Ceryx Medical

Clinical Investigation Plan: RSA-PACE

Version 1.2 (22/07/25)

Full Title: Respiratory sinus arrhythmia pacing post-CABG surgery in patients with HFrEF

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This protocol has regard for the HRA guidance and BS EN ISO 14155

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Signature Page

The undersigned confirm that the following Clinical Investigation plan (CIP) has been agreed and accepted, and that the Chief Investigator agrees to conduct the Clinical Investigation in compliance with the approved CIP and will adhere to the principles outlined in the Good Clinical Practice (GCP) guidelines, the Sponsor's (and any other relevant) Standard Operating Procedures (SOP), BS EN ISO 14155 "Clinical investigation of medical devices for human subjects – Good clinical practice", and other relevant 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; and that any discrepancies and serious breaches of GCP from the trial as planned in this CIP will be explained.

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Abbreviations

ABHI	Association of British HealthTech Industries
ADE	Adverse device effect
AE	Adverse event
AF	Atrial fibrillation
AHI	Apnoea hypopnoea index
ANCOVA	Analysis of covariance
BiV	Biventricular pacing
bpm	Beats per minute
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CI	Cardiac index or Chief Investigator
95%CI	95% confidence interval
COMET	Core Outcome Measures in Effectiveness Trials
CPAP	Continuous positive airways pressure
CRF	Case report form
CRO	Clinical research organisation
CRO-mCIA	Clinical research organisation model clinical Investigation Agreement
CRP	C-reactive protein
CSA	Cross sectional area
CTU	Clinical Trials Unit
CVA	Cerebrovascular accident
CVUHB	Cardiff and Vale University Health Board
DAP	Diastolic arterial pressure
DMC	Data Monitoring Committee
DoB	Date of birth
EF	Ejection fraction (left ventricular)
eGFR	Estimated glomerular filtration rate
EDV	End diastolic volume
ESV	End systolic volume
(m)FAS	(modified) full analysis set
FBC	Full blood count
FIH	First in human
GCP	Good Clinical Practice
GDPR	General Data Protection Regulations
GLS	Global longitudinal shortening
HCRW	Health and Care Research Wales
HES	Hospital Episode Statistics
HF	High frequency
HFrEF	Heart failure with reduced ejection fraction
HRA	Health Research Authority
HRV	Heart rate variability
IABP	Intra-aortic balloon pump
IB	Investigator's Brochure
ICE	Intercurrent events
ICHOM	International Consortium for Health Outcomes Measurement
IFU	Instructions for Use
ISF	Investigator Site File
LCOS	Low cardiac output syndrome

LOA	Limits of agreement
LOS	Length of stay
MAP	Mean arterial pressure
MAPSE	Mitral annular plane systolic excursion
MHRA	Medicines and Healthcare products Regulatory Agency
MVC	Maximum voluntary contraction
NACSA	National Adult Cardiac Surgery Audit
NIBP	Non-invasive blood pressure device
NT-proBNP	N-terminal pro b-type natriuretic peptide
NHYA	New York heart association
OSA	Obstructive sleep apnoea
PAC	Pulmonary artery catheter
PCR	Polymerase chain reaction (Covid-19 test)
PD1, PD2, etc	Pacing Day 1, Pacing Day 2, etc
PEDW	Patient Episode Database Wales
PID	Personal Identifiable Data
PIS	Participant Information Sheet
PP	Post-pacing (visit) – 7 days after pacing ends
PPI	Patient and public involvement
PVC	Premature ventricular contraction
RA	Right atrium/atrial
R&D	Research and development
RCT	Randomised controlled trial
REC	Research Ethics Committee
ROC	Receiver operating characteristics
RR	Respiratory rate
RSA	Respiratory sinus arrythmia
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Systolic arterial pressure
SD	Standard deviation
SDV	Source data verification
SEM	Standard error of the mean
SIV	Site Initiation Visit
SOC	Standard of care
SOP	Standard Operating Procedure
TAPSE	Tricuspid annular plane systolic excursion
TIA	Transient ischaemic attack
TMF	Trial Master File
TMG	Trial Management Group
TMP	Trial Monitoring Plan
TOE	Transoesophageal
TSC	Trial Steering Committee
U/E	Urea & electrolytes
UHL	University Hospital Llandough
UHW	University Hospital Wales
USADE	Unexpected serious adverse device effect
VT	Ventricular tachycardia
VTI	Velocity time integral

Study synopsis

Theory	That reintroduction of RSA variability to the heart rate using cardiac pacing will benefit cardiac function in patients with heart failure with reduced ejection fraction (HFrEF).
Primary Objective	To assess the performance of the Cysoni-XT in delivering RSA-like pacing, and to assess its safety compared to standard atrial pacing, in patients with HFrEF following coronary artery bypass graft surgery (CABG).
Primary Hypothesis	The Cysoni-XT can deliver RSA-like pacing in patients with HFrEF following CABG, with no observed increase in the incidence of safety events.
Design	First-in-human, multicentre, open-label, randomised controlled trial
Participants	Patients with HFrEF having CABG for revascularisation of the myocardium
Device	Cysoni-XT - modified temporary external pacemaker (Osypka) with additional pacing RSA module (Ceryx).
Intervention (device)	Atrial pacing with RSA-like variability post-surgery.
Comparator	Monotonic AAI right atrial pacing post-surgery
Sample size	N=32 (16 per arm) at 6th pacing day (N=54 enrolled)
Trial duration	18 months
Follow-up period	30 days post-surgery
Lead site	University Hospital Wales and University Hospital Llandough, Cardiff and Vale University Health Board, Heath Park, CF14 4XW Cardiff, UK
Purpose	Risk-benefit profile of the technology
Co-primary endpoints	1. Performance (intervention group only): Proportion of the time spent with RSA-like pacing being delivered, out of the time that the Cysoni-XT is active and receiving valid respiratory signals. 2. Safety: Incidence proportion of new-onset atrial fibrillation (AF) post-surgery.
Secondary endpoint	Serious adverse device-related events (SADEs).
Observations (clinical effect)	Cardiac function: Change in cardiac output/index over 6 days post-surgery Change in stroke volume/index over 6 days post-surgery Change in ejection fraction over pacing duration post-surgery Time course of cardiac changes Arterial blood pressure, intrinsic heart rate, systemic vascular resistance Recovery from exercise (static handgrip) Episodes of apnoea and hypopnea Post-surgical recovery (length of stay) Dose-response between RSA delivered and improvement in cardiac function Intrinsic RSA levels Biomarkers: including cardiac and renal function
Additional safety observations	Other measures of post-surgery arrhythmias Withdrawal rate due to arrhythmias Withdrawal of pacing due to declining condition 30 day mortality Procedure or device related adverse events Cardiac-related incidents

Criteria at screening	**Inclusion**	**Exclusion**
	Adult patients (≥ 22 years) scheduled for isolated, on- or off-pump CABG	Requirement for concurrent valve replacement surgery
	Established diagnosis of heart failure with reduced ejection fraction (HFrEF).	
	Elective or urgent admission route	Emergency CABG admission
	Echocardiography assessment of left ventricular ejection fraction (EF) of 20%-45% (within 1 month of planned surgery)	History of paroxysmal or permanent atrial fibrillation or flutter
	Patient is in sinus rhythm	History of AV-node dependent tachycardia
	Any number of coronary vessels scheduled to be grafted. Must include left anterior descending artery.	Patients lacking capacity to consent
	Patient is able to provide written informed consent	Pregnancy
		Implanted pacemaker or defibrillator
		Intrinsic resting HR > 110bpm
		Patient tests positive for Covid-19 within 14 days of intended CABG (using PCR or lateral flow test)
		Patient is unable to breathe through their nose or failure to obtain suitable respiration signals via nasal cannula (where assessed).
		Failure to obtain Uscom signals

Pacing Day 1 - Withdrawal criteria post-surgery
Requirement for ventricular pacing post-surgery
Surgical complications: peri-operative stroke
Failure of pacing wires
Pericardial effusion/tamponade
Need for inotropes >48hrs
Chest infection requiring augmented oxygen
Need for intra-aortic balloon pump (IABP) for >48hrs
Renal failure requiring haemofiltration for >48hrs
Patient not extubated within 24hrs post-surgery
Intrinsic resting HR > 110bpm
Patient not suitable for pacing for > 24 hrs post extubation
Persistent inability to obtain respiratory signals.

During pacing (Pacing Day 1 to Lead Removal) - withdrawal criteria
Patient unable to tolerate RSA pacing equipment/set-up
Haemodynamically significant arrhythmia resulting from RSA delivery
Failure to capture right atrial (RA) pacing, technical failure to deliver RSA-like pacing
AF for 24hrs or more as a single episode, or cumulative duration of AF of 48 hrs or more over the pacing period.
Other brady- or tachy-arrythmias, or heart conduction issues that interfere with or prevent the heart from being paced at trial-determined rates for a cumulative duration of 72 hours or more.
Coronary graft failure
Pulmonary oedema
Loss of capacity
Persistent inability to obtain respiratory signals.

Role of Sponsor and Funder

The Sponsor and funder for this study is Ceryx Medical Limited. The Chief Investigator is Prof Zaheer Yousef, who is an employee of Cardiff and Vale University Health Board, which is the lead site. CEDAR (Centre for Healthcare Evaluation, Device Assessment and Research) is acting as a clinical trial unit (CTU) or Clinical Research Organisation (CRO) and is also part of Cardiff and Vale University Health Board. The study has been designed in collaboration with clinical investigators from multiple sites, pre-clinical researchers, Ceryx staff, and CEDAR researchers, and with input from consultant statisticians, device regulatory experts, and NHS Research and Development departments.

Ceryx have full responsibility for the design, conduct, and management of the study. Final approval of the CIP and associated design documents (Statistical Analysis Plan, Data Management Plans, etc) is the responsibility of Ceryx. The management of the study design and conduct is delegated to CEDAR, with specific tasks as detailed in this CIP and the standard tripartite NHS agreement (CRO-mCIA). Following approvals from Health and Care Research Wales (HCRW) and the Health Research Authority (HRA), Research Ethics Committee (REC), and the Medicines and Healthcare products Regulatory Agency (MHRA), Ceryx will have no role in the day-to-day conduct or management of the study, other than:

- as advisers on the Trial Steering Committee (TSC),
- supply of study devices and consumables,
- investigation of device-related issues (adverse events or device deficiencies), including reporting to the MHRA,
- processing of device-recorded data to extract outcome measures.

Analysis of the results will be conducted by CEDAR, Ceryx, and contract statisticians. Writing of manuscripts for journal publication will be conducted by CEDAR researchers and clinical investigators, however Ceryx will have final discretion on the publication of material produced from this study.

Role of Committees

Trial Management Group (TMG)

The TMG will comprise the CRO/Trial Manager and the Principal Investigators at each site (including the Chief Investigator) and will oversee the day-to-day management of the Clinical Investigation.

Trial Steering Committee (TSC)

The TSC will comprise at minimum:

- an Independent Chair with expertise in trials and/or medical device studies
- a representative of the Sponsor
- a representative of the CRO (CEDAR)
- the Chief Investigator
- a representative from the trial statisticians (Select)
- a representative from the Patient and Public Involvement group

The role of the TSC is to:

- To provide advice to the TMG
- To monitor conduct, progress, and patient safety
- To consider new information relevant to the research question
- To respond to recommendations from the DMC.
- Review any disagreements regarding recommendations between the DMC and Sponsor.
- To agree proposals for substantial CIP amendments

Data Monitoring Committee (DMC)

- The DMC will comprise experts who are independent of the trial and the sponsor, at minimum: Two experienced cardiologists, at least one of which will have particular expertise in pacing.
- A medical statistician with experience of clinical trials.

The role of the DMC is to:

- To review unexpected suspected adverse device-related events (USADEs) and any safety events that require expedited reporting (to MHRA, REC, or investigators).
- To monitor trial data and make recommendations to the TSC on whether there are ethical, statistical, or safety reasons why the trial should not continue.
- To monitor trial data against the assumptions made in the initial study design and make recommendations to the TSC on whether changes to the design, sample size, analysis or endpoints are warranted.
- To determine if additional interim analysis of trial data should be undertaken, to consider the data from the planned interim analyses, and to advise the TSC regarding the release of data and/or information.
- To consider additional safety issues for the trial and relevant information from other sources.
- To review proposed changes to the CIP.

The DMC will be governed by a Charter, describing their responsibilities, organisation, documentation, and procedures. The DMC will consist of 2 independent clinicians and a statistician with relevant experience, and will be supported by staff from CEDAR.

