Controlled trial of **H**igh-risk coronary **I**ntervention with **P**ercutaneous left ventricular unloading

(CHIP-BCIS3)

Trial Protocol Version 1.4

Sponsored by King's College London

This project is funded by the National Institute for Health Research (NIHR) HTA CET (130593).

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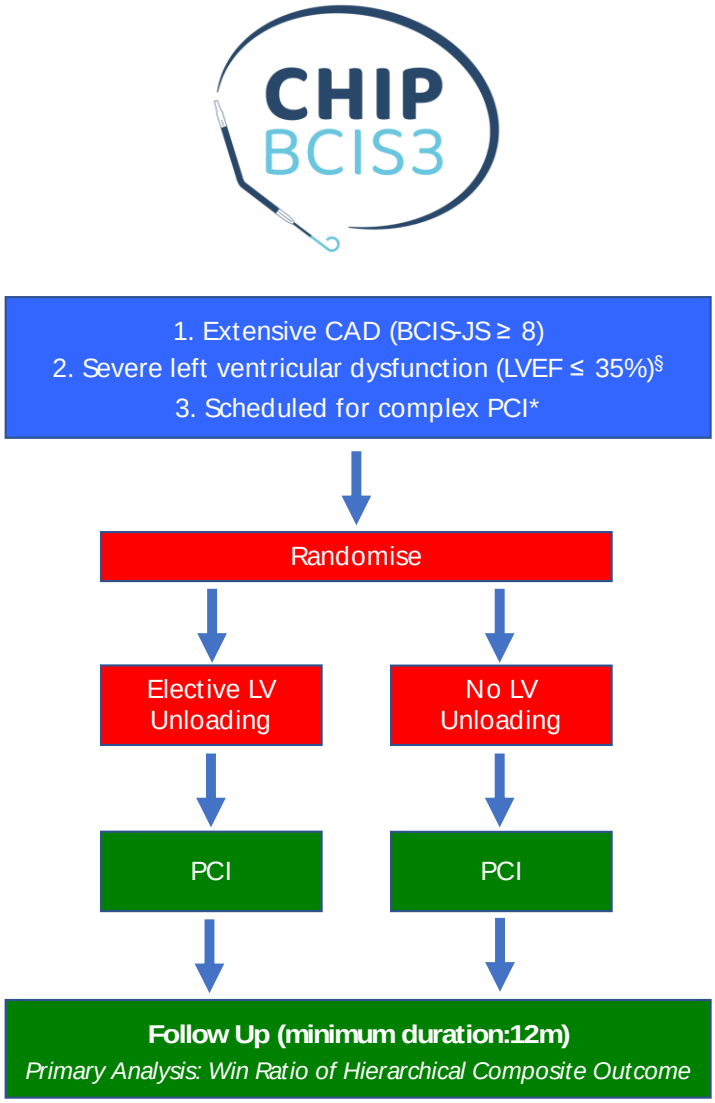
1. Trial Summary

1.1 Protocol Summary

Study Title	**C**ontrolled trial of **H**igh-risk coronary **I**ntervention with **P**ercutaneous left ventricular unloading (**CHIP-BCIS3**)
Aim	To establish whether, in patients undergoing high-risk percutaneous coronary intervention, a strategy of percutaneous left ventricular unloading is superior to standard care in terms of patient outcomes, quality of life and cost-effectiveness
Trial Design	Prospective randomised open-label multicentre trial
Primary Outcome	Composite hierarchical outcome of death, stroke, spontaneous myocardial infarction, cardiovascular hospitalisation or periprocedural myocardial infarction, analysed using a Win Ratio method
Major Secondary Outcomes	• Individual components of the primary outcome (as well as repeated occurrences of these events) • Completeness of revascularisation • Major bleeding (BARC 3 to 5) • Major vascular complication (VARC) • Procedural complication • Unplanned revascularisation • Health related quality of life/functional status • Resource utilisation and cost effectiveness • Length of stay
Inclusion Criteria	1. Extensive coronary disease (BCIS-JS ≥ 8) 2. Severe Left Ventricular Dysfunction§ 3. Scheduled to undergo complex PCI*
Exclusion Criteria	1. Cardiogenic shock or acute STEMI at randomisation 2. Contraindication to pLVAD insertion
Sample Size	250 (125 in each group) would provide >80% power to detect a hazard ratio of 0.62, requiring approx. 150 first events during entire follow-up duration (equates to risk ratio ~0.70 at 12 months). The sample size was extended to 300 patients in May 2024 to further improve statistical power.

1.2 Trial Flowchart



§ LVEF ≤ 35% (or ≤ 45% with severe mitral regurgitation)

*** Complex PCI: at least one of the following**

- *Unprotected left main intervention in the presence of*
  - *an occluded dominant right coronary artery or*
  - *a left dominant circulation or*
  - *disease involving the entire bifurcation (Medina 1,1,1 or 0,1,1)*
- *Intended calcium modification (by rotational or orbital atherectomy, lithotripsy or laser)*
  - *in multiple vessels or*
  - *in the left mainstem or*
  - *in a final patent conduit or*
  - *where the anatomic SYNTAX score is ≥32*
- *Target vessel is a chronic total occlusion with planned retrograde approach*

1.3 Trial Organisation

1.3.1 NIHR HTA CET Grant Applicants

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

Prof. Tim Clayton, London School of Hygiene and Tropical Medicine

Prof. Peter Ludman, Queen Elizabeth Hospital, Birmingham

Dr. Peter O'Kane, Royal Bournemouth Hospital, Bournemouth

Dr James Spratt, St George's Hospital, London

Dr. Simon Walsh, Belfast Health and Social Care Trust, Belfast

Dr. Ian Webb, King's College Hospital, London

Mr Richard Evans, London School of Hygiene and Tropical Medicine

Assistant Prof. Zia Sadique, London School of Hygiene and Tropical Medicine

Dr. Matthew Ryan, King's College London

1.3.2 Trial Steering Committee (TSC)

Prof. Nick Curzen, University of Southampton (Chair)

Mrs Jacqueline Grudzinskas, PPI Representative

Mr Hameed Khan, PPI Representative

Dr. Rasha Al-Lamee, Imperial College London

Dr. Adam De Belder, Royal Sussex County Hospital, Brighton

Prof. Divaka Perera, King's College London

Prof. Tim Clayton, London School of Hygiene and Tropical Medicine

Dr. Ly-Mee Yu, University of Oxford

Prof. José Henriques, University of Amsterdam

1.3.3 Data Monitoring Committee (DMC)

Prof. Rod Stables, University of Liverpool (Chair)

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

Dr Miles Behan, Edinburgh Royal Infirmary

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

1.3.4 Trial Management Group (TMG)

Prof. Divaka Perera, King's College London

Prof. Tim Clayton, London School of Hygiene and Tropical Medicine

Mr Richard Evans, London School of Hygiene and Tropical Medicine

Dr Matthew Ryan, King's College London

Dr Saad Ezad, King's College London

Mrs Lynn Laidlaw, PPI Representative

Ms Megan Knight, London School of Hygiene and Tropical Medicine

Mr Matthew Kwok, London School of Hygiene and Tropical Medicine

1.3.5 Clinical Trials Unit (CTU)

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

1.3.6 Clinical Events Committee (CEC)

Dr Stephen Hoole, Royal Papworth Hospital (Chair)

Dr Peter Henrikson, University of Edinburgh

Dr Rong Bing, University of Edinburgh

Dr Paul Bambrough, Royal Papworth Hospital

Dr Heeraj Bulluck, Leeds General Infirmary

Dr Natalia Briceno, Wexham Park Hospital

Dr Nicholas Jenkins, Sunderland Royal Hospital

Dr Abdul Mozid, Leeds General Infirmary

1.3.7 Recruiting Centres

At each site;

- Principal Investigator
- Trial Coordinator

A current list of sites is provided on the trial website http://chip-bcis3.lshtm.ac.uk/.

