameters feed through into uncertainty in final modelled costs, life years, QALYs and overall cost-effectiveness. Previous research has found CABG to be most cost-effective in patients with more severe forms of HF (42). Therefore, our analysis will stratify patients according to risk, based on LVEF(<35% vs ≥35%), to explore the impact of heterogeneity in this patient population. As a scenario analysis, we will capture the wider economic burden on this patient population by undertaking the lifetime economic evaluation from a societal perspective.

TRIAL ORGANISATION, REGULATION AND OVERSIGHT

1.54 TRIAL ORGANISATION

The STICH3-BCIS4 trial is sponsored by the University of Leicester and funded by the NIHR HTA programme. Professor Gavin Murphy, British Heart Foundation (BHF) Chair in Cardiac Surgery / Consultant Cardiac Surgeon, and Professor Divaka Perera, Professor of Cardiology at King's College London are co-Chief Investigators (CI). Professor Perera is the lead of the sub-study.

STICH3-BCIS4 will be conducted in full conformity with the current version of the Declaration of Helsinki (last amended October 2000, with additional footnotes from 2002 and 2004) and the UK Policy Framework for Health and Social Care Research (2017). It will also be conducted according to ICH-GCP, relevant regulations and the SOPs and quality management procedures of the Sponsor, host organisations and LCTU.

1.55 TRIAL COORDINATION CENTRE

The UK Clinical Research Collaboration (UKCRC) accredited **Leicester Clinical Trials Unit** (Professor Gavin Murphy is LCTU Director), will coordinate the trial. Trial management responsibilities will include sponsorship, HRA and Health and Care Research Wales (HCRW) approvals, trial location set-up, and support with queries, serious adverse event monitoring, data quality, and location close-down, developing and programming the electronic eCRFs, trial procedure manuals, trial documentation, data monitoring, data management and analysis, and providing progress and data reports to the EC (see section 1.58), DMC, and participating locations. The LCTU will also be responsible for ascertainment of outcomes post discharge via ONS/NHS Digital data access requests. Sub-study analysis will be conducted at the cardiac MRI core laboratory at King's College London.

1.56 PARTICIPATING LOCATIONS

The Coordinating Centre will maintain a list of participating locations. At least 28 UK locations will be involved. Hub and spoke NHS organisations whom have agreed service level agreements may be approached and selected, appropriate contractual agreements will be agreed between Hub (lead trial location) and spoke (other trial location) in accordance with UK (or national governing body equivalent) regulatory guidelines. Participant Identification Centres (PIC) can be utilised in location setup where appropriate. This will be governed by a PIC contractual agreement and will be applicable where one location identifies and refers potentially suitable participants to a recruiting location(governed by mNCA contractual agreement) and where this is the only trial related research activity the PIC will be

responsible for. If more than participant identification is required, the appropriate regulatory contractual agreement(s) will be guided by sponsor.
In total, 10 of the 28 trial locations will be invited to join the sub-study; these are high volume cardiac MRI units who have expressed interest in taking part.

1.57 EXECUTIVE COMMITTEE

The EC will include the co-CIs and grant applicants. The EC will be responsible for providing clinical and methodological guidance, including overall study design, execution, analysis, and publication of the main trial results. The EC will oversee the management of the clinical trial locations and provide guidance around the publication strategy. While the trial is ongoing, the EC will review and agree to any protocol modification that may become necessary ahead of submission and is responsible for maintaining the scientific integrity of the trial.

1.58 TRIAL STEERING COMMITTEE

The TSC consists of the co-CIs, representatives of the Sponsor and LCTU, and one each of an independent statistician, clinical trialist, lay representative, patient representative and an independent Chairperson. The TSC will meet by tele/videoconference regularly, as required, throughout the trial period to discuss enrolment rates and non-adherence, and to provide operational insight and assist with issue resolution.

1.59 DATA MONITORING COMMITTEE

An independent DMC will ensure patient safety, review data accumulation with respect to quality and quantity, provide feedback to the TSC, and ensure the study follows the highest ethical standards. The DMC will be provided data on safety regularly throughout the trial period, in accordance with the DMC Charter. The safety data will include SAEs only as described in the SAE section above. We will only conduct additional safety reviews if otherwise directed by the DMC.

1.60 INTERNATIONAL STICH-3 CONSORTIUM

The EC of the international prospective individual patient data meta-analysis (STICH-3) will include PIs of each participating national RCT, and will be responsible for the operations of the analysis. The data coordinating centre located at the Sahlgrenska University Hospital, Sweden (SWEDEHEART team) will be responsible for collecting, cleaning and harmonising the data from all national RCTs required for this trial. The statistical analyses will also be performed at the Sahlgrenska University Hospital, Sweden .