CIP Contributors

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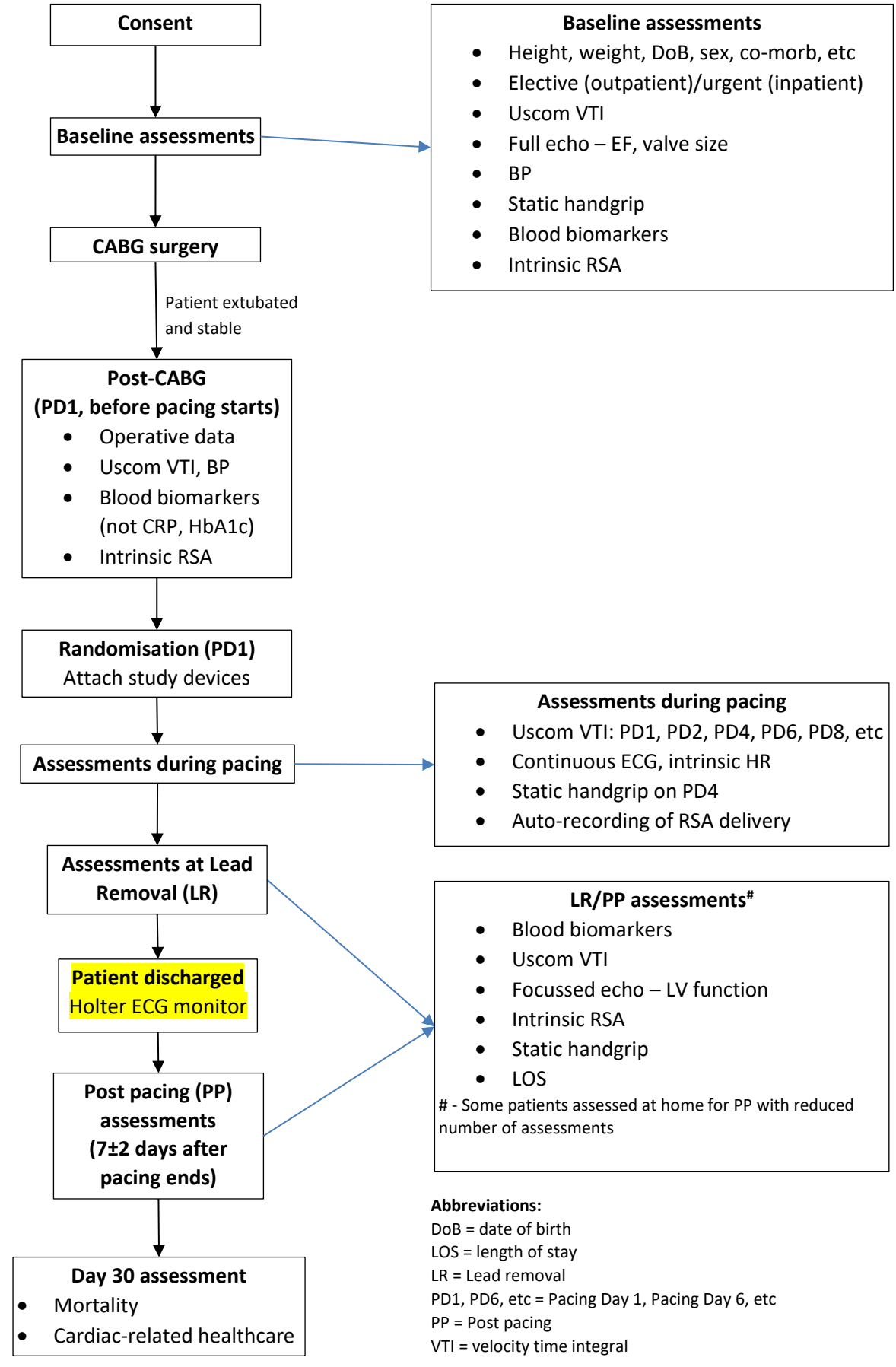
Trial Flowchart



Abbreviations:
DoB = date of birth
LOS = length of stay
LR = Lead removal
PD1, PD6, etc = Pacing Day 1, Pacing Day 6, etc
PP = Post pacing
VTI = velocity time integral

1 Background

1.1 Respiratory sinus arrhythmia

In young, healthy individuals at rest, heart rate (HR) is not fixed but varies periodically by about 5-15 bpm. (The same is obviously true of the inverse of HR, R-R interval.) This is referred to as heart rate variability (HRV) and occurs at a range of frequencies up to about 0.4 Hz (Task Force, 1996). High levels of HRV are a marker of good cardiovascular and autonomic health. The variations with the largest amplitudes are those at the respiratory frequencies - heart rate increases with inspiration and decreases with expiration. This is referred to as respiratory sinus arrhythmia (RSA) or high frequency (HF) variations. With increasing age and in chronic disease conditions, HRV and RSA are diminished.

RSA provides a mechanism for coupling the cardiovascular and respiratory systems, which need to work together to optimise delivery of oxygen via the blood stream to tissues. It is present across multiple species, and although much is known about the causative mechanisms, the physiological function is still debated (Elstad et al. 2018). Potential benefits of RSA include: (1) matching of ventilation and pulmonary blood flow; (2) improvement in cardiac efficiency; (3) stabilisation of arterial blood pressure and flow. Our group conducted modelling studies that contested the ventilation-matching theory, and instead suggested that RSA was a mechanism for saving energy for the heart (Ben-Tal et al. 2012; Ben-Tal et al. 2014). RSA resulted in a 3% energy saving in the work of the heart, improving efficiency to maintain constant levels of arterial partial pressure of CO_2 (Elstad et al. 2018).

1.2 Heart failure

Heart failure is a clinical syndrome of symptoms and signs of congestion (shortness of breath, fatigue, ankle swelling, elevated jugular venous pressure and pulmonary crackles). It is caused by structural or functional abnormalities of the heart which leads to inadequate cardiac output (CO) and hence poor blood flow to the rest of the body. The most common causes in developed countries are coronary artery disease (CAD) and hypertension. Other causes include valve disease, arrhythmias, cardiomyopathies, congenital heart disease, infection, drugs, infiltrative diseases, storage disorders, pericardial disease, metabolic conditions and neuromuscular diseases. It is important to identify the underlying aetiology which will allow tailoring of specific treatment (McDonagh et al. 2021).

In the UK there are around 650,000 people on the GP heart failure register (British Heart Foundation 2022). Heart failure is associated with a poor quality of life, increased hospitalisations and mortality. The Olmsted County cohort from 2000 to 2010 showed that heart failure had a 1-year mortality of 20% and 5-year mortality of 53% (Gerber et al. 2010). Furthermore, heart failure patients are admitted to hospital once a year on average (Barasa et al. 2014).

Heart failure with a left ventricular ejection fraction (LVEF) of ≤ 40% is called ‘heart failure with reduced ejection fraction’ (HFrEF) (McDonagh et al. 2021). Initially the reduction in CO and change in systemic haemodynamic is compensated by neurohormonal up-regulation in order to maintain the Frank-Starling mechanics. This promotes cardiac re-modelling and ultimately leads to cardiac dysfunction and a reduced CO. This in turn reduces systemic tissue perfusion and venous return to the heart, resulting in symptoms and signs of congestion (Kemp and Conte 2012). The aim of both

medical and device therapy in HFrEF is to promote reverse remodelling, improve CO and LVEF (Adamo and Mann 2020). Current heart failure treatment for HFrEF focusses on blockade of maladaptive neurohormonal activation using a range of medications, such as angiotensin-converting enzyme inhibitors (ACE-I); beta-blockers; mineralocorticoid receptor antagonists (MRA) and sodium-glucose co-transporter 2 (SGLT-2) inhibitors. As a result, these medications improve quality of life, reduce hospitalisations and mortality (McDonagh et al. 2021), but do not produce substantial improvement in cardiac performance or reverse the damage to the heart. Medication shows around a 5%-9% improvement in LVEF (Hayashi et al. 2003; Januzzi et al. 2019).

Once optimally managed with medical therapy, a biventricular pacemaker (cardiac resynchronisation therapy, CRT) is recommended for symptomatic patients with a broad QRS complex and LVEF of ≤ 35%. This has further shown to improve morbidity and mortality (McAlister et al. 2007; Schrage et al. 2022) and can increase LVEF by around 1%-5% on average (McAlister et al. 2007). However, there is a wide variation in response, with the greatest effects in so-called 'super-responders' achieving improvements of around 17%.

The 5-year mortality rates were as high as 70% until the last decade of the 20th century. Treatment from medication and devices has improved outcomes from heart failure, however mortality still remains high (Lyons and Bradley 2015).

In heart failure, RSA is attenuated severely, and its demise is a prognostic indication for cardiovascular disease, including sudden cardiac death (La Rovere et al. 1998). Haigney et al. (2014) demonstrated that patients with HF had smaller changes in the R-R interval (ΔRR) over a respiratory cycle than healthy controls, despite apparently greater inspiratory efforts. Those with LVEF < 30% had an even greater reduction in RSA magnitude.

1.3 Sleep apnoea

Sleep apnoea is common in heart failure patients and it is likely the relationship between the two is bidirectional. This includes both obstructive (OSA) and central sleep apnoea and can lead to development and progression of heart failure (Khattak et al. 2018). This is secondary to intermittent hypoxia, increase in pre-load, after-load, sympathetic nervous system activity, and vascular endothelial dysfunction. Treatment of sleep apnoea improves cardiac function in heart failure patients, however there are no randomised trials to show improvement in morbidity and mortality (Lyons and Bradley 2015). OSA is an independent risk factor for all-cause mortality and morbidity. Severe OSA has been associated with 1.9 times increased risk in all-cause mortality and 2.65 times increased risk of cardiovascular mortality (Ge et al. 2013). Kaneko et al. (2003) suggested that improvement of LVEF secondary to continuous positive airways pressure (CPAP) was likely because of the sustained reduction in left ventricle after-load. Furthermore, the withdrawal of CPAP showed worsening LVEF, suggesting that CPAP had reversed OSA.

1.4 Coronary artery bypass graft surgery (CABG)

Coronary artery bypass graft surgery (CABG, heart bypass, cardiac revascularisation) is performed to treat coronary artery disease (CAD), whereby one or more of the arteries supplying the myocardium are blocked. This procedure is usually performed using a cardiopulmonary bypass machine ('on-pump'), although it can also be conducted off-pump while the heart is still beating. Autologous vessels are harvested from the leg or chest to bypass the diseased arteries.

New onset arrhythmia is a relatively common sequela of CABG surgery, with atrial fibrillation (AF) as the most prevalent type. Published rates of new onset AF (incidence proportions) are around 18%-30% (section 4.4.2), with the peak onset at around 2-3 days post-surgery (Philip et al. 2014; Filardo et al. 2018; Gorczyca et al. 2018; Kosmidou et al. 2018). Most of these episodes of arrhythmia are temporary, lasting up to a few hours (Filardo et al. 2018). Patients having CABG routinely have temporary epicardial pacing leads sutured to the outside of the myocardium for the immediate post-operative period. Ventricular leads are universal, whereas atrial wires are placed according to the surgeon's preference (Lazarescu et al. 2014; Kiely et al. 2020). They are connected to an external pacemaker whilst in hospital, in order to treat temporary arrhythmias, low cardiac output syndrome (LCOS), bradycardia, or heart block. Leads are usually removed by gentle traction around day 4 if not clinically needed, but this may be delayed for administrative reasons (Kiely et al. 2020).

CABG is recommended as the first choice of revascularisation strategy for patients with CAD and HFrEF who are suitable for surgery (Neumann et al. 2019; McDonagh et al. 2021). However, reduced CO in the post-surgical recovery period can be a significant issue. LCOS is defined by a range of clinical signs, including cardiac index of less than 2.0 L/min/m^2 (Algarni et al. 2011). It is a common consequence of cardiac surgery, occurring in up to 10%-14% of patients, and leads to increased mortality and morbidity (Algarni et al. 2011; Duncan et al. 2022). Patients with reduced LVEF are at increased risk of LCOS (Algarni et al. 2011; Mehta et al. 2017) and post-surgical LCOS may be a risk factor for the development of new onset AF (Gorczyca et al. 2018). LCOS is treated with fluid replacement and/or inotropic support. In refractory cases, mechanical support may be employed, such as intra-aortic balloon pumps (IABP). Improving CO in these patients in the short-term may therefore be directly beneficial to their recovery and future progression.

2 Medical device/intervention

2.1 Description of the investigational device

The intervention in this study is a modification of the pacing output from a standard external pacemaker such that it will approximate the RSA variation found in healthy subjects. A CE marked pacemaker (PACE203, Osypka AG), currently in common use in post-CABG patients, is the basis for the technology under investigation. The PACE204 (Osypka) is the same device, adapted to receive an additional input signal based on the respiratory signal (RSA module). The resulting Cysoni-XT is therefore not CE marked. The respiration signal (see below) will be combined with the ECG signal to determine the appropriate pacing interval. The pacing impulse will be delivered by the Osypka PACE204 pacemaker unit.

The median pacing rate will be at least 10 bpm above the patient's intrinsic rate (see Section 4.5) – this is overdrive pacing. Pacing impulses will be grouped together during inspiration such that the heart rate will typically be up to 6 bpm higher than median during inspiration and 6 bpm lower during expiration. This will approximate the natural temporal relationship between the heart beat and respiration in healthy people – the RSA. The pacemakers have limits that will keep the timing of the pacing impulse within a normal physiological range.

Participants in the comparator arm will either use the temporary external pacemakers in use clinically (where agreed locally) or Ceryx will provide standard, CE marked PACE101 (Osypka) single

chamber external pacemakers. The comparator pacemakers will deliver standard monotonic AAI pacing to the right atrium at a rate of at least 10 bpm higher than the patient's intrinsic HR (Section 4.5).

In both arms, the respiratory signal will be continuously recorded using air pressure at the nasal orifice. This will be detected using standard nasal prongs, standard nasal cannulae, and a pressure sensor. The sensor is an established, CE marked device used in sleep studies (SleepSense AC Pressure Sensor, S.L.P. Inc). Oxygen can be provided via the cannulae if required, without detriment to the air pressure signal. Oxygen tubing will connect to the SleepSense sensor via a bacterial filter. For participants in the RSA intervention arm, the SleepSense device will be incorporated into the prototype RSA module – encased in a box with the hardware to process the respiration signal and deliver the timing signal to the pacemaker. (The pressure sensor is therefore not CE-marked in this application.) An encrypted removable data storage device (e.g. SD card) will also be included in the Ceryx RSA module. All required devices will be attached to a bedside wheeled stand (Figure 1).