1.4 List of Abbreviations and Definitions

ACE	angiotensin converting enzyme
ACS	acute coronary syndrome
BARC	Bleeding Academic Research Consortium
BCIS-JS	British Cardiovascular Intervention Society Jeopardy Score
BNP	brain natriuretic peptide
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CCS	Canadian Cardiovascular Society
CE	certification for use in the European Union
CEA	cost-effectiveness analysis
CEC	clinical events committee
CET	clinical evaluation and trials
CHIP	Complex, high-risk and indicated percutaneous coronary intervention
CNS	central nervous system
CT	computed tomography
CTO	chronic total occlusion
CTU	clinical trials unit
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form

EF	ejection fraction
EQ-5D-5L	EuroQoL survey
FBC	full blood count
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA_1c	haemoglobin A_1c
HES	hospital episode statistics
HRQoL	health related quality of life
HSQ	health service questionnaire
HTA	health technology assessment
IABP	intra-aortic balloon pump
IPG	Interventional procedures guidance
IVUS	Intravascular ultrasound
JS	jeopardy score
KCCQ	Kansas City Cardiomyopathy Questionnaire
KCL	King's College London
LAD	left anterior descending coronary artery
LBBB	left bundle branch block
LSHTM	London School of Hygiene and Tropical Medicine
LV	left ventricle
LVEDP	left ventricular end diastolic pressure
LVEF	left ventricular ejection fraction
LVSD	left ventricular systolic dysfunction
MAE	major adverse events
MACE	major adverse cardiovascular events
MCS	mechanical circulatory support
MI	myocardial infarction
MICE	multiple imputation using chained equations
MRI	magnetic resonance imaging
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NSAE	non-serious adverse event
NT-proBNP	n-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
OCT	optical coherence tomography
PCI	percutaneous coronary intervention
PIC	Participant Identification Centre
pLVAD	percutaneous left ventricular assist device
QALY	quality added life year
RCT	randomised controlled trial
REC	research ethics committee
RI	revascularisation index
SAE	serious adverse event
SBP	systolic blood pressure
STEMI	ST-elevation myocardial infarction
SYNTAX	synergy between PCI with taxus and cardiac surgery
TMG	trial management group
TSC	trial steering committee
TTE	transthoracic echocardiogram
UK	United Kingdom
URL	upper reference limit
VA-ECMO	veno-arterial extra-corporeal membrane oxygenation
VF	ventricular fibrillation
VT	ventricular tachycardia

2. Background

2.1 High-Risk PCI

Coronary artery disease (CAD) is the top cause of death globally and a leading cause of morbidity and mortality in the UK[1]. Revascularisation, the process of restoring normal coronary blood flow through either coronary artery bypass grafting or percutaneous coronary intervention (angioplasty and stenting, PCI), is a cornerstone in the management of patients with CAD. In the context of an acute coronary syndrome (ACS), revascularisation is associated with improved mortality, freedom from heart failure and improved health related quality of life (HRQoL) when compared to medical therapy alone[2]. These benefits need to be balanced against the adverse events associated with the procedure itself which become more likely with increasing age, comorbidity and the complexity of coronary disease. This creates a conundrum; high-risk patients with comorbidities and extensive coronary disease are more likely to benefit from revascularisation, but safely delivering this treatment is challenging and associated with high rates of early adverse events including periprocedural myocardial infarction, pulmonary oedema, cardiogenic shock and cardiac arrest[3]. Because of these factors, high-risk patients are often under-treated with associated poor health outcomes[4].

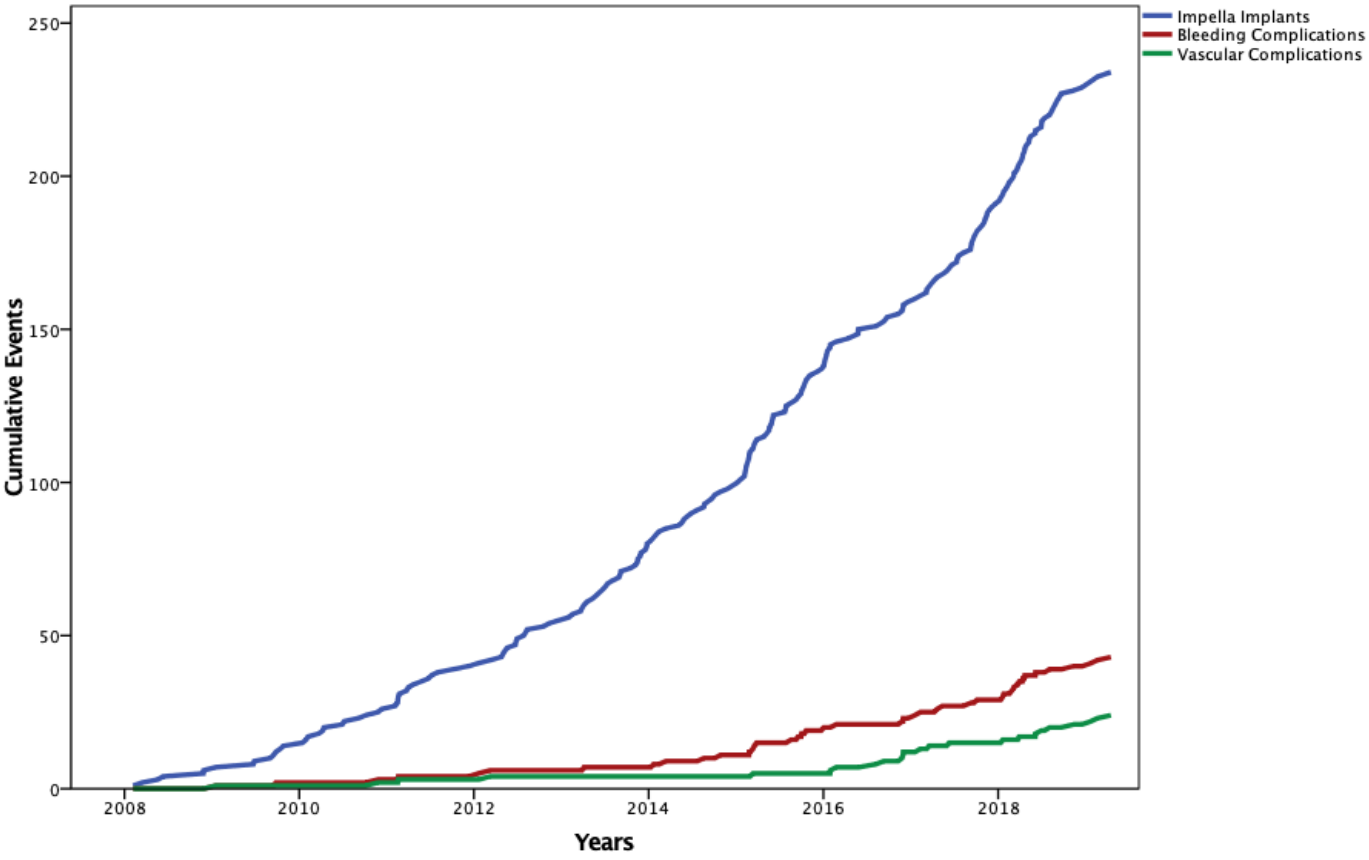
2.2 LV Unloading

Several strategies have been developed in an attempt to prevent periprocedural adverse events during high-risk PCI procedures. Of these, percutaneous left ventricular (LV) unloading shows promise. Unloading involves the placement of a mechanical pump which draws blood from the left ventricle and returns it into the aorta at flow rates approaching native cardiac output. Unloading has favourable physiological effects, reducing cardiac work and pulmonary capillary wedge pressure whilst improving cardiac power output[5]. Whether these physiological effects translate into better clinical outcomes remains, however, unclear.

There is a lack of robust evidence for the efficacy of LV unloading in complex PCI procedures. Despite this, usage has increased significantly in recent years and hence NICE published Interventional Procedures Guidance (IPG633) in November 2018[6]. The guideline noted the limited quality of evidence on efficacy and serious, infrequent, but well-recognised safety concerns related to LV unloading. Whilst permitting use within the NHS, they recommended this be limited to specialised centres with clinicians and teams who had specialised training and experience in complex PCI. The committee highlighted the urgent need for new data and recommended the following key efficacy outcomes; procedural success, completeness of revascularisation, haemodynamic stability, survival to hospital discharge, survival at 30 days and the rate of major adverse cardiac events. Recommendations for safety outcomes were vascular damage, bleeding, haemolysis and damage to the left ventricle.