1.61 ASSESSMENT AND MANAGEMENT OF RISK

1.61.1 Risks to Rationale

The heart failure population is increasing, and reviews of HES in England demonstrates that the number of people eligible for the trial has remained constant over the last decade. This suggests that the need for better evidence to guide revascularisation in iLVSD will not abate with time. To our knowledge, there are no novel treatments or devices in development or likely to emerge in the next 10 years that will supplant revascularisation with CABG or PCI in people with iLVSD.

1.61.2 Risks to Participants

The intervention and comparator are both standard care and administered by clinical staff caring for trial participants. The risks and benefits of the two strategies are finely balanced and this is why we need an adequately powered RCT using an adequate primary outcome, over an adequate duration of follow-up, to prove which strategy is better.

1.61.3 Risks related to CABG

In the STICH trial, CABG surgery posed a relatively high immediate postoperative morbidity (25%: renal failure, cardiac arrest and ventricular arrhythmias) as well as an early risk of death (4%). Contemporary observational data in patients with iLVSD reports lower mortality rates (3%) (47). In STICH, early mortality hazards of CABG became balanced with those of medical therapy after 2 years, with significant reductions in cardiovascular mortality relative to PCI within 5 years. The EuroSCORE II will be used by the Heart Team to identify patients with a prohibitively high surgical risk. Stroke is a major and severe complication of surgery. Systematic review of trials comparing CABG versus PCI in people who do not have iLVSD report rates of stroke as 0.4% after PCI and 1.1% after CABG at 30 days, and 2.6% versus 3.2 % at 5 years (48). In the *in-silico* model of STICH3-BCIS4, there was no difference between PCI and CABG in people with HF with respect to stroke at 5 years; Adjusted Treatment Effect (ATE) -0.3% (95% Confidence Interval – 1.5% to 1%).

1.61.4 Risks related to PCI

There is sparse contemporary RCT data on the early risks of PCI in iLVSD. In a recent observational analysis from Canada between 2008 and 2016, people (n=2397) with iLVSD (EF<35%) undergoing PCI experienced stroke, heart failure rehospitalisation, and mortality rates of 0.7%, 5.6%, and 4.8% at 30 days respectively (49). Rates of stent thrombosis and in-stent restenosis in patients with iLVSD who receive multiple stents are unknown. The rates of major bleeding post-PCI in patients with iLVSD in the REVIVED trial was 3.2% at 2 years. In REVIVED, there was no difference between PCI and medical therapy with respect to quality of life at 12 months.

1.61.5 Risks to the Trial

Randomisation with allocation concealment will utilise a centralised, web-based system. The trial is unblinded and non-adherence will be documented to assess performance bias. To mitigate this, rates of non-adherence and/or crossover observed in previous trials of PCI versus CABG are included in the sample size estimate. As this is a pragmatic trial, there are no hospital visits, imaging, blood, or other tests, that are in addition to normal care. This will mitigate attrition bias. The use of routinely collected data will mitigate against detection bias and attrition bias. The primary outcome has high accuracy of HES / ONS coding and is unlikely to be misclassified. The trial protocol will be registered in a public registry prior to enrolment of the first participant. A SAP will be published prior to data lock. The primary analysis will be by ITT and include all randomised participants unless the participant withdraws consent for follow-up. The trial will be reported as per the Consolidated Standards of Reporting Trials (CONSORT) extension for trials using cohorts and routinely collected data (50, 51).

1.62 RESEARCH ETHICS COMMITTEE AND OTHER REGULATORY REVIEW AND REPORTS

The trial will not commence until a favourable Research Ethics Committee (REC) opinion is obtained. Before any trial location can enrol patients into the trial, the CI / PI or designee will ensure that appropriate approvals from participating organisations are in place. Specific arrangements on how to gain approval from participating organisations are in place and comply with the relevant guidance. The Trial Coordinating Centre will not request Sponsor Green Light until they can evidence that all necessary approvals are in place, both at a regulatory and a location level.

ResearchApp™ (Healthbit®) and Healthbit IQ™ (Healthbit ®) are regulatory compliant patient data capture technologies. Healthbit® conforms with GDPR guidelines and utilises Microsoft Azure Cloud for the provision of its data storage services with additional security information available on request. Healthbit® stores all data in a UK data centre, has received Cyber Essentials Plus certification and is ISO 27001 compliant awaiting certification. The system uses role-based access rights, encrypted passwords, and regular back-ups.