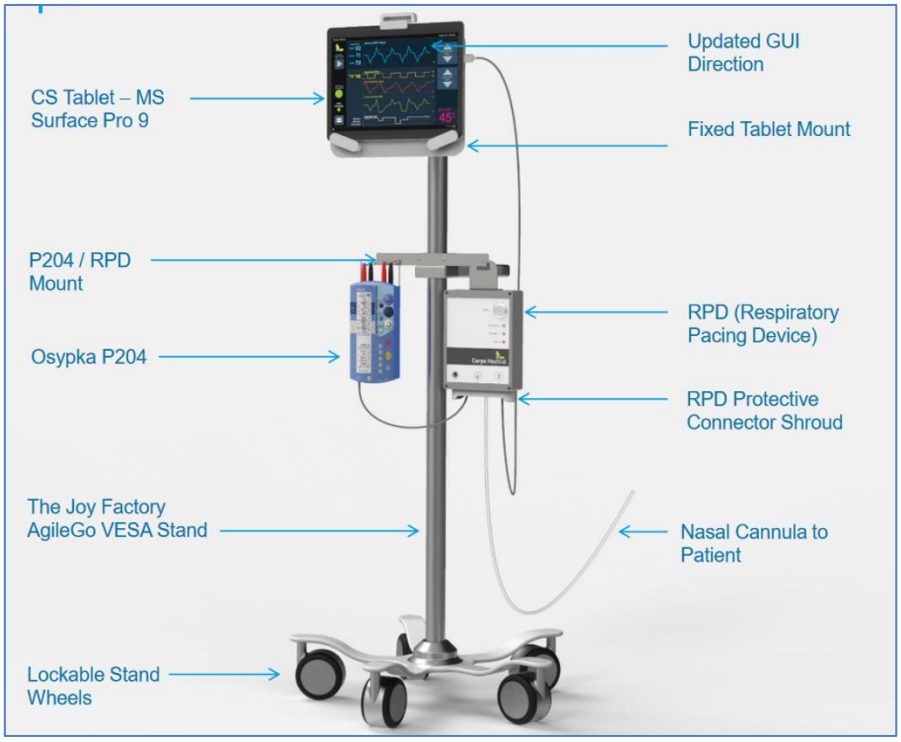


Figure 1: Equipment for investigational arm

Osypka pacemakers, Uscom Doppler scanners, Ceryx RSA modules, SleepSense sensors, handgrip transducers, ECG monitors, and data recording devices are multi-patient use (following appropriate cleaning). Sufficient sets of the equipment will be supplied by Ceryx to each site, depending on estimated recruitment at that site.

The investigational pacemaker devices will be distinguished from standard Osypka devices by different colouring and by labelling in accordance with requirements of BS EN ISO 14155 (British Standards Institute, 2020). Leads used for pacing are standard, clinically used components. There are therefore no new components or investigational devices that will come into direct contact with patients.

The intended purpose of the Cysoni-XT is to restore RSA-like modulation of heart rate. Additional data is provided in the Investigator's Brochure (IB) and Instructions for Use (IFU).

2.2 Manufacturer of the investigational device

Osypka Medical manufacture the external pacemakers to be used in the study. The Ceryx RSA modules, incorporating the SleepSense sensors, are manufactured by Hydrix Limited on behalf of Ceryx Medical Limited. Ceryx is the legal manufacturer of the investigational devices.

2.3 Identification and traceability of the investigational devices

Investigational devices will be given unique study IDs, associated with the serial numbers (or other unique identification numbers provided by the manufacturer). A log of devices will be maintained which will identify (amongst others) which participants they have been used for, which data storage devices were used with them, and any device-related adverse incident or device deficiencies (Section 5.1). This log will be used to ensure equipment is traced and all investigational devices are returned to the Sponsor at the end of the study (unless required by the MHRA).

2.4 Intended indications and populations

The artificial restoration of RSA by a pacemaker device is intended to be used in patients with HFrEF. Theoretically this could improve cardiac function, patients' capacity for activity, and quality of life. Longer term product development includes the incorporation of RSA variability into permanently implanted pacemaker devices, for the long term treatment of these patients. If feasible and effective, the hope is that improvements in LVEF and CO, plus potential remodelling of the myocardium, will alleviate symptoms and possibly partially remit the condition. It may also slow the progression of the disease.

Another intended population and indication is represented by the patients in this Clinical Investigation. In patients undergoing CABG, reduced CO following surgery is a significant complication that increases morbidity and mortality (see Section 1.4). The risk of developing LCOS increases with reduced ejection fraction. This suggests that improving LVEF and CO in the post-surgical period could provide significant benefits for patients with HFrEF undergoing CABG procedures. This may be in the form of reduced morbidity, reduced need for cardiac support, increased capacity for activity, reduced length of stay, or even reduced mortality. Additionally, arrhythmias are common in the post-surgical period and are the reason why all patients have temporary epicardial pacing wires implanted. Recent *in vitro* work by researchers related to this study group has indicated that RSA pacing may have a protective function regarding arrhythmias (unpublished data). Therefore, if feasible and effective, there is substantial potential for patients in this study to benefit from the artificial restoration of RSA-like HR variability. If so, RSA variability could be added to temporary pacing devices in future.

2.5 Users of the investigational devices

The investigational pacemaker devices will require minimal additional training beyond that required for standard external pacemaker devices. Programming and maintenance of the devices (battery changes, data downloading, rate setting) are within the capabilities of the clinical staff who usually care for CABG patients, and will most likely be managed by clinical research staff or cardiac physiologists. Patient care and management will be the same as for standard external pacemakers.

3 Justification for the design of the Clinical Investigation

This Clinical Investigation will assess the safety and performance of using a modified pacemaker to restore RSA-like variability in post-CABG patients with HFrEF. It will also start to examine whether the beneficial effects seen in animal studies (Section 3.2) could be replicated in humans. It will compare outcomes between patients having standard (monotonic) atrial pacing and those having atrial pacing with additional RSA-like variability. Based on animal studies we theorise that RSA-like pacing can be delivered for at least 40% of the pacing time (assuming suitable respiratory signals), with no additional risk to patients beyond standard atrial pacing, and that cardiac function will improve gradually over several days and decrease again to baseline values within about a week of the end of pacing (see section 3.2). Assessments will be carried out over the duration of pacing and after 7 further days of no pacing (post-pacing, PP). Pacing will start after patients are removed from ventilator support post-surgery and will last several days, until patients are ready for discharge, or until a clinical decision is made to remove the pacing leads (Lead Removal).

3.1 Clinical development stage

This is a first-in-human clinical investigation of RSA pacing in humans and therefore the technology is at pilot stage.

3.2 Pre-clinical investigations - restoring RSA using pacemakers

Following modelling work (Ben-Tal et al. 2012; Ben-Tal et al. 2014; Elstad et al. 2018), Ceryx's founders postulated that reinstating RSA in heart failure would be beneficial and may improve pumping efficiency. They developed a hardware pattern generator that used a signal from the diaphragm electromyogram to modulate the vagus nerve drive to the sinus node (Nogaret et al. 2013, 2015). They then tested this in acute rat models and restored the normal RSA in these animal preparations.

This early work was followed by an investigation into the longer-term artificial restoration of RSA, using pacemakers developed by Ceryx that utilised the hardware pattern generators. The studies used conscious animals with induced heart failure and reduced ejection fraction and tested the effect of pacing for 8 hours a day for 2 weeks (O'Callaghan et al. 2020; Shanks et al. 2022). O'Callaghan et al. (2020) compared RSA pacing in rats (controlled from the diaphragm electromyogram), with monotonic pacing and with no pacing. Rats treated with RSA pacing showed a statistically significant 25 ± 8% (mean ± standard error of the mean, SEM) increase in stroke volume (SV) and a 23 ± 6% increase in CO after 14 days compared to the pre-pacing period. Rats with monotonic pacing or no pacing did not significantly improve their cardiac function over the same period. Measurements were taken when rats were not being paced, indicating that the pacing may have a lasting effect through remodelling the ventricular myocardium. The data suggested that the improvements were due to increased ejection fraction in RSA-paced rats, as LVEF increased by 11 ± 6% in the RSA paced group compared to a decrease of 9 ± 7% in the monotonic group. This was despite RSA pacing being effected for less than 50% of the intended time (3-4 hours per day), due to natural HR increasing above the pacing rate when rats were active.

Ceryx conducted a follow-up study in an ovine heart failure model in which sheep were paced for 4 weeks (Shanks et al. 2022). CO was recorded continuously using a flow probe on the ascending aorta. In the RSA-paced animals, 24hr average CO increased by 1.4 ± 0.5 (SEM) L/min compared to

baseline, whereas in monotonic or unpaced sheep there was no improvement. In these sheep, with a baseline CO of around 7-8 L/min (unpublished data), this is around 18%-20% improvement. RSA pacing also significantly increased SV, LVEF, and fractal shortening. Changes in CO occurred 2-3 days after commencement of pacing and peaked after around 4-6 days, whereas LVEF appeared to continue to increase over the 4 week period. The increase in CO was maintained throughout the four-week pacing period, and persisted for 2-3 days after pacing was ended, reducing to pre-pacing levels over a week. The lag between pacing and effect suggests that the change is not due to mechanical haemodynamic changes. The work additionally demonstrated that the improvement in CO was associated with re-emergence and alignment of key structures and proteins within myocytes involved in excitation contraction coupling. Brain natriuretic peptide (BNP) also reduced in the RSA paced animals.

In the sheep, RSA pacing occurred for around 42% of the time (i.e. approximately 10 hours per day), mostly overnight. RSA was not maintained during periods of fast breathing due to stress caused by laboratory staff being in the sheep area, or during thermoregulation (panting), swallowing, chewing, and drinking.

In addition to the improvement in cardiac pumping efficiency, the sheep also demonstrated a reduction in the number of apnoeic episodes. Episodes of 3-6 seconds of apnoea were reduced by nearly 50% in RSA-paced animals in the 4th week.

The finding from two different heart failure animal models that RSA pacing was associated with an approximately 20% improvement in cardiac function, and also that it reduced apnoeic episodes, is highly clinically relevant. Standard cardiac pacemakers cause the heart to beat at a monotonic rate. Although some can increase or decrease the rate according to physiological demand, this does not include mimicking the natural breath-by-breath variations of HRV. The animal studies demonstrated the physiological feasibility of achieving this with artificial pacemakers, and also reported significant improvements in haemodynamic parameters.

3.3 Pacing post-CABG

Cardiac pacing is a normal part of post-CABG care. In the immediate post-surgical period following CABG, patients may be paced for the treatment of conduction abnormalities, tachycardia, bradycardia, and low cardiac output (Østergaard et al. 2006; Reade 2007a,b; Manuel 2022). Cote et al. (2020) reported 11.7% of 6,783 patients required pacing on admission to ICU following CABG, with lower LVEF as a risk factor for needing pacing. Kiely et al. (2020) reported that 25% of CABG patients required pacing, most for less than 12 hours. Where required, pacing durations are typically up to 4-5 days (Reade 2007a; Kiely et al. 2020), but may be carried out for periods of up to 10 days or more (Naito et al. 2005; Aser et al. 2014; Lazarescu et al. 2014; Kiely et al. 2020; Manuel 2022), especially when patients require implantation of permanent pacemakers.

Biatrial pacing at high pulse rates (up to 100 pulses/min) has been shown to reduce the incidence of AF post-CABG, although the effect of right atrial pacing may be less clear (section 4.4.2).

Several studies have also examined the effect of different pacing modalities on cardiac performance post surgery. Østergaard et al. (2006) reported an increase in mean CO of around 0.7 L/min following the initiation of clinically-required atrial pacing in 16 patients following CABG. Other authors have investigated the immediate or short-term effects of ventricular, biatrial, biventricular,

and biatrial-biventricular modes (Naito et al. 2005; Healy et al. 2008; Pichlmaier et al. 2008; Russell et al. 2012). From these studies, pacing generally increases CO by around 0.5-1.2 L/min (with the exception of VVI mode; Russell et al. 2012). Such pacing seems to have rather short-term haemodynamic benefits, as both Russell and Pichlmaier studies showed an increase in CO at 6hrs after surgery and initiation of pacing, which generally returned close to starting values at 18 hrs. In contrast, the animal studies demonstrated that RSA pacing produces a gradual improvement in CO of around 20-23% over several days.

3.4 Potential benefits of the intervention

Based on our previous modelling and animal studies, we propose that the reintroduction of RSA-like variation in heart rate could benefit patients with HFrEF following CABG. RSA appears to reduce the work required by the heart, and reinstating it in animal models of HFrEF improved LVEF and CO, in addition to beneficial remodelling of the myocardium. In this Clinical Investigation, increases in CO in participants could be up to 20% within a week of initiating RSA pacing. This is similar to increases found from other pacing modalities, but is more likely to be maintained. It is also greater than effect sizes from medication and CRT devices in chronic HF populations (Section 1.2). This magnitude of increase in CO is clinically meaningful and could lead to reduced morbidity, faster recovery, increased capacity for activity, and reduced mortality in this patient group. RSA-like pacing may also produce a reduction in hypopnea-apnoeic episodes (which are detrimental in the short and long term), in the incidence of arrhythmias in the post-surgical period, and/or a reduced risk of LCOS.

3.5 Potential risks of the Clinical Investigation

3.5.1 Pacing and pacing leads

There are no additional risks to participants in this Clinical Investigation regarding the CABG surgery or implanting of pacemaker leads. Post-CABG patients who have a clinical need for pacing (for arrhythmias) require right ventricular pacing, whereas participants in this study will be paced at the right atrium (atrial pacing). However, placement of both atrial and ventricular leads is relatively common in clinical practice (Section 1.4). Pacing will be at a rate higher than the patient's intrinsic resting HR (overdrive pacing) to ensure that the pacing impulse captures the myocardial depolarisation and that HR is driven by the pacemaker for the majority of the time. Clinical experience shows that cardiac surgery patients can have surprisingly high heart rates during the day, often into the 140's bpm. However, we have limited the maximum instantaneous pacing rate to around 126 bpm. We expect this will still capture the depolarisation for a large proportion of the pacing time in most participants, when they are asleep or otherwise resting.

In normal clinical practice, pacing is not used prophylactically post-CABG, so participants in this Clinical Investigation would not normally be paced without clinical need. However, epicardial (temporary) pacing for up to a week (or longer) is not unusual in clinical practice.

There are small, but finite risks associated with the use and removal of epicardial pacing leads. Lazarescu et al. (2014) reported painful stimulation in 7.2% of 236 patients, bleeding on removal in 0.8%, and non-removal in 2-3%. Mishra et al. (2010) quote an overall rate for major complications of 0.04%. The only difference in lead use between standard care and this Clinical Investigation is the longer duration of placement. Typically, in patients who do not require pacing for clinical reasons,

the leads are removed around 4 days post-surgery. We consider the main risk from extended periods of temporary pacing is the potential for increased complications from the epicardial leads.