The recent upsurge in LV unloading has been primarily driven by countries which have arrangements for reimbursement for use of this technology, including the USA, Germany and Japan. Our group have recently audited the use of LV unloading in high-risk PCI at the 4 largest volume centres since the technology was introduced to the UK, a little over a decade ago – the data demonstrate increasing use over time and confirmed the uncommon but significant bleeding and vascular complications (Figure 1). Many other UK centres have recently started to utilise these devices.

Figure 1: Cumulative Number of Impella Implantations (Blue), Bleeding Complications (Red) and Vascular Complications (Green).



LV unloading could provide clinical benefit via two distinct mechanisms – firstly, by preventing major periprocedural complications, which in turn would be expected to reduce mortality, critical care admissions and length of stay; secondly, by allowing operators to undertake more complex and complete revascularisation, the latter having been shown to be associated with improved mortality, reduced rehospitalisation and subsequently improved health-related quality of life. If LV unloading during high-risk PCI is clinically effective, increased use may have significant positive implications both for patient outcomes and healthcare resource utilisation. Conversely, if ineffective, limiting use could reduce both clinical and fiscal costs. Bleeding and vascular complications have significant HRQoL and healthcare resource implications, including increased hospitalisation and critical care utilisation.

The most widely adopted LV unloading device is the Impella (Abiomed, Danvers, MA, USA). Whilst it would be optimal for any new healthcare technology to be first evaluated in carefully designed clinical trials before being adopted widely and incorporated into guidelines, the unique set of circumstances surrounding the introduction of the device in the United States (where reimbursement far exceeded costs for many years) has meant that the FDA has approved use of the device based almost entirely on registry data. Consequently, no randomised trial of percutaneous LV unloading devices in high-risk PCI is planned or ongoing. A single industry-funded RCT (DanGer-Shock, ClinicalTrials.gov identifier NCT01633502) is investigating the role of LV unloading in patients with cardiogenic shock: this is a wholly separate condition for which data cannot be translated into the high-risk PCI setting.

2.3 Current Evidence

Whilst there is no universally accepted definition, to be considered high-risk the PCI would typically include a combination of complex coronary anatomy, impaired cardiac function, the likely duration of ischaemia during the procedure and patient frailty/comorbidity[7]. The indication for revascularisation may be either stable coronary disease or acute coronary syndrome, though the latter generally indicates a higher risk.

Recent systematic reviews of the evidence for LV unloading in high-risk PCI have been conducted by NICE[6] and Health Quality Ontario[8]. Both concluded that there is currently inadequate data to make any strong recommendation as to the use of LV unloading in high-risk PCI.

There are no randomised data on the safety and efficacy of LV unloading assisted PCI compared to the current standard of care (PCI without mechanical support). One randomised trial sought to compare the Impella versus intra-aortic balloon pump (IABP), the PROTECT II study[9]. Patients undergoing high-risk PCI, defined as unprotected left main disease or last patent vessel with an LVEF ≤35%, or three-vessel disease with an LVEF ≤30% were randomised 1:1 to receive an Impella 2.5 catheter or intra-aortic balloon pump (IABP) before PCI. The planned sample size was 600 but the data and safety committee recommended premature termination due to likely futility (as no difference was observed after 300 patients completed primary follow-up) hence only 452 patients were enrolled. The trial demonstrated the expected high rates of early major adverse events (MAE), but no significant difference between arms at 30 days (40% vs. 35%, respectively, p = 0.277). Selected sub-analyses were published indicating benefit (as-treated, excluding the first case performed at each centre) adding to the ambiguous interpretation of the data, despite the negative primary endpoint. Key safety data including bleeding and vascular complications were also absent from the report.

Methodological issues are apparent across both PROTECT II and many other previous trials of mechanical circulatory support and must be borne in mind in designing future studies if they are to provide definitive data.

Firstly, prior trials have defined risk only by simple coronary anatomic characteristics and LVEF. The complexity of intervention is a key factor in determining procedural risk and the likelihood of adverse events. Defining the participant population based on such complexity will test the utility of LV unloading in the circumstances where it may be efficacious, with higher event rates reducing the necessary sample size to show benefit. In order to recruit a sufficient number of such characterised patients, a network of centres is required which has both appropriate clinical experience and a track record of recruitment to trials in high-risk PCI.

Additionally, primary analyses were planned at early time-points; this limits the assessment to periprocedural events and complications. As patients undergoing high-risk PCI continue to accrue adverse events at significant rates, longer term follow-up provides large numbers of clinically important events[10]. Furthermore, most trials to date have used non-hierarchical composite endpoints with time-to-first-event analyses; whilst this approach is common in cardiovascular trials, it has significant weaknesses. Instead, considering these data in a hierarchy of clinical importance and capturing the impact of recurrent events by using innovative methods of statistical analysis will significantly increase power whilst focusing the assessment of outcomes on endpoints that are meaningful to both patients and healthcare providers.

A recent registry, arising from the Premier Healthcare Database (representing 20% of acute hospitalisations in the USA per annum) highlights the increase in LV unloading for high-risk PCI. The use of unloading increased from <5% of MCS supported procedures in 2010, to 33% of MCS procedure in 2016. The registry also indicated an increased risk of death, bleeding and stroke in patients treated with LV unloading after propensity matching, highlighting the safety risks and need for randomised data.[11]

This project therefore addresses a significant need for research, identified by the NICE Interventional Procedures Guideline Committee, and is being proposed at a critical time, where LV unloading use is not widely established in clinical practice, but is creeping into current practice in the absence of a significant evidence base and, were the American experience to be replicated, represents a substantial economic burden on the NHS.

3. Hypothesis

In patients undergoing high-risk percutaneous coronary intervention, a strategy of percutaneous left ventricular unloading is superior to standard care in terms of patient outcomes, quality of life and cost-effectiveness.

4. Study Design

A multicentre, open-label randomised controlled superiority trial.

5. Health Technology

The health technology being assessed is percutaneous left ventricular assist/unloading devices (pLVAD), specific to their use in high-risk PCI, as covered by NICE IPG 633. The comparator will the current standard of care, high-risk PCI without elective mechanical circulatory support.

6. Trial Population

6.1 Target Population

Patients undergoing high-risk PCI defined by 1: extensive coronary disease; 2: severe left ventricular systolic dysfunction; 3: scheduled to undergo complex PCI.

6.2 Inclusion Criteria

1. Extensive coronary disease defined by a British Cardiovascular Intervention Society (BCIS) Jeopardy Score ≥ 8*

2. Severe left ventricular systolic dysfunction defined as a LVEF ≤ 35% (or ≤ 45% in the presence of severe mitral regurgitation)#

3. Complex PCI defined by the presence of at least one of the following criteria:
   - Unprotected left main intervention in the presence of
     - an occluded dominant right coronary artery *or*
     - a left dominant circulation *or*
     - disease involving the entire bifurcation (Medina 1,1,1 or 0,1,1)
   - Intended calcium modification (by rotational or orbital atherectomy, lithotripsy or laser)
     - in multiple vessels *or*
     - in the left mainstem *or*
     - in a final patent conduit *or*
     - where the anatomic SYNTAX score is ≥32
   - Target vessel is a chronic total occlusion with planned retrograde approach

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

\# *Biplane/3D echocardiography or cardiac MRI can be used to assess the qualifying LVEF.*

6.3 Exclusion Criteria

1. Cardiogenic shock or acute STEMI at randomisation (including current treatment with a mechanical circulatory support device)
2. Contraindication to pLVAD insertion

3. Inability to give informed consent
4. Previously enrolled in CHIP or current enrolment in another interventional study that may affect CHIP outcomes

7. Endpoints

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

7.1 Primary Endpoint

A combined hierarchical endpoint incorporating death, stroke, myocardial infarction and cardiovascular hospitalisation, analysed with the Win Ratio method (see section 10 below).