1.63 REGULATORY REVIEW AND COMPLIANCE

Once the initial Sponsor review process is complete, a Sponsor reference number has been allocated, and all requested documentation has been received and checked, authorisation from the UoL's Research Governance Office (RGO) will be issued to book further review of the proposed research. The NHS REC and the HRA will then review the proposal, following submission. Agreement in principle

is subject to the research receiving all relevant regulatory permissions. Submission for regulatory approvals will be submitted via the Integrated Research Application System (IRAS). The CI will ensure regulatory approvals, confirmation of capacity and capability (C&C) from the NHS locations and Sponsor Green Light are in place before patients are approached at each of the participating locations.

For any required modification to the trial, the CI or designee, in agreement with the Sponsor (following their review) and EC, will submit information to the appropriate body in order for them to issue approval for the modification. The CI or designee will work with trial locations (R&D/I departments at NHS locations as well as the trial delivery team) so they can put the necessary arrangements in place to implement the modification to confirm their support for the trial as amended and where required. Modificationss will be implemented upon receiving Sponsor Green Light.

The University of Leicester Research Governance Office's SOPs will be followed for the duration of the trial. Annual progress reports will be submitted by the CI to the REC annually on the anniversary date of when favourable opinion was given (within one calendar month).
The CI will notify the REC when the trial has ended by completing the 'End of Study Notification Form' and will submit a final report of the results within one year of notifying the REC.
A trial master file (TMF) will be maintained for the duration of the trial and will be stored for 6 years after the trial has ended. The only time this could be exceeded, is if samples are being retained beyond the scope of the original study i.e., consent has been provided for future research. In these circumstances ICFs would have to be retained for as long as the samples are in existence, as we have a legal requirement to prove the samples were obtained with consent.

Direct access will be granted to authorised representatives from the Sponsor and host institutions for monitoring and/or audit of the trial to ensure compliance with the regulations.

1.64 PEER REVIEW

The trial has undergone independent peer review as part of the NIHR HTA funding process.

1.65 PROTOCOL COMPLIANCE

A protocol deviation is defined as any undetected change or departure from the protocol which does not result in harm to the trial participants or significantly affect the scientific value of the trial. Examples of deviations in the STICH3-BCIS4 trial include crossover events, randomising ineligible patients, allocated treatment change or discontinuation by the treating physician at any time, allocated treatment performance outside of the required timeframe (situation dependent).

patients who crossed over, had their allocated treatment changed or discontinued by the treating physician at any time, had their allocated treatment performed outside of the required timeframe or withdrew consent

Frequent reoccurrence of protocol deviations by the same location, particularly where the same deviation is repeated, may meet the criteria for a serious breach of ICH-GCP and will be reported in line with UoL SOPs. For the purpose of this regulation, a 'serious breach' is a breach which is likely to affect to a significant degree:

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

In the event where the protocol is not adhered to, the details should be documented on "Protocol Deviation Form" on Healthbit®. In addition to the ITT analysis, a secondary per protocol analysis will be undertaken. The CI will document this in adherence to the University's Standard Operational Procedure SOP: Identifying and Reporting Deviations and Serious Breaches of ICH-GCP and/or the Protocol for Trials. The CI will seek advice from the research supervisors and the Sponsor.

1.66 MONITORING

The University of Leicester, as Sponsor, operates a risk-based monitoring and audit programme, to which this trial will be subject. The LCTU operates a risk-based Quality Management System, which will apply to this trial with quality checks and quality assurance audits performed as required.

As part of the quality management process, the trial will be subject to a risk assessment which will be developed by the LCTU in association with the Sponsor. The Senior/Trial Manager will undertake quality checks and assurance audits to ensure compliance with protocol, ICH GCP, and regulatory requirements. All source data, trial documents, and participant notes will be made available for monitoring, audits and inspections by the Sponsor (or their delegate), NHS Host Organisation and the regulatory authorities, should a monitoring visit be undertaken.

1.67 INDEMNITY

Sponsorship and insurance for trial design and management will be provided by the UoL.

If a participant is harmed due to negligence, this will be covered by the local NHS Trust's indemnity arrangements for all participants in clinical trials. If a trial participant wishes to make a complaint about any aspects of the way they have been treated or approached during the research project, the standard

National Health Service complaint system will be available to them. Details of this are made available to participants in the PIS.