- Kiely et al. (2020) reported no complications of lead use or removal in 164 patients, of whom 44 (27%) had leads in place for longer than 6 days (86% ventricular, 5% atrial, 9% both).
- Carroll et al. (1998) reported no bleeding following removal in 145 patients with ventricular leads that had been in place for 3-17 days. Temporary arrhythmias were common during removal – 66% had one or more premature ventricular contractions (PVC) and 7% had non-sustained ventricular tachycardia (VT). Heart failure was a risk factor for PVCs, but duration of lead placement was not significantly associated with arrythmias.
- Mullin et al. (2009) reported no difference in reported sensations on removal of leads in 144 patients (both atrial and ventricular leads) for leads in place for 2-5 days compared to 6-16 days.
- Lazarescu et al. (2014) reported that 3% of atrial and 2% of ventricular leads could not be removed in 236 patients (60% of whom had both atrial and ventricular leads). In the discussion, the authors comment that "impossible removal concerned wires removed late (mean of 10 ± 6th postoperative day)". However, this data is not reported in the results and it is not reported whether the retained atrial and ventricular leads tended to occur together.

The results from Lazarescu et al. (2014) appear to be inconsistent with the other studies. This may be due to differences in lead type, placement, attachment, or removal methods. Taken together, this evidence indicates that there may be a small increase in risk of epicardial lead complications by extending the attachment beyond 4 days. As in standard of care (SOC), study participants will have their pacing leads removed by nurses or physicians at the direction of cardiothoracic surgeons, and will remain under observation for several hours afterwards to allow for the detection of any complications. Leads that cannot be removed by 'gentle traction' are cut and allowed to retract into the body (Reade 2007a).

3.5.2 Elimination of intrinsic RSA in comparator group

Patients with HFrEF are likely to have little or no intrinsic level of RSA (Section 1.2). Additionally, CABG is known to have a temporary detrimental effect on levels of HRV, with recovery to pre-surgery values within 6 months (Lakusic et al. 2015). However, there is the possibility that some participants may have a physiologically significant level of intrinsic RSA present. Such patients who are randomised to the comparator group would have any remaining natural variation temporarily removed by the monotonic pacing. However, temporary pacing is used routinely in this patient group to treat or prevent arrhythmias and several studies have included monotonic atrial pacing in post-CABG patients without reporting any detrimental effects (section 3.3). Therefore we conclude that temporary use of monotonic pacing in the comparator group will not pose any additional risk to participants.

3.5.3 RSA-like pacing

The risks of RSA-like modulation of pacing versus monotonic atrial pacing are not known. Clinical contributors to this CIP theorised that the only potential negative effect of RSA pacing (with respect to standard atrial pacing) may be an increased risk of arrhythmias. O'Callaghan et al. (2020) and Shanks et al. (2022) did not report any detrimental effects on the animals that might have been due to this form of pacing, including arrhythmias. In contrast, there is the suggestion that RSA may have

a protective effect against arrhythmias, similar to other forms of pacing. Therefore, safety will be assessed primarily by the number, duration, and type of arrhythmias experienced by participants during and after RSA-like pacing. However, arrhythmias are a relatively common sequelae of cardiac surgery and therefore a comparator group with monotonic atrial pacing is needed in order to assess the level of arrhythmias that occur in the absence of RSA modulation of pacing.

There is also the possibility of errors in the design or provision of the RSA temporal relationship, i.e. an inconsistent phase-relationship that does not always increase HR with inspiration and decrease it with expiration. Shanks et al. (2022) tested sinusoidal variations in heart rate at respiratory rates, but with a reversed temporal relationship to breathing. They found this produced substantial reductions in CO and increases in BP. In this Clinical Investigation, this would only be possible as a result of a significant malfunction of the devices. Additionally, the pacemakers have defined ranges of allowed pacing intervals and will not pace the heart outside of these limits. Mis-timing of the pacing is therefore extremely unlikely. Additionally, patients will have bedside monitors with visual displays of vital parameters and it should be possible to visually check that HR is increasing during inspiration.

As SOC, patients are closely monitored in intensive care units (ICU) and cardiac wards, and these Clinical Investigation participants will have additional monitoring and assessment to ensure that any negative effects are detected as soon as possible. In addition, interim analyses of safety outcomes will be conducted after 10 and 20 participants have been paced.

3.5.4 Nasal prongs

Participants in both groups will wear nasal prongs looped over the ears for the duration of pacing to detect the respiratory signals. Patients do not normally wear these unless they require supplemental oxygen. These are routinely worn without harm, and patients with chronic respiratory conditions may require them permanently. Oxygen can be supplied via the nasal tubing if required, without detriment to the pressure signal.

We do not think the risk of harm from the oxygen tubing or nasal cannula (prongs) is significant in this study population. In a survey in a US hospital, Duerst et al (2022) identified 4 pressure injuries from polyvinyl nasal cannulae over 2979 patient days; collected over 2 months and across 75 critical and Covid care beds. The injuries occurred after 9, 10, 10, and 22 days of wear. Of these, 3 were stage 1 injury, and 1 was stage 3; 3/4 were on the ear, with the other on the cheek. The incidence was reduced to 0 over the following 2 month period by using a softer material cannula and improving staff education. However, Björklund and Ekström (2022) found only skin irritation or chafing in 151 Swedish patients using long term oxygen therapy at home (19% incidence, median 2.2 years duration). This suggests that any risk of harm is generally low and highly unlikely to occur before around 9 days of use. Few participants in our study are likely to still be in hospital after 9 days. To mitigate the remaining risk, in addition to normal nursing care, we will conduct daily checks of equipment fit and condition, skin condition, and patient comfort around the face and ears. Patients will be provided with padding and/or skin protection dressings if required.

3.5.5 Clinical investigation assessments

Much of the data recorded for the Clinical Investigation will be taken from SOC tests and investigations. Participants will have some additional study assessments, but these are mostly within

the normal types of assessments for such patients. These include blood tests, echocardiograms, and blood pressure. SV and CO will be assessed non-invasively using an external ultrasound probe positioned at the suprasternal notch (Uscom). Intrinsic RSA will be measured using recordings of heart rate at rest. Exercise recovery will be assessed using a static handgrip test at baseline and post-surgery on Pacing Day 4 (PD4), Lead Removal (LR), and 7 days post-pacing (PP). Patients awaiting CABG surgery routinely have treadmill exercise tests, and the static handgrip exercise is considered to be no more demanding than this.

3.5.6 Covid risks

Risks of surgery are greatly increased in patients who contract Covid in the perioperative period (Sanders et al. 2021). Infection control procedures for managing Covid risks may include regular testing and isolating patients prior to and following surgery. The intention is to maintain such patients in a 'green' (uninfected) clinical environment. Study procedures will be conducted in accordance with local Covid precautions in place at each site at the time of conduct. This study does not involve additional Covid infection risk to the participants. Participants who contract Covid following consent will be withdrawn from the study.

3.6 Risk-benefit of the Clinical Investigation design

3.6.1 Population and setting

The feasibility of reinstating RSA using pacemakers has been shown in animal models, as has the potential timescale and magnitude of benefit. One intended indication for the technology is for long-term treatment using permanently implanted pacemakers. However, implanting novel pacemakers in patients who would not normally have them, in order to investigate safety and potential benefit, is a relatively high-risk research intervention, especially for a comparator group who may gain no benefit. This current Clinical Investigation design is a lower risk intervention in patients who will all have temporary pacing available for other indications, plus a high level of clinical monitoring. Recovery from cardiac surgery is an intended indication and setting for this RSA technology. Patients with HFrEF are at the highest risk of poor outcomes (including LCOS) and therefore may have the most to gain from the potential benefits of RSA pacing.

3.6.2 Comparative design

It would be possible to assess feasibility and performance of the prototype Cysoni-XT in humans in a non-comparative, case series design. However, this would not provide sufficient information to assess safety of the *RSA modulation* of atrial pacing, which is the novel component of the treatment. There is a relatively high likelihood of arrhythmias, and patients with HFrEF recovering from major heart surgery have a complex and evolving physiological condition. Therefore in a single arm study it would be difficult to determine whether any negative outcomes were attributable to the novel RSA modulation, rather than (say) the surgery, patient characteristics, other interventions, or the use of atrial pacing. Atrial pacing itself may affect both arrhythmias and cardiac function (section 3.3). Therefore, in order to make an effective assessment of the safety of RSA pacing technology we need to determine whether there is any *increase* in the level of arrhythmias compared to a group where the only difference is the RSA modulation. The same argument applies for potential benefit – it is the RSA *modulation* of atrial pacing that is novel, and so any effects due to atrial pacing alone should be measured and compared.

The use of historical controls as an alternative comparator is unlikely to provide reliable comparative arrhythmia data, as the recording of episodes is unlikely to be as detailed or granular as in this study. Additionally there is unlikely to be any routine collection of CO values, and where this is available it may not be comparable due to the use of different measurement methods.

Although participants would not normally be paced without clinical need, atrial pacing is a common intervention in these and other patient groups, and takes place with little by way of negative consequences. Participants in the comparator arm may also benefit from reduced risk of arrhythmias and increases in CO, and are not likely to be at increased risk of negative outcomes due to participating in this Clinical Investigation.

3.7 Summary

In summary, this Clinical Investigation design is justified by the following factors:

- RSA-like pacing attempts to restore a temporal relationship that occurs naturally in healthy states.
- The RSA modulation produces small changes in the timing of pulses from the external pacemaker that are within the normal physiological range.
- Adjusting pacing rates is common. Patients with implanted or temporary pacemakers often have adjustments made to their pacing rates.
- No additional procedures beyond SOC are required to implement the intervention or comparator treatments. All patients will already have external pacemaker leads following CABG surgery.
- External pacing is a common and low risk intervention during recovery from CABG.
- External pacing for several days following cardiac surgery is sometimes used in clinical practice and research. Any potential risks of extended lead placement are small and uncertain.
- Standard modes of pacing have reported short-lived benefits on CO in post-CABG patients.
- Most study assessments are either SOC or are minimally-intrusive (e.g. Uscom VTI).
- Post-CABG patients have a high and continuous level of monitoring as SOC. Participants will have increased levels of cardiac surveillance.
- No negative effects of RSA-like pacing were reported in prior animal studies.
- Overdrive pacing at rates up to 100 bpm have been used in previous studies in similar patients.
- Patients recovering from open heart revascularisation procedures are complex and physiologically dynamic. Arrhythmias and haemodynamic changes are relatively common and atrial pacing *per se* may also affect these outcomes. Therefore, only a comparative design using standard atrial pacing as a comparator can fully inform a safety analysis of the novel RSA modulation of atrial pacing.

It is the assessment of the trial management group (TMG) that the potential benefits of the study outweigh the potential risks, and that this trial is categorised as Type B, ‘Somewhat higher than the risk of standard medical care’.

4 Clinical Investigation design

4.1 General

This is a first-in-human (FIH) Clinical Investigation of a modification of an existing medical technology. It will be a comparative, multicentre, open-label randomised controlled trial (RCT) design. RSA-like modulated atrial pacing will be compared against monotonic atrial pacing in patients with HFrEF who have had CABG surgery.

4.2 Trial setting

This is a multicentre study. Three sites are expected, and additional sites may be added if needed to achieve enrolment targets. Sites must be secondary or tertiary care, experienced in CABG surgery, with appropriate critical care facilities and sufficient suitable patient populations.

4.3 Objectives and hypotheses

The purpose of this Clinical Investigation is to explore the risk/benefit profile of the use of RSA-like pacing in patients with HFrEF following CABG. Based on the prior animal models we hypothesise being able to produce RSA-like variation in HR with no increase in risk over several days of pacing, which may lead to temporary improvements in cardiac function.

Primary objective: To assess the performance of the Cysoni-XT in delivering RSA-like pacing, and to assess its safety compared to standard atrial pacing, in patients with HFrEF following CABG.

Primary hypothesis: The Cysoni-XT can deliver RSA-like pacing in patients with HFrEF following CABG, with no observed increase in the incidence of safety events.

Observations:

- compare the effect of RSA-like pacing versus monotonic pacing on cardiac function over several days following CABG (CO is used for sample size calculation);
- determine the time course of any changes in cardiac function over several days of RSA-like pacing, and whether any improvement is maintained after 7 subsequent days of no pacing;
- compare the effect of RSA-like pacing versus monotonic pacing on response to, and recovery from, exercise (static handgrip);
- compare the effect of RSA-like pacing versus monotonic pacing on renal and cardiac biomarkers;
- explore whether there is a dose-response relationship (or minimum threshold) between proportion of time/duration of RSA-like pacing and any improvement in cardiac function;
- compare the effect of RSA-like pacing versus monotonic pacing on episodes of hypopnea-apnoea in humans;
- compare the effect of RSA-like pacing versus monotonic pacing on post-surgical recovery;
- characterise intrinsic RSA levels in CABG patients with HFrEF.

4.4 Endpoints

Study visits and data collection points are summarised in the Schedule of Events in Appendix 1. The co-primary endpoint for this Clinical Investigation includes performance and safety of the investigational technology.

4.4.1 Co-primary endpoint – performance

Any clinical effect of reinstating RSA in this patient group is dependent on the ability of the Cysoni-XT under investigation to deliver sufficient, appropriately-timed cardiac pacing signals. As the effects in humans is unknown, 'sufficient' here means that enough heartbeats have been paced in an RSA-like manner to achieve similar effects to those seen in the animal models (O'Callaghan et al. 2020; Shanks et al. 2022). No thresholds for clinical effect were determined in these experiments, however RSA pacing was achieved in rats for an average of 3-4 hours per day and in sheep for 10 hours per day (approximately 42% of the available time). Pacing was not achieved when heart rates exceeded the pacing rate due to the animals being active or stressed, or during measurements.

RSA-modulated pacing impulses can only be delivered when a respiratory signal is detected and is of sufficient quality. When this signal deteriorates or is absent (e.g. if the nasal canula is removed), or exceeds normal physiological ranges (6-35 breaths/minute), the Cysoni-XT defaults to monotonic AAI pacing at the median rate. Also there are several reasons why RSA-timed pulses may not be delivered to the heart. For example, if the impulse timing would place it in the electrophysiological refractory period (which would be prevented by the pacemaker). Accounting for this, the performance measure looks at the respiratory cycles in which RSA-modulated pacing impulses are applied to the heart, as a proportion of the total number of valid respiratory cycles. (Where 'valid' refers to recorded cycles of suitable quality.)

$$RSA\ performance\ measure = \frac{Time\ when\ RSA\ impulses\ are\ applied\ to\ the\ heart}{Time\ of\ valid\ respiratory\ cycles}$$

We will measure this endpoint (the proportion) for each participant in the intervention group individually and calculate the average proportion over the group (using the mean or median depending on distribution). Based on the sheep study (Shanks et al. 2022) we hope to achieve RSA-like pacing for a group average proportion of 40% using this performance measure. If any device malfunctions and does not function as expected during normal conditions of use, this will be excluded from this performance measure.