7.2 Major Secondary Endpoints

Combined primary endpoint analysed with a time-to-first-event method
Individual components of the primary endpoint (as well as repeated occurrences of these events)

7.3 Other Secondary Endpoints

Major bleeding
Vascular complication
Procedural complication
Acute kidney injury
Unplanned revascularisation
Completeness of revascularisation
Health related quality of life/functional status
Resource utilisation and cost effectiveness
Serial cardiac troponin (T or I) levels
Length of stay

7.4 Endpoint Definitions

Disabling Stroke	Stroke is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction, resulting in persistent moderate disability (modified Rankin Scale ≥3) at the time of discharge from the acute hospital admission.
Acute Myocardial Infarction	1. **Spontaneous MI (>48 hours after PCI/CABG)** Detection of a rise and/or fall of cardiac Troponin I or T, with at least one value higher than the 99th percentile upper reference limit (URL) AND symptoms consistent with ischaemia OR dynamic electrocardiogram (ECG) changes (including ≥1mm ST elevation or ST depression, new left bundle branch block (LBBB) or >3mm T-wave inversion) OR imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology. 2. **Peri-procedural MI (<48 hours after PCI/CABG)** **Following PCI:** Detection of a rise in cardiac troponin I or T, with the threshold of significance determined by the pre-procedure baseline value. ***Baseline ≤URL:*** At least one value higher than five times the URL ***Baseline > URL and stable or falling:*** At least one value higher than 5xURL above the baseline value or 20% above the baseline value, whichever is greater. ***Baseline > URL and rising:*** At least one value higher than 5xURL above the predicted value* or 20% above the predicted value, whichever is greater. **the predicted value will be calculated via linear extrapolation of the trend from at least two troponin values taken within 48 hours before the procedure.* **Following CABG:** As for PCI, but with a threshold of 10xURL. *In addition to classifying patients dichotomously as having suffered a periprocedural MI or not, baseline and peak troponin I or T values measured within 24 hours of a procedure will be recorded. This will provide a continuous measure for adjudication of ties in patients reaching the periprocedural myocardial infarction endpoint within the Win Ratio.* *Absolute values of troponin, ECGs and supporting information will be collected for all patients who experience a periprocedural MI, so that sensitivity analyses based on alternative definitions can be explored.*
Cardiovascular Hospitalisation	Hospital or virtual ward admission (lasting ≥24 hours) with a primary diagnosis of heart failure or sustained ventricular arrhythmia. Prolonged hospitalisation for complications of the PCI procedure: acute heart failure, major bleeding and major vascular complication are included within the definition where the length of admission is extended by ≥24 hours from the expected time of discharge following the procedure and the associated endpoint definition has been met and was the primary reason for prolongation of the hospital admission. *Heart failure hospitalisation will be defined as Hospital admission (lasting >24 hours) for deteriorating symptoms or signs of heart failure, where there is a documented diagnosis of heart failure and the patient receives initiation or intensification of treatment for heart failure. Initiation or intensification of*

	treatment includes at least one of the following: increase in oral diuretic dose or addition of another oral diuretic; intravenous diuretic therapy; intravenous vasoactive therapy (vasodilator, inotrope or vasopressor); mechanical circulatory support (MCS) (including intra-aortic balloon pump (IABP), pLVAD, extra-corporeal membrane oxygenation (ECMO)); or cardiac transplantation. *Heart failure during or after the assigned PCI procedure itself is defined as prolongation of the planned admission by at least 24 hours due to acute heart failure requiring initiation or intensification of treatment as defined above (including continued use of pLVAD for >24hours after PCI in patients randomised to the elective pLVAD arm, for a clinical suspicion of heart failure). Elective admission for implantation or revision of ICD/cardiac resynchronisation therapy (CRT) devices will NOT constitute an endpoint.* *Sustained ventricular arrhythmia is defined as Ventricular tachycardia or fibrillation persisting for more than 30 seconds and/or associated with haemodynamic compromise, and/or requiring cardioversion/defibrillation (external or via implantable cardioverter defibrillator). Suspicion of arrhythmia without documentation on a recorded surface ECG or electrograms from an indwelling device will not constitute an endpoint.* Elective admission for planned cardiac procedures (staged PCI, device insertion, cardioversion or catheter ablation) will not constitute an endpoint.
Major Bleeding	Major bleeding will be defined using the Bleeding Academic Research Consortium (BARC) categories below: **Type 3: Major Bleeding** Type 3a • Overt bleeding plus haemoglobin drop of ≥30 to <50g/L (provided haemoglobin drop is related to bleed) • Any transfusion with overt bleeding Type 3b • Overt bleeding plus haemoglobin drop ≥50g/L (provided haemoglobin drop is related to bleed) • Cardiac tamponade • Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/haemorrhoid) • Bleeding requiring intravenous vasoactive drugs Type 3c • Intracranial haemorrhage (does not include microbleeds or haemorrhagic transformation; does include intraspinal) • Subcategories; confirmed by autopsy, imaging or lumbar puncture • Intra-ocular bleed compromising vision **Type 4: CABG-Related Bleeding** • Perioperative intracranial bleeding within 48 hours • Reoperation following closure of sternotomy for the purpose of controlling bleeding • Transfusion of ≥5 units of whole blood or packed red blood cells within a 48-hour period • Chest tube output ≥2L within a 24-hour period • If a CABG-related bleed is not adjudicated as at least a Type 3 severity event, it will be classified as 'Not a bleeding event'

	Type 5: Fatal Bleeding Type 5a • Probable fatal bleeding: no autopsy or imaging confirmation, but clinically suspicious Type 5b • Definite fatal bleeding: overt bleeding or autopsy or imaging confirmation
Vascular Complication	Vascular complications will be defined according to the valve academic research consortium (VARC) criteria below: **Major complication** • Aortic dissection or aortic rupture • Vascular (arterial or venous) injury# or compartment syndrome resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment • Distal embolization (non-cerebral) from a vascular source resulting in death, amputation, limb or visceral ischaemia, or irreversible end-organ damage • Unplanned endovascular or surgical intervention resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment • Closure device failure resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment **Minor complication** • Vascular (arterial or venous) injury# *not* resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment • Distal embolization treated with embolectomy and/or thrombectomy, *not* resulting in death, amputation, limb or visceral ischaemia, or irreversible end-organ damage • Any unplanned endovascular or surgical intervention, ultra-sound guided compression, or thrombin injection, *not* resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment • Closure device failure *not* resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment
Access related non-vascular complication	Non-vascular structure, non-cardiac structure perforation, injury, or infection resulting in death, VARC type ≥2 bleeding, irreversible nerve injury or requiring unplanned surgery or percutaneous intervention. Non-vascular access site (e.g. trans-apical left ventricular) perforation, injury, or infection resulting in death, VARC type ≥2 bleeding, irreversible nerve injury or requiring unplanned surgery or percutaneous intervention.

Major Procedural Complication	VT/VF requiring defibrillation. Cardiorespiratory arrest or acute pulmonary oedema requiring assisted ventilation. Prolonged hypotension (Mean arterial pressure ≤75 mmHg for >10 min despite fluid resuscitation and/or vasoactive drugs and/or requirement of mechanical circulatory support).
Acute Kidney Injury	Acute kidney injury defined as prolongation hospital admission or readmission ≥ 24 hours with rise in creatinine to 200% of baseline value or need for new renal replacement therapy within 30 days of procedure.
Completeness of Revascularisation	Change in anatomic BCIS-JS and anatomic SYNTAX score between the time of randomisation and the completion of the final planned PCI procedure.
Unplanned Revascularisation	Any unplanned target vessel or non-target vessel revascularisation by PCI or CABG, excluding staged PCI (with plan documented at the index procedure).
Length of stay	Duration of admission in complete days following the index PCI procedure and any subsequent planned staged PCI procedure

8. Safety Reporting

8.1 Definition

Unexpected events that have not been defined as endpoints (section 7) or expected complications of the PCI procedure (listed in section 7.4) should be reported as either a serious adverse event (SAE) or non-serious adverse event (NSAE) depending on their severity.