1.68 ACCESS TO THE FINAL TRIAL DATASET

The CI will have access to the full dataset. Direct access will be granted to authorised representatives from the Sponsor and host institutions for monitoring and/or audit of the study to ensure compliance with regulations. Select and agreed items of the dataset will be sent via API to the SWEDEHEART team at the end of the trial data collection period once data queries have been resolved and the database has been locked.

1.69 PATIENT AND PUBLIC INVOLVEMENT AND ENGAGEMENT

Patient and Public Involvement and Engagement (PPI&E) plays an important role in the design of the trial. Patient and public members in the Clinical Study Group on Organ Protection, part of the National Cardiac Surgery Clinical Trials Initiative, co-lead the BCIS trials team and are involved in all aspects of trial governance, operations, interpretation and dissemination.

A focus group of National Cardiac Surgery PPI&E group members, led by our PPI co-applicants, highlighted the importance of quality of life and productivity on those affects by HF. PPI&E members were concerned that important quality of life aspects due to HF may not be captured by a single questionnaire. PROMS will include disease specific questionnaires: the clinical summary score of the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the overall score of the Seattle Angina Questionnaire-7 (SAQ-7) as well as the generic health related quality of life questionnaire EQ-5D-5L. The disease specific questionnaires address domains specific to HF which are highly relevant to patients but are not captured by the EQ-5D-5L.

Healthcare resource use and productivity impact will be captured at the times specified using a bespoke questionnaire. PPI&E members highlighted the financial impact of HF on patients and informal carers, in terms of their ability to engage in and sustain paid employment. This will allow for capture of the financial burden on patients and both formal and informal carers within the health economic evaluation.

DISSEMINATION POLICY

The STICH3-BCIS4 trial protocol will be prospectively registered on International Standard Randomised Controlled Trial Number Registry (ISRCTN). A detailed study protocol will be published before start of pooled analysis in a peer-reviewed journal. The findings will be disseminated by usual academic channels (i.e., presentation at international meetings as well as by peer-reviewed publications) and through patient organisations and newsletters to patients, where available. The anonymised trial data will be made available to other researchers in ethically approved studies after the publication of the main trial findings. Participants will receive information at the end of the trial reporting on the trial results, where they have provided specific consent via the ICF.

Publication authorship will follow the International Committee of Medical Journal Editors (ICMJE) recommendations, a set of guidelines for standardising the ethics, preparation and formatting of manuscripts submitted to biomedical journals for publication.

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1.70 APPENDIX 1 - MODIFICATION HISTORY

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1.	1.1	N/A: further changes requested by REC.	Carla Richardson	Changes made in light of REC review of initial application: 1. Change to Consultee Consent pathway in line with REC/HRA guidance. 2. Clarification provided of how long follow-up will be (4 years) 3. Clarification of end of study.
2.	1.2		Carla Richardson	Term “too unwell” removed where referencing seeking Consultee consent.
3.	2.0	31/07/2024	Luke Ingram	Change to Exclusion Criteria. “Valvular heart disease or any other cardiac conditions (e.g., LV aneurysm) as the primary indication for surgery is an exclusion criterion.” has been amended to: "Valvular heart disease indicating the need for mechanical repair/replacement or any other structural cardiac surgery (e.g. LV aneurysm resection)".
4.	3.0	06/01/2025	Luke Ingram	Addition to Schedule of Processes to include chest x-ray for participants allocated to coronary artery bypass graft (CABG) research arm. Change of time window for screening and baseline visit in Schedule of Processes.

				Addition of Hub + spoke locations and participant identification centres (PIC). Change to reporting of adverse event of special interest to include renal replacement therapies for events of new onset end-stage of renal failure. Previously this was limited to dialysis.
5.	4.0	23/10/2025	Amy Huckvale	Addition of detailed guidance for reporting Serious Adverse Events (SAEs) Expanded instructions on documentation and timelines for SAE reporting to the Sponsor. Terminology update: the term *'consultee'* has been replaced with *'friend/relative'*, and references to the *Personal Consultee Declaration Form* and *Personal Consent to Contact Form* have been removed. These have been consolidated into a single document—the F*riend/Relative Follow-Up Consent Form*.
6.	5.0	20/03/2026	Amy Huckvale	Addition of the Stress Perfusion CMR Sub-Study, including rationale, design, outcomes and analysis. Sub-study data flow added into the data flow diagram. Updated terminology to reflect clinical trial regulatory updates. The term 'Amendment' has been replaced by 'Modification' and 'Site' has been replaced by 'location'