Table 1: Primary outcome measure - performance

Co-primary Outcome	Measure	Endpoint	Timepoint	Method
Performance	Proportion of pacing duration (with valid respiratory signals) for which RSA-timed impulses are delivered to the heart (intervention group only)	Individual proportions averaged across the intervention group	Pacing duration	Ceryx RSA module recording

4.4.2 Co-primary endpoint – safety (AF)

The potential risks from RSA-like pacing are theoretical, as no negative effects were reported from the chronic animal studies. The risks are primarily thought to be new onset arrhythmias, and the possibility of mismatching the timing of the heart rate variation, leading to a decline in cardiac function (Section 3.5.3). Assuming that RSA-like variation in HR is achieved in the participants in the intervention group, it is probably not possible to identify whether any subsequent arrhythmias are specifically related to the *RSA modulation* of pacing, or to other factors. However, if the participants are well-balanced in the two arms, then rates of arrhythmias *unrelated* to RSA should be similar.

Therefore, any significant increase in the intervention group may be an indicator of negative effects of the artificial restoration of RSA.

Arrhythmia types are defined in Appendix 2. Patients will have continuous Lead II monitoring during pacing, plus additional ECGs recorded during the Lead Removal and Post-Pacing assessments, and they may be provided with Holter-type ECG monitoring for use at home between Lead Removal and Post Pacing visits. Any episode of arrhythmia, captured on an ECG between the initiation of pacing (Pacing Day 1, PD1) and the post-pacing visit (PP), and lasting 30 seconds or longer, will be recorded. These ECG extracts will be reviewed by cardiologists or cardiac physiologists to identify the type of arrhythmia. The type of arrhythmia, time point, and duration of each episode will be recorded for each participant.

AF is the most common new-onset post-surgery arrhythmia and incidence proportion is the most commonly reported measure of new-onset AF (proportion of patients with any episode of AF is a binary measure; Section 1.4). Therefore, we will use the incidence proportion of new-onset AF recorded following the initiation of pacing as the primary safety measure. A review of the literature from the last 20 years shows high variability of AF incidence proportion in patients with atrial pacing (Table 2). AF episode duration is not always defined in the literature, but varies from 10 sec to 10 mins. Although rates here appear to be consistently lower with atrial pacing than without, other authors have found atrial pacing to be less effective than other modes (Archbold & Schilling 2004; Singhal and Kejriwal 2010; Ruan et al 2021). This variation may be due to differences in lead placement, patient populations, follow-up duration, and other practices. The most similar population for our study is Eberhardt et al. (2009), in patients with low LVEF.

Table 2: Incidence proportion of post-CABG new-onset AF, with and without atrial pacing

Reference	**Year**	**AF incidence (RA pacing)**	**AF incidence (no pacing)**	**N**	**AF definition**	Notes	**Follow-up/pacing duration (hrs)**
Singhal & Kejriwal	2010	5.2%	31%	19			
Eberhardt	2009	~30%±10%	-	30	10s	LVEF <40%	4
Neto	2007	1.25%	25%	80			3
Ozin	2005	11.4%	45.7%	35	30s		4
Ozin	2005	11.6%	37.1%	35	≥10mins	'Sustained AF'	
Naito	2005	59.1%	-	22			8.8 ± 2.4
Hakala	2005	27%	29%	41,24	≥5mins		2
Fan	2003	34%	42%	36,31	≥10mins	'Sustained AF'	5

This variability supports the comparative design of this Clinical Investigation, showing that arrhythmia rates in the absence of RSA *modulation* of pacing cannot be assumed, but must be measured in a similar patient group. The success criteria for this endpoint will be no statistically significant increase in this incidence proportion for RSA-like pacing compared to monotonic atrial pacing.

Table 3: Primary outcome measure - safety

Co-primary Outcome	Measure	Endpoint	Timepoints	Method
Safety	Incidence of new-onset AF (binary)	Incidence proportions in each group	PD1 to Post-pacing (PP) visit	Any ECG recording

This binary outcome does not account for large variations in pacing duration, size of groups, number of AF episodes per participant, or duration of arrhythmia. Therefore, multiple additional analyses will be conducted to explore any differences in arrhythmias between the groups (Section 4.4.5).

4.4.3 Secondary endpoint – safety (SADEs)

As this is a FIH study using a prototype investigational device, we will also include the incidence of Serious Adverse Device-related Events (SADEs, section 5.1) as a secondary safety endpoint. Again this endpoint is concerned only with differences between the RSA-modulation of atrial pacing and atrial pacing *per se*. (All other procedures should be identical between the study groups.) This will include all events that occur from the initiation of pacing until the end of the participants' involvement in the trial. The success criteria will be no statistically significantly increase in SADEs (including USADEs) in the intervention arm over the comparator arm.

Table 4: Secondary outcome measure - safety

Secondary Outcome	Measure	Endpoint	Timepoint	Method
Safety	Incidence of SADEs	Incidence proportion in each group	PD1 to D30	Safety event reporting procedure

4.4.4 Measured observations

To examine the clinical effect of RSA-like pacing on patients with HFrEF we will measure several cardiovascular variables. LVEF, SV and CO are basic measures of cardiac function. In heart failure, CO (systemic blood flow) is the primary determinant of a patient's physical capacity.

CO can be measured using transthoracic or transoesophageal (TOE) Doppler echocardiography, dilution methods (dye or thermodilution), or pulse contour analysis. Although TOE Doppler and thermodilution methods are used for clinical care in intensive care settings, they are too invasive or disruptive, and are not suitable for comparison with pre-surgery baseline and post-pacing (PP) measurements. Imaging echocardiography/Doppler requires a trained operator and a darkened room, which may not be appropriate for multiple measurements during the pacing period. Patients with a fresh surgical sternal wound may also not be able to tolerate repeated echocardiograms during the first few post-surgical days. This study will use the Uscom 1A device (Uscom, Australia) which uses Doppler ultrasound measurement of flow velocity across the aortic valve, from a probe at the suprasternal notch[1]. This is a non-invasive, quick, and portable device that measures blood velocity and integrates it over a cardiac cycle (velocity time integral, VTI). This is converted to SV by

[1] https://www.uscom.com.au/

multiplying by the cross sectional area (CSA) of the valve. CSA will be determined from the baseline echocardiogram (or using built-in estimates related to patient height). Measurements from the pulmonary artery can be substituted if necessary. (See Section 4.7.5 for a review of the validity of the Uscom measurement method.)

A 10% change in CO would be considered clinically significant, although not necessarily sufficient to improve patient function. In the animal models, CO was increased by around 20%-23%. Main analyses of these clinical observations will be based on values at baseline (before surgery), before initiating pacing (PD1), after 6 days of pacing (PD6), and 7 days following the cessation of pacing (post pacing, PP). Additional values will be taken at other timepoints during the pacing period; for safety, and to determine the time course of changes.

The main between-group comparison will use the cardiac parameters collected on Pacing Day 6, as the increase in CO in sheep had effectively stabilised by this time (Shanks et al. 2022). Median post-operative length of stay (LOS) was 7 days in Wales in 2019-20 (mean 9.2 days; NACSA 2021a). Recent local Health Board data indicates that patients with lower LVEF (≤40%) tend to have longer stays – median of 7 days versus 6 days (unpublished data). Therefore, 6 days of pacing is likely to be achievable for most of the participants in this study without extending their hospital stay. Basic haemodynamic variables will be measured every other day during pacing, with several additional assessments at the end of pacing (Lead Removal, LR; which will have a variable duration). Cardiac function may continue to improve beyond 6 days and therefore we will continue to pace and measure outcomes until the patient is ready for discharge, or until there is a clinical decision to stop pacing and remove the leads (whichever is sooner).

Episodes of apnoea (absence of breath for 10s or more) and hypopnea (reduction in breathing for 10s or more) will be detected by the RSA module. Apnoea-hypopnea index (AHI) is the number of apnoea or hypopnea episodes, divided by the duration of recording. AHI is usually determined during sleep as this is when such episodes occur. However, we expect post-CABG patients to have frequent and unstructured periods of sleeping and waking, and recording of sleep periods would be problematic in these circumstances. Therefore, we will include any episodes of apnoea and hypopnoea over the duration of the recording.

Table 5: Secondary outcome measures
(CSA = cross sectional area, PD = Pacing Day, LR = Lead Removal, PP = post pacing, VTI = velocity time integral)

Outcome	Measure	Timepoint	Method
Cardiac function – CO/CI	Change from PD1. Recorded with & without pacing	PD6, LR, PP	Uscom VTI, CSA (echocardiography) CO = VTI x CSA x HR Average of 3 recordings, at rest
Cardiac function – SV/SI	Change from PD1. With & without pacing	PD6, LR, PP	Uscom VTI, CSA SV = VTI x CSA Average of 3 recordings, at rest
Cardiac function – LVEF	Change from baseline. With & without pacing	LR, PP	Echocardiography
Cardiac function – CO/CI	Time course of change from PD1	PD2, PD4, PD6, PD8, (etc), LR, PP	Uscom – as above

Outcome	Measure	Timepoint	Method
Cardiac function – SV/SI	Time course of change from PD1	PD2, PD4, PD6, PD8, (etc), LR, PP	Uscom – as above
Cardiac function – intrinsic HR	Daily, without pacing	Baseline, daily (PD1 to LR), PP	ECG
Blood pressure (BP)	Mean, systolic, and diastolic arterial pressures (MAP, SAP, DAP) With & without pacing	Baseline PD1, PD2, PD4, PD6, PD8, (etc), LR, PP	Standard non-invasive BP (NIBP) device Averaged over 3 measurements, during rest
Systemic vascular resistance (SVR)	Calculated from BP and CO	Baseline, PD1, PD2, PD4, PD6, PD8, (etc), LR, PP	SVR = MAP / CO
Feasibility/dose – RSA pacing duration	Duration of RSA beats paced as intended	PD1-LR	RSA module Total duration when heart beats are captured with RSA pacing
Exercise capacity – heart rate recovery	HR recovery from end of static handgrip	Baseline, PD4, LR, PP	Isometric contraction, 2 mins at 30% of maximum. Record HR for up to 5 mins following release.
Exercise capacity – BP change	BP recovery from end of static handgrip	Baseline, PD4, LR, PP	Isometric contraction, 2 mins at 30% of maximum. Record BP for up to 5 mins following release.
Apnoea and hypopnea	Periods of apnoea and hypopnea (min 10s duration)	PD1-LR	RSA module Apnoea-hypopnea index (AHI)
Post-surgical recovery	Length of stay (LOS) LOS at different care levels	LR, D30	Daily CRF recording & medical record review
RSA levels	Intrinsic RSA level	Baseline, PD6, LR, PP	3 min ECG recording at rest
Biomarkers	Cardiac, renal, cardiovascular	Baseline, PD1, LR, PP	Standard blood tests

Standard outcome measures for clinical studies are collated by the Core Outcome Measures in Effectiveness Trials (COMET[2]) initiative and the International Consortium for Health Outcomes Measurement (ICHOM[3]). Standard reporting outcomes have been defined for heart failure (Burns et al. 2020) and cardiac surgery (Myles et al, 2014; Benstoem et al. 2017), but these are not appropriate for this short-term study in the immediate post-surgical period and are not included.

[2] https://www.comet-initiative.org/

[3] https://www.ichom.org/

4.4.5 Additional safety outcomes

Atrial pacing has been shown to reduce the incidence of AF post-CABG (section 4.4.2). However, it is unknown whether RSA modulation of pacing would affect the generation of arrhythmias, or what type of arrythmia is most likely to be affected. The co-primary safety endpoint has been chosen as the most likely and most reported measure of post-CABG arrhythmias, however incidence proportion does not account for large variations in pacing duration, size of groups, number of arrhythmia episodes per participant, or duration of arrhythmias. Additionally, the study may show that AF is not the most relevant arrhythmia to assess for the safety of this intervention. To account for this, additional analyses of the arrhythmia data will be conducted. Any episode of arrhythmia (see Appendix 2 for definitions), captured on an ECG and lasting 30 seconds or longer, will be recorded, along with the type and duration.

At each timepoint (up to PP), the number and proportion of patients with any episodes of arrhythmias (incidence proportion), as well as the total number of episodes per patient, will be determined to account for different treatment group sizes. Between group comparisons will be conducted at a fixed timepoint at which most participants have data (e.g. PD6), and at Lead Removal (variable timepoint). Estimates of the absolute and relative risk reduction will be calculated for the comparison of the incidence proportions, and incidence rate ratios and their absolute differences will be estimated for the comparison of episode counts per patient. Analysis of the Lead Removal data will need to be adjusted for the total duration of recording and will include analysis of incidence densities (i.e. person-time rates), and the time to the first arrhythmia. Consideration will also be given to the potential for competing events (such as mortality) and the need to account for these in the analysis of the primary outcome.

The above analyses may be explored separately by type of arrhythmia, where sufficient occurrences are observed for a given type.

In addition to new-onset arrhythmias, safety outcomes of a novel pacing device could include mortality, device-related adverse events, or morbidity. Any potential negative effect of the RSA modulated pacing will be recorded and reviewed. As they are expected to be rare, any occurrences of cardiac-related incidents and mortality up to D30 will be summarised descriptively.

Patients will be contacted by telephone at or just after 30 days following surgery (D30) to record patient-reported episodes of cardiac-related problems, healthcare consultations (particularly unscheduled care), and cardiac symptoms. This will be checked against medical records. Thirty day mortality will also be recorded.