8.2 Unexpected Serious Adverse Events

SAEs should be reported to the Clinical Trials Unit (CTU) within 7 days of the site becoming aware of the event. The report should include an assessment of causality by the Principal Investigator at each site (see section 5.4.2). The Chief Investigator will be responsible for the prompt notification of findings that could adversely affect the health of patients or impact on the conduct of the trial.

8.3 Unexpected Non-Serious Adverse Events

Unexpected NSAEs should be evaluated by the Principal Investigator. This should include an assessment of intensity (see section 8.4.1) and causality (see section 8.4.2) and reports made within 14 days of the site becoming aware of the event. The CTU will keep detailed records of all unexpected adverse events reported. Reports will be reviewed by the Chief Investigator to consider intensity, causality and expectedness.

8.4 Reporting Unexpected Adverse Events

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

8.4.1 Assessment of Intensity

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

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

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

8.4.2 Assessment of Causality

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

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

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

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

8.5 Notification

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

9. Ethical Considerations

9.1 Consent

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

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

Patients at Participant Identification Centres (PICs) who meet the required eligibility criteria may be given the Participant Information Sheet (a localised version from the associated recruiting trial site). The review of eligibility and initial approach to the patient must be made by a member of their direct care team. It is then dependent on the patient to contact the relevant trial site to undergo informed consent and any further study procedures.

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

9.2 Declaration of Helsinki and Good Clinical Practice

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

9.3 Ethical Committee Review

The National Research Ethics Service Committee London - Bloomsbury have reviewed and approved the trial (REC reference 21/LO/0287). Copies of the letters of approval are to be filed in the trial site files at each centre.

10. Statistical Considerations

10.1 Win Ratio

The analysis will be undertaken by use of the Win Ratio, an increasingly recognised approach to allow for the hierarchy of events as well incorporating repeat events such as myocardial infarctions or hospitalisations[12,13]. The Win Ratio is the ratio of "winners" on the intervention compared to "losers" thus a value above 1 indicated a benefit of the intervention. Confidence intervals can be calculated as well as p-values and the process extended for repeat component events.

The combined hierarchical endpoint is all-cause death, stroke, spontaneous myocardial infarction (MI), cardiovascular hospitalisation and peri-procedural MI. The outcome hierarchy is as follows:

(1) All-cause death
(2) Stroke (defined as disabling stroke thus not including transient ischaemic attacks)
(3) Spontaneous MI
(4) Cardiovascular hospitalisation
(5) Peri-procedural MI

The Win Ratio will use an unmatched pairs approach with each individual in the intervention arm compared to each individual in the standard care arm, using the stepwise sequence below, to adjudicate a winner/loser or declare a tie. For each comparison the common follow-up is defined in which follow-up is censored at the duration of the shorter follow-up interval. For example, if one patient has been followed for 1 year and the second patient for 2 years then for that specific comparison events up to one year will be considered.

- Step 1: Compare all-cause mortality – if one has died, the survivor is the winner, if both have died, the patient who survives longer is the winner and if neither has died (or both die at the same interval from randomisation) proceed to step 2
- Step 2: Compare time to occurrence of disabling stroke, as above. If no winner, proceed to step 3.
- Step 3: Compare time to occurrence of spontaneous MI (as per Universal Definition) as above. If no winner, proceed to step 4.
- Step 4: Compare the number of cardiovascular hospitalisations (as defined in the trial protocol). The patient with the least number of hospitalisations occurring within the common follow-up period is the winner. If the same number of hospitalisations have occurred, the patient who survives longer before the first hospitalisation is the winner. If neither have had a cardiovascular hospitalisation in this period, proceed to step 5.
- Step 5: Compare periprocedural MI. If only one has had a periprocedural MI, the patient who does not have a MI is the winner. If both have had a periprocedural MI, the patient with the smaller infarct size, as measured by peak Troponin level (expressed as a multiple of the 99th centile, to allow comparison of different Troponin assays) is the winner, unless the difference in increase in troponin level between patients is $\leq$5x the URL, in which case a tied will be declared. If neither patient has had a periprocedural MI, the stepwise comparison is concluded and the result declared a tie.

This approach is designed to optimise the impact of individual components of a composite endpoint, by allocating greater weight to more important events, increasing the range of events considered and allowing capture of recurrent events. The requirement for a $\geq$ 5x URL difference in troponin level in determining wins based upon peri-procedural MI is designed to ensure a clinically meaningful

difference in all declared wins. When analyses of recurrent events has been applied to simulated data and major contemporary heart failure trials precision has been shown to improve when treatment discontinuation is low following the first event[14]. Since the intervention is high-risk PCI and not drug therapy crossover rates are expected to be negligible allowing a smaller sample size whilst maintaining power. In contrast, a traditional composite endpoint trial using time to first event analysis weights each event equally and only incorporates the first event hence many more serious outcomes, such as death, may not included and no account is taken of later events. The sample size using such an approach would require a larger treatment difference to be detected (as illustrated below) or require a prohibitively large and expensive trial and would not be able to complete recruitment in a reasonable timeframe.

10.2 Power Calculation

Based on an accrual period of 3 years and minimum follow-up of 12 months major events will be recorded for a minimum of 12 months and a maximum of 4 years. Major events over this duration can easily be incorporated into the Win Ratio analysis to maximise power and more appropriately account for the impact of more serious clinical outcomes. Calculations for the unmatched pairs Win Ratio analysis are not well established at present and require many underlying assumptions. Hence, we have first calculated sample size using a conventional approach (incorporating modest power).

In the PROTECT II trial the composite endpoint comparable to that proposed in CHIP was 40% at 30 days and 50% at 90 days. Assuming a more conservative event rate of 50% at 12 months in the control arm a trial of 250 (125 in each group) would have well in excess of 80% power to detect a hazard ratio of 0.62 requiring approximately 150 first events using all follow-up time (which, at these event rates, represents a risk ratio of 0.70 at 12 months) allowing for 5% losses. Whilst this rate may appear to be high at first, it is based on published data from high risk intervention. Given the established superior statistical power of a Win Ratio analysis and other secondary analyses accounting for repeated events in trials with low crossovers, a sample size of 250 patients was expected to provide good power to detect important clinical differences between the treatment groups. Crossovers will be evaluated throughout the trial.

10.2.1 Sample size extension

Due to successful recruitment, the opportunity arose for the investigators to extend recruitment and increase the sample size to 300 participants. The decision to design and conduct CHIP-BCIS was largely influenced by the position taken by NICE in 2018, when it was felt that there was insufficient evidence to support routine use of this strategy in the NHS and that more research on its safety and efficacy was a priority. Whilst a 30% relative risk reduction would enable NICE to issue clear guidelines on the use of LV unloading in the UK, increasing the sample size would allow an even smaller treatment effect to be assessed and hence provide NICE (as well as other healthcare systems and international guideline committees) with more definitive evidence on which to base their recommendations.

A further advantage of extending the accrual period is that the follow-up period of the 250 patients first recruited to the trial would be extended by the duration of the additional recruitment period. In total, we estimate that the proposed changes would lead to an increase in total follow-up by approximately 140 patient-years, which would allow capture of more clinical events, hence increasing statistical power. Given that the additional events captured will be those occurring later following randomisation, this will also potentially lead to more pairwise comparisons in the primary (win ratio) analysis being determined by components higher-up the hierarchy than peri-procedural MI, thereby also increasing clinical impact.

The TSC initially considered an increase in sample size in July 2023, subject to satisfactory progress in recruitment over the following 6 months. Accordingly, the TSC reviewed recruitment rates again in February 2024 and recommended an increase in the sample size to 300. An application to the funder was made in March 2024 and approved in May 2024.

10.2.2 Secondary Endpoints

Individual components of the hierarchical combined primary endpoint as well as repeated occurrences of these events, health-related quality of life, New York Heart Association (NYHA) functional class, completeness of revascularisation and resource utilisation at 90 days, yearly and at the end of the trial. The combined outcome and individual components will also be analysed using Cox proportional hazard models for the time-to-first event over the follow-up period. Other analyses such as sensitivity and per-protocol analyses will be detailed in the statistical analysis plan.