Table 6: Additional safety outcome measures

Outcome	Measure	Timepoint	Method
Safety - arrhythmias	Multiple measures of all arrhythmias including incidence proportions, person-time rates, and time-to-event	PD1 to Post-pacing (PP) visit	Any ECG recording
Safety - arrhythmias	Withdrawal rate due to unexpected and potentially dangerous arrhythmias	Daily (during pacing)	Clinical decision
Safety - morbidity	Withdrawal of pacing due to declining condition	Daily (during pacing)	Clinical decision

Safety - mortality	Mortality	D30	Medical record review.
Adverse events (AEs)	Device-related AEs. Effects of prolonged duration of pacing wires: haemopericardium, wire migration/retention, infection.	Over 30 days	Monitoring/ assessment visits Medical record review. Phone call.
Cardiac-related incidents	Patient reported symptoms. Unscheduled healthcare consultations. Hospital attendance/ admissions.	D30	Phone call. Medical record review.

4.5 Intervention and comparator

The intervention is atrial pacing with additional RSA-like modulation. Pacing impulses will be grouped together during inspiration, such that HR will increase typically by around 6 bpm above median during inspiration, and decrease by around 6 bpm below median during expiration. The exact level of variation will depend on the rate and depth of breathing. Six pacing rates will be used to accommodate the range of patients' intrinsic HR. The typical minimum pacing rate in each band (median minus 6 bpm) must be high enough above the intrinsic heart rate to ensure capture of the myocardial depolarisation (overdrive pacing). As patient condition will change over the post-surgical period, the participant's intrinsic HR will be measured (without pacing) each morning and evening and the median pacing rate will be set at least 10 bpm higher than this. The values used in Table 7 shows what median rate will be set dependent on the participant's intrinsic HR. Note that the typical maximum and minimum HR in these ranges are instantaneous values, that exist for 1 or 2 beats at a time. If the respiration signal is missing (e.g. during apnoea or if the nasal canula is removed) the intervention pacemakers will pace monotonically at the median value.

The comparator is monotonic right atrial overdrive (AAI mode) pacing at the relevant median rate. This is different to SOC as patients do not usually have pacing without a clinical indication.

Table 7: Pacing rates set according to patient's intrinsic daily HR

Intrinsic HR (bpm)	RSA median (approximate range) pacing rate	Comparator pacing rate
≤ 60	70 (64-76)	70
61-70	80 (74-86)	80
71-80	90 (84-96)	90
81-90	100 (94-106)	100
91-100	110 (104-116)	110
101-110	120 (114-126)	120

Pacing will be initiated after randomisation, after the patient is removed from ventilator support (Pacing Day 1, PD1). This is usually the day after surgery. Pacing will continue until the patient is ready for discharge or there is a clinical decision to stop pacing and remove the leads (whichever is soonest). Data from the lead site indicates that post-surgery LOS is generally between 5-14 days. Participants will not have their hospital stays extended for study purposes.

Pacing is delivered by a pacemaker (Osypka AG), either modulated to respiratory phase by a Ceryx RSA module (intervention, PACE204) or delivering standard monotonic right atrial pacing (comparator, PACE101 or local equivalent). Participants may be temporarily disconnected from the pacemaker and monitoring devices during any visits to the toilet, washing, and physiotherapist-mediated mobilisations, as required and as per usual care. Artefacts on the ECG recording will indicate when the patient is being paced.

Respiration will be measured using air pressure at the nose via nasal prongs and standard oxygen tubing. In the intervention group ECG and respiration will be continuously monitored and recorded by the Ceryx RSA module during pacing. In the control group the RSA module will record the respiration and pacing will be extracted from the ECG monitoring record.

If the study pacing is interrupted for clinical reasons, such as episodes of arrhythmia or infection, it will be reinstated at the earliest opportunity, unless the criteria for withdrawal are met (see section 4.7.6.1).

Participants will receive medical care as considered appropriate by their clinical care team. However, in this study there is a preference for the use of beta-blockers to treat arrhythmias rather than amiodarone, which has significant side effects.

4.6 Subjects

4.6.1 Inclusion and exclusion criteria

Should restoration of RSA prove feasible and potentially beneficial, the patients in this Clinical Investigation would be an intended population for future implementation of RSA pacing. These patients have coronary artery disease (CAD) which limits the blood supply to the heart, and require revascularisation (CABG) surgery. In this Clinical Investigation, we have restricted this population to patients having isolated CABG, i.e. without additional valve surgery. CABG patients with HFrEF are at increased risk of poor outcomes and therefore may be more likely to benefit from this intervention.

Another intended use is in permanently implanted pacemakers in the general HFrEF population. Post-CABG patients will be in a poorer clinical condition, with potentially greater variability, and additional confounding factors, than the patients for this chronic use model. Due to the relatively chaotic physiological condition post-CABG, any benefit may be more difficult to detect in the patient population in this investigation, but this is also a lower risk intervention due to the universal use of temporary pacing leads in this patient group.

Table 8: Inclusion and exclusion criteria

Inclusion	Exclusion
Adult patients (≥ 22 years) scheduled for isolated, on- or off-pump CABG	Requirement for concurrent valve replacement surgery.
Established diagnosis of heart failure with reduced ejection fraction (HFrEF).	
Elective or urgent admission routes	Emergency CABG admission
Echocardiography assessment of left ventricular ejection fraction (EF) of 20%-45% (within 1 month of planned surgery)	History of paroxysmal or permanent atrial fibrillation or flutter

Patient is in sinus rhythm	History of AV-node dependent tachycardia
Any number of coronary vessels scheduled to be grafted. Must include left anterior descending artery.	Patients lacking capacity to consent
Patient is able to provide written informed consent	Pregnancy
	Implanted pacemaker or defibrillator
	Intrinsic resting HR > 110bpm
	Patient tests positive for Covid-19 within 14 days of intended CABG (using PCR or lateral flow test)
	Patient is unable to breathe through their nose or failure to obtain suitable respiration signals via nasal cannula (where assessed).
	Failure to obtain Uscom signals

4.7 Trial procedures

Study visits and data collection points are summarised in the Schedule of Events in Appendix 1.

4.7.1 Identification, screening, consent

Participants will be identified by one of two routes: inpatient (urgent CABG) and outpatient (elective CABG). Identification and screening will be conducted by an investigator with a clinical role in the patient's care.

Inpatient/urgent route: Patients who have been admitted to hospital following an acute coronary syndrome will have a diagnostic angiogram. For those in whom CABG is the preferred option, urgent cases will have CABG surgery during the same hospital admission, whereas emergency CABG happens on the same day as the angiogram. Patients deemed urgent will be identified by their clinical team and screened for eligibility for this Clinical Investigation. In 2019-20, urgent cases constituted around 50% of the CABG population in the UK, but this was closer to 60%-70% in Wales (NACSA 2021a). Mean waiting times between angiogram and surgery was 11 days (14 in Wales, NACSA 2021a). Patients may have an enforced isolation period prior to surgery to reduce the risk of Covid infection. Patients who are deemed eligible will be approached by a member of their clinical care team and provided with information about the study.

Outpatient/elective route: Elective CABG constitutes just under 50% of total CABG surgery in the UK and around 30-40% in Wales. Patients having elective CABG surgery had a mean waiting time of 104 days in the UK in 2019-20 (140 days in Wales; NACSA 2021a). These patients will be identified as they near their date for surgery, for example when they are allocated their pre-operative assessment appointment, or during an appropriate routine clinic appointment. Patients will be sent a letter and a Participant Information Sheet (PIS) or be approached in-person by a member of their clinical care team and provided with information. Following this they will be contacted by telephone by a clinical researcher so that they can ask questions and to arrange a visit time for consent and baseline assessments. Patients will be formally consented at an in-person appointment.

Referral centres: In the UK, CABG is a tertiary care service only provided at specialist centres. Patients requiring this procedure may be referred in from local secondary care providers (Health

Boards or Trusts). Data from the lead site suggests this represents around 40%-50% of CABG procedures. For the urgent admission route, patients may attend the specialist centre for their diagnostic angiogram and then return to the referring site for their pre-surgical inpatient isolation period. Patients who are unstable may stay at the specialist centre instead, and will be screened and approached as above. Alternatively referring centres may conduct their own diagnostic angiogram. Depending on local procedures, inpatients from referring centres will be identified when they are referred for, or when they attend, their diagnostic angiogram, or following the surgeon's decision for a CABG procedure. Once the surgery referral is made to the specialist centre, the patient is then also under the care of the clinical team at the research site. A member of their clinical care team (from either the referring hospital or research site) will approach the patient with information about the study. Elective patients referred from other sites will be identified by members of their care team when approaching their pre-operative assessment, and sent information about the study. Detailed Standard Operating Procedures (SOPs) will be created for each site depending on local practice.

For the majority of participants, no diagnostic testing is required to determine eligibility (other than for Covid-19 infection). Elective patients who have not had an echocardiogram for clinical reasons within 1 month of surgery will require an echocardiogram to determine eligibility. All patients will be informed about the study and provided with a PIS. They will have sufficient time to consider the information and opportunities to ask questions of a researcher trained on the study protocol. Where patients are not located at the research site, the initial discussion with the patient may be conducted remotely, by phone or video call. Where patients are not able to understand spoken or written English sufficiently, efforts will be made to provide information in the patient's preferred language, e.g. via an online translation service. Versions in Welsh will be available at sites in Wales. Written informed consent will be obtained in person (usually at the start of the baseline visit) and before any study procedures are undertaken. Participants will keep one copy of the signed form, a second is attached to the patient's medical notes, and a third is to be kept in the Site File. Screening will include the ability to obtain suitable quality Uscom and (possibly) respiratory signals at the baseline visit. If either of these are not suitable, patients will not have further baseline assessments and will be considered screening failures. Such patients will be recorded on the Screening Log and no other study data will be collected about them. Participants will be considered 'enrolled' once they have passed the baseline assessments. The patient's GP will be informed of their participation in the trial.

4.7.2 Randomisation (minimisation)

Participants will be allocated to study arms following CABG surgery. Participants will be re-checked for eligibility at this point by a researcher with an appropriate clinical role in the participant's care, e.g. clinical research fellow. Participants will be withdrawn prior to allocation if they have a clinical need for biventricular pacing, have significant surgical complications, or are otherwise deemed unsuitable for the trial interventions (see Section 4.7.6.1). Participants will be reviewed and allocated to a treatment group when their condition has stabilised and following extubation, which is expected to happen the day following surgery. When the patient is ready to start pacing, the clinical investigator will contact the randomisation service by phone call to a service using a computer application, or via a website or app. Treatment group will be recorded in the case report form (CRF) and in the patient's medical notes.

Randomisation will be conducted by the CRO during normal office hours. In general, this will occur when the patient is ready to start treatment allocation, but can also be pre-determined by prior

arrangement if the patient is likely to be ready to start pacing outside normal office hours. As minimisation is used, the CRO will take measures to ensure that the randomisation can be rolled back if the pre-determined allocation is not used.

In general, randomisation of treatment allocation reduces the potential for allocation bias and baseline differences between groups. However, as this is a relatively small study, randomisation can produce unbalanced groups. Our design will account for known confounders to try and ensure a fair comparison by including a minimisation element. Specifically, LVEF may have an influence on the safety and cardiac function outcomes. Patients with the lowest EF are at highest risk of complications and poor outcomes from CABG (Yau et al. 1999; Shahian et al. 2012; Hertzberg et al. 2019; Stewart et al. 2021). Any beneficial effect of RSA pacing may also be dependent on baseline cardiac function. For example, patients with the lowest LVEF may gain the most benefit (Perry et al. 2020), but if the effect is based on myocardial remodelling they may also need longer duration of pacing for that benefit to be realised. Additionally, patients with higher LVEF may experience 'ceiling effects', whereby they are unable to achieve much additional benefit from the intervention.

Stratification by site is not used, as we consider it unlikely that there are confounding factors that differ significantly between centres. Participants will be allocated to study arms using a randomisation/minimisation method. Allocation will be 1:1 between arms, computer based, and comprise a random component and a component that minimises differences between the arms for the following potential confounders:

- LVEF – group (1) 20-34%, group (2) 35-45%
- Base intrinsic HR – group (1) ≤ 80bpm, group (2) > 80bpm.
- Urgent or elective admission route.

4.7.3 Blinding & unblinding

Blinding of investigators and clinicians is not possible. Patients will not be blinded to treatment allocation. Additionally, analysts who are processing the ECG and respiratory data will be able to tell the treatment arm from the data. However, this lack of blinding is of reduced importance as most study outcomes are objective. Arrhythmias are defined in Appendix 2 and will be subject to automated detection and then reviewed by a clinician.

Treatment allocation will be recorded in the participant's clinical notes. Clinicians and investigators in the inpatient environment cannot be blinded as pacing mode will be obvious from the ECG trace. Participants could be blinded with the use of sham RSA modules, but could be able to discern their pacing mode from monitoring displays or by taking their pulse. As there are no patient reported outcomes, it is not considered worthwhile to attempt to blind participants. Statisticians conducting the inferential and estimand analysis will use anonymous and blinded group data. Other stakeholders in the study (DMC, Sponsor, CRO, etc) may have access to unblinded comparative outcomes during the study for commercial and safety reasons.

As clinicians and patient notes are not blinded to pacing mode, there is no need for emergency unblinding.

4.7.4 Baseline data

Following signed consent, baseline data will be collected at study visit 1 (screening) and from existing patient records. Elective patients may have this on the same day as their operation pre-

assessment appointment (typically up to 3 months prior to surgery.) Baseline tests should be carried out within 1-2 weeks prior to the planned surgery date, if possible. Urgent CABG patients should be scheduled as soon as possible before surgery, but preferably avoiding times when medication is being substantially altered. Inpatients from referral centres may have baseline assessments conducted at the referring centre.

Relevant medical history will be taken and the participant will have CO (Uscom VTI) and RSA measurements. Blood tests and echocardiograms are SOC, and results will be extracted from medical records onto the CRF by a clinical researcher. However, if elective patients have not had an SOC echocardiogram within 1 month of their surgery data, they will have one as part of the study. Data collection will typically include (but is not limited to) that in Table 9.