10.3 1-year feasibility review

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

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

11. Screening

11.1 Screening Population

All patients undergoing PCI should be screened for eligibility at the time of listing. They may come from the following sources:

- Patients referred to the Heart Team for consideration of revascularisation
- Patients seen in outpatient clinics for consideration of PCI
- Patients referred for advanced imaging to plan complex revascularisation
- Patients currently admitted with acute coronary syndromes or acute heart failure, either at the site or planned for transfer from a referring centre.
- Following coronary angiography in patients who are known to have poor resting LV function
- Participant Identification Centres (PICs)

11.2 Screening Log

Detailed screening logs of all patients with extensive CAD and EF ≤35% considered for the trial will be completed at sites. Details of all patients who undergo pLVAD supported high-risk PCI at the site will also be collected at the same time as the screening log.

The CTU will collect screening logs from the recruiting sites each month. Once recruitment is established, and if the TSC agrees it is appropriate, screening information may be collected less frequently.

12. Assessment of LVEF

12.1 Qualifying Ejection Fraction

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

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

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

13. Viability Testing

Viability testing is not mandated. However, as per current international guidelines, formal testing for myocardial viability is strongly recommended for all patients undergoing PCI with severely impaired left ventricular function.

14. Core Laboratories

14.1 Imaging Core Lab

All trial echocardiograms should be performed in accordance with the minimum standard set out by the British Society of Echocardiography. Viability studies should be carried out in accordance with the relevant national and international society guidelines, dependent on modality.

If the qualifying echocardiogram study was performed less than 6 months before randomisation, this study can also be submitted to the core lab to calculate baseline LVEF. If the qualifying echocardiogram was done more than 6 months before randomisation, or the qualifying LVEF was assessed using MRI, a further transthoracic echocardiogram should be carried out soon after randomisation and this study submitted to the core lab to calculate baseline LVEF. Any viability study performed in the 12 months prior to randomisation should be submitted to the core laboratory.

Baseline echocardiograms and viability studies will be anonymised and submitted to an imaging core laboratory which will determine LV volumes and EF using a Simpson's biplane method and segmental myocardial viability and (where available) ischaemia from the viability study. The core laboratory will be blinded to treatment assignment as well as to the timing of the studies in relation to randomisation.

The core laboratory will subsequently provide the relevant data to the Sponsor and CTU at the London School of Hygiene & Tropical Medicine for analysis against the data held in the eCRF.

14.2 Vascular Core Lab

Both pre-randomisation and trial procedure coronary angiogram, coronary angioplasty images, intracoronary imaging and peripheral vascular imaging will be transferred to a vascular core laboratory. Each participant's pre-randomisation BCIS JS and PCI procedural success will be independently validated by the core laboratory. The core laboratory will calculate a number of other scores reflecting the anatomic complexity of coronary disease, the extent of effective revascularisation and the complexity of CTO lesions.

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

15. Randomisation

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

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

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

16. Percutaneous Coronary Intervention

16.1 Pre-procedure workup

Cross-sectional imaging of the peripheral vasculature with computed tomography (CT) angiography is strongly recommended in all patients prior to enrolment. Where significant peripheral vascular disease or access issues are identified, cases should be discussed in a multidisciplinary meeting with vascular surgeons and/or interventional radiologists to develop a safe access and closure plan prior to randomisation.

16.2 LV Unloading

The choice of pLVAD device is at the discretion of the operator: any CE marked device intended for the purpose of LV unloading during high-risk PCI may be used. Device placement should be performed prior to the start of the PCI and used according to the manufacturer's instructions. Femoral arterial access is preferred, but alternative routes of access (e.g. axillary, transcaval may be utilised where local expertise permits). Use of ultrasound and/or fluoroscopy to guide femoral arterial puncture is mandated; the micro puncture technique is strongly advised where expertise permits. Device position should be documented fluoroscopically and if required, by echocardiography during the procedure. The maximal amount of haemodynamic support should be provided throughout the procedure.

At the end of the PCI procedure device support should be weaned and an assessment made of suitability for removal. Where possible, the device should be removed on-table prior to transfer of the patient. Otherwise, weaning of the device in the recovery area is recommended. The method of vascular closure is at the discretion of the operator and vascular surgical/interventional radiology experts. If ongoing haemodynamic support is required, the patient should be transferred to a critical care environment for ongoing monitoring and management.

Elective mechanical circulatory support is not permitted in the no-unloading arm, but may be used for bail-out following complications of the procedure (see 16.4 below)

16.3 Adjunctive therapy and devices

PCI will be performed according to local protocols. Measurement of LV end-diastolic pressure should be performed in all patients prior to PCI; right heart catheterisation for periprocedural haemodynamic monitoring may be used at the clinicians discretion. Dual antiplatelet therapy should be given in all cases, with pre-loading, and the post-PCI duration based on the individuals bleeding risk and local/national guidelines. Radial access is preferred for the PCI procedure. Drug-eluting stents are recommended. Intracoronary imaging (OCT or IVUS) is mandated for left mainstem PCI and strongly recommended for all other PCI procedures: a final intracoronary imaging acquisition following final balloon inflations is strongly recommended to assess the adequacy of PCI

16.4 Bailout

In patients assigned to receive no LV unloading, bail-out use of mechanical circulatory support will be permitted only in specific circumstances;

- Cardiogenic shock (persistent hypotension systolic blood pressure (SBP) <90mmHg for > 15 minutes and signs of organ hypoperfusion without response to vasoactive drugs)
- Profound hypotension (SBP <60mmHg) for > 3 minutes
- Significant pulmonary oedema requiring high-flow oxygen therapy or refractory to initial medical management
- Incomplete resolution of mechanical complication of PCI with persistently reduced angiographic flow and/or symptoms or signs of ischaemia
- Cardiac arrest requiring CPR

In such situations, the permitted mechanical circulatory support strategies will be IABP and/or veno-arterial extracorporeal membrane oxygenation (VA-ECMO). These events will be captured as pre-specified secondary outcome events. Crossover to pLVAD is not permitted and will be considered a protocol violation.

16.5 Staged Procedures

Where a second stage is required, this must be specified at the end of the first procedure and the second stage should be completed within the subsequent 6 weeks. In patients assigned to LV-unloading, use of an unloading device in the second stage is at the operator's discretion. In the no LV-unloading arm, elective mechanical circulatory support is not permitted, unless the procedure is a re-attempt following a prior failed PCI due to haemodynamic instability, in which case an IABP may be utilised.

16.6 Completeness of Revascularisation

It is strongly recommended that PCI is considered and, if feasible, attempted on all significant coronary lesions in major proximal coronary vessels (or side branches >2.5mm in diameter) subtending viable myocardium. Lesion significance is defined as >70% diameter stenosis on angiography or for lesions between 50 and 70% diameter stenosis, when accompanied by demonstrable reversible ischaemia on invasive or non-invasive testing. Planned target lesions will need to be identified by the operator and recorded by the trial coordinator before the procedure.

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

16.7 Protocol adherence

Every effort should be made to adhere to the assigned treatment strategy.

In cases where, following randomisation to no LV-unloading, it is decided PCI cannot safely be performed without LV unloading (either due a change in clinical status or a failed attempt), consideration should be given to revascularisation with CABG; otherwise the patient should not undergo revascularisation.

In cases where, following randomisation to LV-unloading, it is decided pLVAD insertion cannot safely be performed, PCI may be performed with an alternative MCS device or without device support.

17. Coronary physiology substudy

17.1 Aim

One of the proposed beneficial mechanisms of action for the pLVAD is to improve coronary flow and to potentially protect the coronary microvasculature during PCI. Post PCI physiology measurements have failed to show an improvement in flow with a pLVAD however, pre-PCI where autoregulation is likely to be disabled an improvement in flow may be seen but this is yet to be investigated. This substudy therefore aims to establish whether LV unloading with pLVAD leads to an improvement in coronary flow pre PCI and a greater improvement in coronary flow reserve from before to after PCI, than standard high-risk PCI without pLVAD. The results of the substudy will give a deeper mechanistic understanding of how a pLVAD impacts on myocardial oxygen supply and therefore could potentially help explain the findings of the main CHIP-BCIS3 study.

17.2 Site selection

Participation in the substudy is optional for trial sites participating in the main trial.

17.3 Consent

Patients approached to participate in the main trial at substudy sites will be invited to join the substudy. Participation in the substudy will be optional and patients may participate in the main trial without participating in the substudy.

17.4 Sample size

We aim to recruit a minimum of 44 patients to detect a difference in post-PCI CFR of 0.5 (at a significance level of 5% and power of 90%) between the elective unloading and standard care groups.

17.5 Methods

Measurements of coronary flow will be made pre- and post- PCI using a coronary pressure guidewire equipped with a temperature sensor (Abbot Pressurewire X), using standard clinical methods.
In both groups transit time will be measured at rest and repeated with hyperaemia induced with intravenous adenosine.
In the elective unloading group transit time will also be measured with the pLVAD active at maximal setting both before and after PCI.

18. Medical Therapy

It is recommended that all patients receive guideline directed medical therapy following the procedure. Drug classes to be considered include:

- Aspirin
- P_2Y_{12} inhibitor
- High-potency statin
- ACE inhibitor
- Beta-blocker
- Mineralocorticoid receptor antagonist
- Anticoagulation where appropriate

19. Data Collection and Follow-Up

19.1 Data handling

Data will be collected via an electronic Case Report Form (eCRF), managed by Sealed Envelope Ltd. and hosted by Rackspace. In accordance with GCP, the electronic data entry system will be validated and Working Practice Documents covering its use will be drafted and maintained.

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

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

conditions of Research Ethics Committee Approval. Personal patient data will be stored for a maximum of 8 years at the research sites.

Data will be pseudonymised and will not contain any identifiable data, apart from NHS number which will be encrypted and stored separately from the other data. This will be used to link patients to HES data through NHS England. NHS numbers will be stored for up to 10 years following enrolment.

19.2 NHS England

There will be two occurrences of data linkage with HES data through NHS England (formerly NHS Digital). A list of trial IDs, date of randomisation, NHS numbers and dates of birth will be prepared and securely sent to NHS England. In turn, NHS England will provide number of events of death, stroke, myocardial infarction and cardiovascular hospitalisation that occur between the date of randomisation and date the data linkage was run. These data will be used to validate the main trial dataset and identify with high sensitivity any endpoints missed by traditional follow up methods.

19.3 Tests required for eligibility

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

- Demographics and medical history
- Coronary angiogram
- LVEF assessment

19.3.1 Time limits for screening tests

Eligibility criteria	Test	Time limit
Extensive coronary disease	Coronary angiogram	Clinically valid
Severe LV systolic dysfunction	Echocardiogram, cardiac MRI	1 year prior to randomisation

19.4 Trial Checklist

	Tests required for eligibility	Baseline	Pre-PCI	Peri-procedural	Post-procedure (6 hours)	Post-procedure (24 hours)	At discharge (up to 24 hours) post-PCI	At 90 days post-randomisation	At 1-year post-randomisation	Yearly Follow-up	End of trial follow-up
Clinical assessments (standard of care)											
Demographics and med. history	X										
Coronary angio	X										
LVEF assessment	X										
Viability assessment		X									
FBC	X						X				
Creatinine and electrolytes	X		X				X				
HbA1C		X									
Full lipid profile		X									
Troponin T/I		X	X		X	X					
Haemodynamics				X							
Procedural details including device insertion				X							
Vasoactive medication				X							
ECG		X				X					
Intravascular imaging				X							
Trial specific assessments											
LVEDP				X							
BNP/NT-proBNP		X									
NYHA/CCS		X						X	X	X	X
EQ-5D-5L		X						X	X	X	X
KCCQ		X						X	X	X	X
Primary Endpoint							X	X	X	X	X
Secondary Endpoints							X	X	X	X	X
SAEs							X	X	X	X	X
Cardiac Medication		X					X	X	X	X	X

Baseline (up to 6 months prior to randomisation):

- Coronary anatomy and planned PCI procedure
- Viability study (If available)
- Cross-sectional imaging of peripheral vasculature (If available)
- LVEF
- Full blood count
- Creatinine and electrolytes
- HbA1c
- ECG
- Troponin T or I
- BNP/NT-proBNP
- NYHA/CCS
- EuroQoL EQ-5D-5L
- KCCQ
- Cardiac Medication

Pre-PCI (within 24 hours of procedure):

- Troponin T or I
- Creatinine and electrolytes

Peri-procedural

- Haemodynamics
- Procedural details including device insertion
- Vasoactive medication
- Intravascular imaging

Post-procedure (6 hours after end of procedure)

- Troponin T or I

Post-procedure (24 hours after end of procedure if patient remains in hospital)

- Troponin T or I
- ECG

At discharge – if PCI is staged please collect for each stage of the procedure:

- Death
- Stroke
- MI
- Cardiovascular Hospitalisation
- Creatinine and electrolytes
- Cardiac medication
- SAE

90 days after randomisation (telephone follow-up, or in person if the participant is due to attend hospital for a clinical visit):

- Death
- Stroke
- MI
- Cardiovascular Hospitalisation
- Major bleeding
- Unplanned further revascularisation
- NYHA/CCS
- EuroQoL EQ-5D-5L
- KCCQ
- Cardiac medication
- Acute Kidney Injury
- SAE

Yearly after randomisation (telephone follow-up, or in person if the participant is due to attend hospital for a clinical visit):

- Death
- Stroke
- MI
- Cardiovascular Hospitalisation
- Major bleeding
- Unplanned further revascularisation
- NYHA/CCS
- EuroQoL EQ-5D-5L
- KCCQ
- Cardiac medication
- SAE

End of trial follow-up (telephone follow-up, or in person if the participant is due to attend hospital for a clinical visit):

- Death
- Stroke
- MI
- Cardiovascular Hospitalisation
- Major bleeding
- Unplanned further revascularisation
- NYHA/CCS
- EuroQoL EQ-5D-5L
- KCCQ
- Cardiac medication
- SAE

19.5 Definition of end of trial

The end of trial is defined as the final lock of the trial database prior to unblinding and analysis.

19.6 Adverse Events

Expected adverse events (see section 7.4 for endpoint definitions) should be reported in the eCRF. An additional SAE form is not required.

Unexpected adverse events (see section 8 for requirements) should be reported on the relevant SAE or NSAE forms and faxed/emailed to the CTU within 7 days of notification for SAE and 14 days of notification for NSAE.

19.7 Participant ID Log

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

20. Health Economic Analysis

The primary outcome for the cost-effectiveness analysis (CEA) will be incremental costs, quality-adjusted life years (QALYs) and net monetary benefit at 12 months following randomisation. The CEA will take an NHS and personal social services perspective. Resource use data collected through trial CRFs and follow-up questionnaires will be combined with appropriate unit costs to report total costs. Health-related quality of life (HRQoL), assessed using the EuroQol EQ-5D-5L questionnaire, will be combined with survival data to report QALYs. Secondary outcomes for the cost-effectiveness analysis will include resource use, costs and QALYs at 90-days.