Table 9: Baseline data collection

Standard of care (SOC) assessments	
Demographics	E.g. height, weight, DoB, sex
Medical history	Duration of HF, NYHA class, co-morbidities
Referral route	Elective (outpatient)/urgent (inpatient)
Full Echocardiogram	Including aortic cross sectional area (CSA), LVEF, other LV functions and dimensions
Blood pressure	SAP, DAP, MAP
Blood biomarkers	Renal, cardiac, cardiovascular
Study-related assessments	
Blood biomarkers	NT-proBNP
Uscom	Velocity time integral (VTI)
Exercise recovery	Static handgrip (HR, BP, perceived breathlessness)
Intrinsic RSA	3 min ECG
Full Echocardiogram	*For elective patients who have not had one within 1 month of surgery*

4.7.5 Trial assessments

The list of outcome measures and the timepoints for these are given in Section 4.4, the Trial Flowchart at the start of this CIP, and summarised in the Schedule of Events in Appendix 1. Participants will be paced until they are ready to be discharged or until surgeons deem it clinically appropriate to remove the leads, whichever is earlier. Patients are observed for several hours between lead removal (LR) and discharge. The LR assessments must be conducted before leads are removed, therefore these may occur on the day of discharge (if conducted in the morning) or the day prior to discharge. All blood tests are standard assays and most are SOC for these patients, both before and following surgery. The exception to this is NT-proBNP, which is for study purposes. Blood pressure will be measured with a standard clinical automated NIBP monitor and the average of 3 readings used as the study value. The main additional assessments for this study are cardiac function (SV, CO, etc; Uscom), RSA assessment, exercise recovery (handgrip), additional echocardiograms at LR and PP, and blood tests at PP. (If participants have their PP visit at home they will not have blood tests or echocardiograms at this visit.) For assessments conducted during the pacing period (e.g. HR, CO, intrinsic RSA) these should be carried out at approximately the same time of day each time. This

is to account for potential effects of circadian rhythms, although this may not be significant if patients do not have regular sleep-wake cycles.

Arrhythmias will be assessed using continuous clinical monitoring, Holter recordings at home, and additional ECG recordings at LR and PP visits. Episodes will be compared to the definitions given in Appendix 2. The primary method of counting will be a review of the continuous ECG recordings. This will be done by automated arrhythmia detection software, with review by at least 2 clinicians. In addition, during the pacing period, participants will be paced at 120 bpm for 30 seconds every morning to test for heart block, which would prevent the heart from being paced at trial pacing rates. Most clinical (haemodynamic) measures are conducted at LR. Vital signs and Uscom data will be collected every other day from PD2 until LR. Data collected at PD6 will be used to test the between-groups change in CO. Participants will not have their stay extended due to study requirements, and will be discharged when medically appropriate.

Due to the uncertain and variable clinical condition of patients immediately post-CABG there may be multiple reasons why not all outcomes are measured at all intended timepoints. Additionally, clinical events may prevent the use of pacing up to PD6 for some patients. In this case we will use an estimand framework in the analysis to account for these intercurrent events (ICE; ICH 2019). These are events occurring after initiation of pacing, that affect either the interpretation or the existence of the measurements. These may include withdrawal, loss of pacing due to lead fibrosis, participants unable to manage the handgrip test, or inability to acquire a suitable Uscom signal.

4.7.5.1 Echocardiograms

Participants will have a standard echocardiogram assessment as part of SOC before surgery. For urgent route patients this will be conducted during the admission. For elective route patients, a new echo will be conducted if one has not been recorded within 1 month of surgery. These studies will be used to confirm LVEF and to measure the cross-sectional area (CSA) of the aortic valve. CSA will be used to convert Uscom velocity time integral (VTI) into SV and CO measures. Shorter echocardiograms that are focussed on LV function will be conducted as study procedures at LR and PP (for patients able to attend hospital).

4.7.5.2 Velocity time integral, stroke volume and cardiac output

The main haemodynamic outcomes for this study are CO and SV. Measurements will be taken using the Uscom 1a device, a non-invasive Doppler ultrasound device. This is placed at the suprasternal notch with the beam aimed inferiorly at the ascending aorta. The device measures blood velocity at the aortic valve and automatically detects the envelope of the Doppler-measured velocities. This is integrated across the lumen to determine continuous velocity time integral (VTI) which is converted to beat-to-beat SV values by multiplying by the cross sectional area (CSA) of the valve. The device is suitable for use following open cardiac surgery (Chand et al. 2005; Tan et al. 2005) and has been tested against other clinical measurement methods with reasonable levels of accuracy. Uscom shows good agreement with measurements using thermodilution (TD) via pulmonary artery catheter (PAC, Table 10) and better repeatability (Wong et al. 2008).

Table 10: Uscom CO agreement with PAC thermodilution

Study	Uscom-PAC TD (LOA) L/min	Population	N (subjects)	N (measurements)

Chand et al. (2005)	+0.14 (-0.39 to 0.11)	Post CABG surgery (off-pump)	40	40
Chong & Peyton (2012)	-0.39 (-0.25 to -0.53)	Meta-analysis of 6 studies (incl. Wong et al. 2008)	NA	320
Tan et al. (2005)	-0.18 (-1.78 to 1.43)	Post cardiac surgery	22	40
Wong et al. (2008)	-0.39 (-2.25 to 1.47)	Liver surgery	12	71

PAC – pulmonary artery catheter; TD – thermodilution; LOA – limits of agreement

Although clinically widespread, the PAC thermodilution method is not validated and not ideal as a reference measurement (Phillips et al. 2012; Hodgson et al. 2016). Also, most clinical methods for determination of CO average the value over several heartbeats, whereas the Uscom can provide beat-to-beat values. Hodgson et al. (2016) compared Uscom SV to transoesophageal Doppler in patients having a fluid challenge prior to abdominal surgery. Comparing 135 measurements in 25 patients, the Uscom-Doppler agreement was -5.9 (-32 to 20) ml. Using receiver operating characteristic (ROC) analysis for detecting 10% changes in SV, the authors reported an area under the curve (AUC) of 0.94. This confirms that Uscom provides high discrimination between patients with and without a 10% change in SV. Comparison in an ovine model shows closer agreement of Uscom CO to an implanted aortic flow probe than was achieved with PAC thermodilution (Phillips et al. 2012). Bias and LOA were 0.0 (-1.6 to 1.6) L/min versus -0.8 (-3.3 to 1.7) respectively. ROC analysis for a 5% change in CO showed an AUC of 0.74 for Uscom, whereas PAC did no better than random chance with an AUC of 0.52.

Uscom also has good repeatability when measurements between operators, or repeated measurements with the same operator, are assessed. Repeated measures (intra-operator reliability) has been assessed during surgery (Huang and Critchley. 2013) and in pregnant and non-pregnant women (Mangos et al. 2018), and inter-observer reliability in emergency department patients (Dey and Sprivulis 2005; Napoli et al. 2012; Hodgson et al. 2016). There is a learning curve effect, and a training set of around 20 patient scans is considered suitable before an operator can achieve good reliability (Dey and Sprivulis 2005; Hodgson et al. 2016). Good image quality is also a requirement of reliable measurements, with authors using a variety of score systems to rate this (Dey and Sprivulis 2005; Huang and Critchely 2013; Hodgson et al. 2016). However, most of these reports did not account for beat-to-beat variability in values of SV or CO, which limits the ability to determine repeatability of measures.

The Uscom measurements will be taken without pacing at baseline and PP, and both with and without pacing at PD1, PD2, and then every other day until LR (i.e. PD4, PD6, PD8, etc). Respiratory frequency variation will be present in both SV and CO in the intervention group during pacing, and may be present at other measurements. Therefore beat-to-beat values should be averaged over at least one respiratory cycle to determine an appropriate mean value. The Uscom device can record up to 14 seconds of data. It will be complex for the operator to attempt to define respiratory cycles from the visual data, therefore we will record 3 x 14s data segments at each time point. The patient's blood pressure must be entered to determine the full set of Uscom parameters. The validity of the Uscom values are operator-dependent and may be affected by patient factors, such as reduced tolerability immediately post-surgery. Therefore we will assess recording quality and the

effect of different methods for analysing this data (such as mean versus maximum) on the trial values.

4.7.5.3 Intrinsic and paced RSA

At baseline, PD1, LR, and PP, measures of intrinsic RSA will be taken (i.e. without pacing). ECG will be recorded for 3 mins while participants are resting supine. This will be analysed offline to calculate intrinsic RSA.

During pacing, Lead II ECG and respiration will be continuously recorded. In the intervention group the paced heart rate will be assessed for RSA using the same analysis and measures as for the intrinsic RSA. This will enable the effect of the RSA pacing intervention on HRV to be quantified using traditional measures and compared to published values for other patient groups and healthy controls.

4.7.5.4 Static handgrip (exercise response and recovery)

We will use a handgrip transducer reporting in Newtons to assess heart rate and BP recovery following exertion. This will be measured at baseline, PD4, Lead Removal, and at hospital-based Post Pacing visits. Using their dominant hand, participants will conduct 4 maximal contraction efforts in the supine position, separated by at least 1 minute rest. The maximum voluntary contraction (MVC) will be the maximum of these. Following a 10 minute rest, we will then assess participants' recovery from 30% of MVC. Participants will aim to hold this workload isometrically for 2 minutes. HF and BP will be measured up to 5 minutes following release. Heart rate recovery index is the difference in HR between the end of the exercise and each minute thereafter and is considered a marker of autonomic function (Kubrychtova et al. 2009). Change in BP following the cessation of effort will also be measured. Participants will rate their breathlessness (perceived exertion) using the Borg CR10 scale (Borg 1998; Bausewein et al. 2007; Williams 2017).

4.7.5.5 Post pacing assessments

Most participants will be discharged home before the post-pacing (PP) visit occurs. Participants will be given an appointment date for their PP assessment at the Lead Removal assessments and may be provided with a Holter-type ECG monitor for use until the following visit. This will be 7 ± 2 days following the end of pacing. (Ideally, measurements will be taken after 7 days, but allowance is made for leads being removed at weekends.) Depending on the patient's condition they will either be provided with transport or travel expenses to attend the visit in hospital, or they can have the visit at home. For those patients who are able to travel to hospital, all PP assessments will be carried out. For those who cannot, the home visit will consist of the Uscom VTI measurement and intrinsic RSA (including 3 minutes of ECG recording). The participant remains quietly seated or lying down for these assessments. Many patients at this stage of their recovery will still be struggling to manage activities of daily life. The home assessments will assess the primary outcome of safety by checking participants' heart rhythm. They will also indicate whether there are any persistent consequences of the RSA pacing. We expect further withdrawal between LR and PP visits, but by prioritising patients' welfare and comfort we hope to reassure potential participants while ensuring sufficient data to support the study's scientific integrity.

4.7.6 Withdrawal

Participants may be withdrawn at any point on the clinical judgement of their care team. Patients may withdraw themselves at any point. They will be asked for a reason, but do not have to provide one. Any study data recorded up to that point will be retained. Clinical decisions and participant explanations will be recorded in the CRF. Participants who withdraw following the initiation of pacing will continue to be closely monitored during their hospital stay as SOC. Such patients will continue with routine aftercare. Participants who lose capacity after providing consent will be withdrawn from the study and any data collected up to that point will be retained for analysis.

Data from the lead site indicates that around 30%-35% of patients are discharged before the 6th day post-surgery. Withdrawal of 40% from enrolment up to PD6 has been included in the enrolment estimation (Section 4.7.6.1 and 4.8.1), and an estimand framework is used in the analysis to account for missing data due to intercurrent events (ICE) following initiation of pacing (see Section 4.8.3), so participants lost to withdrawal will not be replaced. If withdrawal is higher than this and puts the integrity of the study at risk, study procedures will be reassessed and advised by the TSC and DMC. If withdrawal is lower than expected, recruitment will be stopped when the required number of participants has reached PD6.

4.7.6.1 Withdrawal criteria

Participants may be withdrawn following consent and before randomisation (post-surgery, PD1) for multiple reasons. For example, their condition may alter significantly prior to surgery so that they no longer meet the inclusion criteria (including changes to the planned surgery), or baseline measurements may not be possible between consent and surgery dates. Additionally, complications during or after surgery may mean continuation in the study is not suitable, for safety or practical reasons. These are listed in Table 11.

Table 11: PD1 withdrawal criteria (post-surgery, pre-randomisation)

Requirement for ventricular pacing
Surgical complications: peri-operative stroke
Failure of pacing wires
Pericardial effusion/tamponade
Need for inotropes > 48hrs
Chest infection requiring augmented oxygen
Need for intra-aortic balloon pump (IABP) for > 48hrs
Renal failure requiring haemofiltration for > 48hrs
Patient not extubated within 24 hrs post-surgery
Intrinsic resting HR > 110bpm
Patient not suitable for pacing for > 24 hrs post extubation
Persistent inability to obtain respiratory signals.

Data for some of these criteria for isolated CABG operations during 2019-20 are available from NACSA (2021a):

- in-hospital mortality is about 1% (slightly higher for urgent, and slightly lower for elective patients),
- re-surgery for bleeding is 1.1% in Wales and 1.83% in England,

- neurological events (cerebrovascular accidents and transient ischaemic attacks) are 0.8-0.9%,
- deep sternal wound infection are around 0.2-0.3%.

Participants may also be withdrawn for technical or clinical reasons during pacing (Table 12). During AF, the atria are depolarising at very high rates and so atrial pacing will not 'capture' the heart under these circumstances. Short periods of new-onset AF following cardiac surgery are relatively common within a couple of days post-surgery (section 1.4). Short periods of AF are unlikely to require interventions that may affect study outcomes. They should also not significantly affect the ability to pace the heart for a sufficient duration to produce any haemodynamic benefit. Patients will be withdrawn if AF is continuous for 24 hrs or a cumulative duration of 48hrs over 6 days. We are allowing for withdrawal of 25%-30% of participants for persistent AF and other arrhythmias.

Table 12: PD1 to Lead Removal, withdrawal criteria (during pacing)

Patient unable to tolerate RSA pacing equipment/set-up
Haemodynamically significant arrhythmia resulting from RSA delivery
Failure to capture right atrium (RA) pacing, technical failure to deliver RSA pacing
AF for 24hrs or more as a single episode, or cumulative duration of AF of 48 hrs or more over the pacing period.
Other brady- or tachy-arrythmias, or heart conduction issues that interfere with or prevent the heart from being paced at trial-determined rates for a cumulative duration of 72 hours or more.
Coronary graft failure
Pulmonary oedema
Loss of capacity
Persistent inability to obtain respiratory signals.