The primary sources of the resource use data will be the eCRFs, and individual health service questionnaires (HSQs) on the use of personal health services administered to surviving patients at regular intervals. Resource use data from the index hospital stay will be taken from the eCRF. Use of hospital resources from readmissions since discharge from index hospital stay and use of resources in primary care and community health services will be assessed by HSQs. To minimise recall bias the HSQ will be administered at 90 days and 12 months following randomisation. Resource use data from the eCRFs and HSQs will be valued using unit costs from the NHS Payment by Results database and unit costs of health and social care (PSSRU) to report the total costs per patient at 90 days and 12 months for both randomised groups. Data on hospitalisations will be collected through NHS England, to minimise the effects of recall bias. HRQoL will be assessed at baseline, 90 days, yearly and end of trial follow-up using the EuroQol EQ-5D-5L questionnaire, with NICE recommended valuation set that maps EQ-5D-5L descriptive system data onto the EQ-5D-3L value set (Hernández Alava et al. 2017; Hernández Alava et al. 2020). HRQoL data will be combined with the survival data to report QALYs at 90 days and 12 months. Quality Added Life Years (QALY) will be calculated by valuing each patient's survival time by their HRQoL at each time point according to the "area under the curve" approach. Baseline HRQoL and other baseline patient/site level variables will be adjusted for in estimating the adjusted effect of randomisation on incremental costs and QALYs. The economic analysis will follow the intention-to-treat principle. Missing data in costs and EQ-5D score will be handled with multiple imputation, assuming the data are missing at random conditional on the observed data. Multiple imputation will be undertaken using the Multivariate Imputation using Chained Equations (MICE) algorithm, with the multiple imputation model including all baseline variables, resource use and outcome (costs and HRQoL) variables. The number of imputations will be determined according to level of missingness in the outcome variables. Multiple imputation model will follow the same structure as followed for the analysis model.

The cost-effectiveness analysis will use Bivariate Seemingly Unrelated Regression model to allow for correlation between costs and QALYs and report the mean (95% confidence interval) incremental costs, and QALYs. We will also calculate the mean (95% confidence interval) net monetary benefits by valuing QALY gains at £20,000 per QALY and subtracting incremental costs. We will report the

probability that the intervention is cost-effective compared to current standard of care at different levels of willingness-to-pay for a QALY gain using the cost-effectiveness acceptability curves.

The following sensitivity analyses will be performed to check the robustness of primary cost-effectiveness results at 12 months:

(a) The costs and QALY could be highly skewed. Several distributions that can give a better fit of cost and QALY data will be considered.

(b) The implications of potential double-counting of inpatient costs across the sources of resource data (eCRF and HSQ).

21. Version History Log

Version	Date Implemented	Details of Key Changes
1.0	25/11/2020	Not applicable
1.2	26/08/2022	• Correction of trial flowchart to match protocol inclusion criteria • Change to membership and chair of the DMC • Change to membership of the TMG • Clarification of exclusion criteria to include current mechanical circulatory support • Clarification that prolongation of hospitalisation requires specific endpoint definitions to be met to be adjudicated as a primary endpoint. • Update to vascular complication secondary endpoint to align with VARC criteria • Change to protocol for bailout use of IABP or VA-ECMO when the patient has developed significant pulmonary oedema requiring high-flow oxygen therapy. • Coronary physiology substudy details added • Amendment to timing of post-PCI troponin and ECG testing • Amendment to criteria for determining wins on the basis of periprocedural MI • Corrections to typos and incorrect
1.3	22 May 2023	• Added Participant Identification Centres (PICs) • Change to membership of the TSC • Clarification of inclusion criteria to include orbital atherectomy • Addition of yearly and end of trial follow-up • Change to post-PCI ECG testing • Update to trial checklist • Update to Health Economic Analysis
1.4	22 May 2024	• Update to sample size from 250 to 300 participants • Update to trial flowchart to include orbital atherectomy • Update to membership of the Trial Management Group • Update to membership of the Clinical Events Committee • Update to Cardiovascular Hospitalisation definition to include virtual ward admission • Clarification that the planned 1-year feasibility review does not constitute a formal interim analysis • Update to organisation responsible for electronic health record data (now NHS England) • Addition of dates of birth to allow optimal data linkage via NHS England • Corrections to typographical errors

22. References

1 Townsend N, Bhatnagar P, Wilkins E, *et al*. Cardiovascular Disease Statistics, 2015. London: British Heart Foundation 2016.

2 Fox K, Poole-Wilson P, Clayton TC, *et al*. 5-year outcome of an interventional strategy in non-ST-elevation acute coronary syndrome: the British Heart Foundation RITA 3 randomised trial. *The Lancet* 2005;**366**:914–20. doi:10.1016/S0140-6736(05)67222-4

3 Kirtane AJ, Doshi D, Leon MB, *et al*. Treatment of Higher-Risk Patients With an Indication for Revascularization. *Circulation* 2016;**134**:422–31. doi:10.1161/CIRCULATIONAHA.116.022061

4 McAlister FA, Oreopoulos A, Norris CM, *et al*. Exploring the treatment-risk paradox in coronary disease. *Arch Intern Med* 2007;**167**:1019–25. doi:10.1001/archinte.167.10.1019

5 Dixon SR, Henriques JPS, Mauri L, *et al*. A prospective feasibility trial investigating the use of the Impella 2.5 system in patients undergoing high-risk percutaneous coronary intervention (The PROTECT I Trial): initial U.S. experience. *JACC Cardiovasc Interv* 2009;**2**:91–6. doi:10.1016/j.jcin.2008.11.005

6 Percutaneous insertion of a temporary heart pump for left ventricular haemodynamic support in high-risk percutaneous coronary interventions. National Institute for Health and Care Excellence 2018. https://www.nice.org.uk/guidance/ipg633

7 Perera D, Stables R, Thomas M, *et al*. Elective intra-aortic balloon counterpulsation during high-risk percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2010;**304**:867–74. doi:10.1001/jama.2010.1190

8 Health Quality Ontario. Percutaneous ventricular assist devices: a health technology assessment. *Ont Health Technol Assess Ser* 2017;**17**:1–97.

9 O'Neill WW, Kleiman NS, Moses J, *et al*. A prospective, randomized clinical trial of hemodynamic support with Impella 2.5 versus intra-aortic balloon pump in patients undergoing high-risk percutaneous coronary intervention: the PROTECT II study. *Circulation* 2012;**126**:1717–27. doi:10.1161/CIRCULATIONAHA.112.098194

10 Perera D, Stables R, Clayton T, *et al*. Long-Term Mortality Data From the Balloon Pump–Assisted Coronary Intervention Study (BCIS-1). *Circulation* 2013;**127**:207–12. doi:10.1161/CIRCULATIONAHA.112.132209

11 Amin AP, Spertus JA, Curtis JP, *et al*. The Evolving Landscape of Impella® Use in the United States Among Patients Undergoing Percutaneous Coronary Intervention with Mechanical Circulatory Support. *Circulation* 2019;**66**:606–34. doi:10.1161/CIRCULATIONAHA.119.044007

12 Pocock SJ, Ariti CA, Collier TJ, *et al*. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. *European Heart Journal* 2012;**33**:176–82. doi:10.1093/eurheartj/ehr352

13 Maurer MS, Schwartz JH, Gundapaneni B, *et al*. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. *N Engl J Med* 2018;**379**:1007–16. doi:10.1056/NEJMoa1805689

14 Claggett B, Pocock S, Wei LJ, *et al*. Comparison of Time-to-First Event and Recurrent-Event Methods in Randomized Clinical Trials. *Circulation* 2018;**138**:570–7. doi:10.1161/CIRCULATIONAHA.117.033065

15 Ryan M, O'Gallagher K, Vetrugno V, et ak. Does "real world" mechanical circulatory support match randomised clinical trials? The United Kingdom Impella (UKpella) registry. *Heart* 2020; 106 (S2): http://dx.doi.org/10.1136/heartjnl-2020-BCS.32 (Conference Abstract).

Appendix 1 – EQ-5D-5L

CONTROLLED TRIAL OF HIGH-RISK CORONARY INTERVENTION WITH PERCUTANEOUS LEFT VENTRICULAR UNLOADING

Health Questionnaire

English version for the UK

CHIP-BCIS3 Patient ID:	C H
Date of birth:	m m y y y y

Baseline ☐ **90 Day** ☐ **1 year** ☐

EQ-5D-5L

CHIP-BCIS3 Patient ID: C H

Date of birth: m m y y y y

Date completed d d m m y y y y

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

Mobility

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

Self-Care

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

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

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

Pain/Discomfort

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

Anxiety / Depression

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

EQ-5D-5L

CHIP-BCIS3 Patient ID:

C	H					

Date of birth:

m	m	y	y	y	y

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

YOUR HEALTH TODAY = ☐