We do not consider these criteria to be independent and therefore loss to the study is not a simple sum of these estimates. Based on these values, we estimate a maximum withdrawal of 40% between enrolment and PD6.

4.7.7 Study duration

A sample size of N=54 is required (see Section 4.8.1). This includes accounting for a withdrawal rate of up to 40% between screening/consent/baseline and PD6 (see Section 4.7.6.1). The maximum expected duration of recruitment is 18 months and additional sites will be recruited to enable this to be achieved (Section 4.8.2). Participants will have their final in-person study visit around 7 days following the cessation of pacing (PP) and will have a telephone call approximately 30 days post surgery. Participants' medical records for the 30 days post-surgery will also be reviewed by a clinical researcher. Participants' total duration in the study depends on the interval between the screening/consent appointment (Visit 1) and their surgery, which will differ between urgent (typically a few days) and elective (typically up to 3 months) routes. This interval is dependent on clinical need and organisational clinical capacity, and is not related to this Clinical Investigation.

4.7.8 Device management and accountability

The investigational trial devices will be supplied to the sites by the Sponsor. These investigational devices will be labelled "Exclusively for Use in a Clinical Investigation". The prototype devices used in the RSA intervention group are not CE or UKCA marked. The Uscom Doppler devices are CE marked

medical devices. The AD Instruments handgrip transducer is CE marked, but is intended for research use only and not for use as a medical device[4]. Data recording devices may also be supplied by the Sponsor where required. All devices (investigational and approved) supplied by the Sponsor will be labelled "For RSA-PACE study use only" and will have contact information included.

Once the devices have been received at site, they must be stored separately in a secure environment when not in use. Devices will have a unique study code attached for tracking purposes. The pacemakers and Ceryx RSA module are battery powered. Pacemakers settings will be recalibrated daily in the morning and evening and battery life checked and replaced if necessary. Reusable devices must be cleaned according to instructions, as necessary, and between patients. If devices are not immediately required for another participant they will be returned to the secure storage. An equipment tracking log will be maintained and the equipment store will be reviewed periodically. Equipment management will be reviewed during study monitoring visits.

Should any device be considered possibly, probably, or definitely related to an adverse event or be subject to a device deficiency (Section 5) it will be removed from the study and quarantined securely. The device(s) will stay quarantined until required by the MHRA or Sponsor, or until appropriate review of the device deems it safe to be reinstated.

At study end, all reusable and unused supplied study equipment will be disposed of according to the CRO-mCIA.

4.8 Statistical design and analysis

4.8.1 Sample size

Sample size is not estimated on the primary outcome measure, as the study is designed to capture preliminary safety and performance information and not to formally test safety outcomes, which would be impractical in a first-in-human study. Sample size has been estimated using a combination of typical pilot study numbers, and numbers needed to detect a realistic difference in the clinical observation measure of 'change in cardiac function from PD1 to PD6'.

Ryckwaert et al. (2001) reported cardiac index (CI) in patients with an LVEF < 40% in the 2 days following elective CABG. Their control group had a CI of 2.2 - 2.7 (SD ±0.1-0.2) L/min/m^2. Using the mean body surface area for this group (1.80 m^2) to convert to CO, shows that CO is around 4-5 L/min. Russell et al. (2012; Russell 2013) investigated the effects of different pacing modes for 18 hours post-CABG in patients with LVEF < 35%. Cardiac output was generally 5-6 (SD of ± 1-2) L/min. (This excludes the VVI pacing mode which seemed to impair cardiac function.) This may be higher than is typical in patients with HFrEF, but these patients are being paced, which is particularly relevant for our study. Standard deviation appeared to reduce over time (from 0 to 18 hrs) post-operatively.

The increases in cardiovascular parameters with RSA pacing in the animal models were presented as mean ± SEM (O'Callaghan et al. 2020; Shanks et al 2022). When converted to standard deviation (SD), these are increases in CO of 23% ± 15% in rats and 20% ± 16% in sheep. If we hypothesise that our intervention group would have a similar increase of 20% ± 15% between PD1 and PD6, and

[4] https://www.adinstruments.com/support/safety-quality-standards

typical CO is 4 L/min, then the increase would be 0.8 ± 0.6 L/min (mean ± SD), versus no change in the control group. To detect this with alpha of 0.05 and 90% power we would need N=24, or N=18 for 80% power. However, animal data was collected during a relatively stable chronic model of HF. Therefore, even if the RSA implemented in humans has a similar effect size, we do not expect to see such a clear difference in this immediately post-surgical population due to the high variability in patient condition. To detect a more modest and realistic 10% ± 10% difference between the groups with an alpha of 0.05 and 80% power, we would need N=32. A 10% change in CO is a clinically meaningful improvement, although not necessarily detectable by patients as a change in functional capacity. (Note that this sample size gives us 80% power to detect any X ± X %, or Y ± Y L/min, difference between the groups; e.g. 5 ± 5% or 0.4 ± 0.4 L/min.)

Sample size is therefore chosen to be N=32 (16 in each arm). This is larger than typical for a pilot FIH study, but appropriate to a pivotal study with this effect size (Section 3.1). To mitigate any safety concerns regarding the FIH use of RSA pacing we will conduct interim analyses of the safety outcomes after 10 and 20 participants have reached PD6. (See section 4.8.3.3 for details.) This sample size (N=32) is the number of participants reaching the Uscom CO measurement at PD6. We have estimated a 40% withdrawal rate between enrolment and PD6 (section 4.7.6) so the initial enrolment target is therefore N=54. If actual withdrawal is less than this, recruitment will be stopped when we have reached the sample size at PD6.

4.8.2 Planned recruitment rate

CABG is the most common cardiac surgery carried out in the UK, with a total of around 14,000 isolated CABG procedures in the UK in 2019-20 (NACSA 2021a). In Wales, only University Hospital Wales (UHW), Cardiff, and Morriston Hospital, Swansea, carry out these procedures.

To estimate the recruitment rate number for this study we need to know the number of isolated CABG procedures on patients with HFrEF and LVEF between 20% and 45%. This data is not publicly available. Initial plans are to begin the study with 3 sites. Recent surgical data (unpublished) indicates around 15 to 75 eligible patients at each site per year. Allowing for screening failures in these estimates and a consent rate of around 50% we consider that the target enrolment (N=54) can be achieved within the intended duration (12-18 months). This also allows for the time required to conduct the interim analyses (Section 4.8.3.3). We will review ongoing recruitment and determine whether remedial action is required to ensure this remains the case.

4.8.3 Statistical analysis plan

This section briefly describes the statistical and analytical methods to be used for the study, focussing on the co-primary and secondary endpoints. A Statistical Analysis Plan, providing a more detailed outline of the statistical methods and definitions for analysis will be produced separately and finalised prior to database lock.

As this is a first-in-human (FIH) study, the expected distributions of many of the variables to be analysed are uncertain and therefore we cannot be fully prescriptive regarding the data analysis and reporting.

Baseline data and observation measures will be fully described (by visit by treatment group, where appropriate) using counts and percentages, or estimates of central tendency (mean and median) and range, as appropriate. All observations will be reported with estimates of dispersion, via standard

deviations (SD) or interquartile ranges (IQR), as appropriate, and 95% confidence intervals (95%CI) will be provided to capture uncertainty in sample estimates, where appropriate.

The following analysis sets will be used in the statistical analyses.

- Enrolled Set: The enrolled set will consist of all participants who sign the informed consent form.
- Safety Set: The safety set will consist of all eligible participants who are initiated on pacing (either treatment group). All analyses using the safety set will group participants according to the treatment they actually receive (monotonic or RSA-like pacing).
- Full Analysis Set (FAS): The FAS will consist of all randomised participants whether or not they experienced significant protocol deviations affecting evaluation of the endpoints. All analyses using the FAS will group participants according to the randomised treatment.

A Modified FAS (mFAS) may be defined in the Statistical Analysis Plan, which applies analysis flags to censor data after certain intercurrent events (ICEs). This will be particularly useful for targeting any hypothetical (or partially hypothetical) estimands.

4.8.3.1 Analysis of Co-primary Performance Endpoint

This measure will be calculated by Ceryx using data recorded in the Ceryx RSA module, as defined in section 4.4.1. Analysis of the co-primary performance endpoint will use the Safety Set for the intervention group – all patients initiated on RSA-like pacing. Any recording duration will be included, as the minimum duration for any effects (positive or negative) is not known. However, any devices that do not deliver the intended RSA-like modulation due to malfunction will be excluded.

Alongside the average proportion (of time spent in RSA-like pacing), the uncertainty in this estimate will be summarised via a 2-sided 95% confidence interval for the mean (assuming an approximately Normal distribution) or the median (using the Binomial distribution to determine which values in the sample are the lower and the upper confidence limits), as appropriate depending on the observed distribution of the individual proportions. We hope to achieve a confidence interval that includes 40% performance using this measure.

4.8.3.2 Analysis of Co-primary Safety Endpoint (AF)

This is the incidence of new-onset AF from pacing initiation up to the final data collection point for each participant (30 days post-surgery). The definition and data collection method are defined in section 4.4.2. Analysis of the co-primary safety endpoint will use the Safety Set, with the proviso that any participant receiving less than 1 hour of intended pacing is excluded from this endpoint. This is to ensure that a reasonable 'dose' of the treatment has been delivered from which any effects might be determined. The incidence proportions (for new-onset AF) will be compared between the intervention and comparator groups via a logistic regression model of the binary incidence data, with fixed effects for treatment group and the minimisation factors used in treatment allocation (4.7.2). An estimate of the difference in incidence proportions between groups and its standard error (SE) will be calculated using the delta method, along with the corresponding 95% confidence interval and p-value (assuming an approximately Normal distribution).

4.8.3.3 Analysis of Secondary Safety Endpoint (SADEs)

Analysis of the secondary safety endpoint will use the Safety Set. Serious Adverse Device-related Events (SADEs) are defined in section 5.1 and includes unexpected SADEs. We expect the number of these to be small.

Similar to the analysis of the co-primary safety endpoint, the incidence proportions (for SADEs) will be compared between the intervention and comparator groups via a logistic regression model of the binary incidence data, with fixed effects for treatment group and the minimisation factors used in treatment allocation (4.7.2). An estimate of the difference in incidence proportions between groups and its standard error (SE) will be calculated using the delta method, along with the corresponding 95% confidence interval and p-value (assuming an approximately Normal distribution).

4.8.3.4 Interim analyses

Recruitment will be paused after 10 and 20 participants have reached PD6. At these times all safety-related outcomes (arrhythmias and adverse events), performance measures and the cardiac function clinical outcomes will be collated, analysed and reported. The data will be presented to the DMC to determine whether participants, and specifically the intervention group, are at increased risk of harm. Any untoward events will be reviewed in the context of typical outcomes for these patients. The clinical and statistical opinion of the DMC will be presented to the TSC and TMG along with their recommendation for continuing, pausing, amending, or stopping the study. Reports will also be made available to local NHS R&D offices, MHRA and REC where requested.

4.8.4 Analysis of Cardiac Output

Analysis of the main clinical observation will use the FAS and/or mFAS.

The main haemodynamic outcome measure that will be subject to inferential statistical testing is change in cardiac output from PD1 to PD6. The difference in the mean change will be compared between the treatment groups. There are multiple potential occurrences that might prevent 6 days of pacing, prevent the measurement of the outcome (CO), or confound this outcome measure. Therefore, we intend to adopt an estimand approach to this analysis (ICH 2019). In brief, analysis will account for the following intercurrent events (ICEs):

- Withdrawal due to lack of capture by pacemaker, e.g. HR too high (considered treatment failure)
- Withdrawal due to significant arrythmia (potentially treatment failure)
- Insufficient pacing delivered over 6 days (treatment failure)
- Withdrawal due to other reasons (unrelated to treatment)
- Death (related and unrelated to the condition under study)
- Inability to measure cardiac output (unrelated to treatment)

Consideration will be given to the appropriate strategies for handling each ICE, details of which will be given in the Statistical Analysis Plan. A hypothetical strategy may be considered for ICEs unrelated to treatment or the underlying condition being studied (such as logistical issues or unrelated AEs), to understand the effect of treatment as though these events had not happened. Whereas for ICEs that may reflect a worsening of the underlying condition and/or lack of toleration of the treatment, a composite strategy may incorporate these events into the outcome by ascribing an unfavourable change in CO value (e.g. 0, reflecting no change). Alternatively, where the PD6 is still recorded

following this type of ICE, a treatment policy may be applied to understand the effect of treatment given the pacing that it was possible to administer in practice.

The primary estimand will be analysed using analysis of covariance (ANCOVA) of the change in CO at PD6, with fixed effects for treatment group and the minimisation factors used in treatment allocation (LVEF – 20%-34% and 35%-45%; baseline intrinsic HR – ≤ 80bpm, > 80bpm; urgent or elective admission) and PD1 CO as a covariate.

As a sensitivity analysis, traditional per protocol and intention to treat analysis may also be conducted. Further details of the analysis of the other secondary outcomes will be described in the Statistical Analysis Plan.

As there are multiple observational outcomes, and to avoid multiple tests of significance and the resulting increase in the risk of Type I errors, p-values will only be reported for change in CO. For the endpoints and other clinical observations, point estimates and 95%CI will be reported to show the range in which the true value is likely to lie and therefore the uncertainty/confidence in the estimate.

Summary statistics will be provided for demographics, blood biomarkers, etc. recorded at baseline.

4.9 Data management

4.9.1 Data handling and record keeping

The PI and clinical research teams will collect all clinical data and enter it onto the case report form (CRF). The data will be collected in a timely manner and be extracted from, and consistent with, the relevant source data. Each participant will be allocated a unique participant study code at trial entry, and this will be used to identify them on the CRF. The participant code list and any other study records containing Personal Identifiable Data (PID), such as consent forms, will be stored securely at each site, along with the Investigator Site File (ISF).

Data will be collected for each participant from the time of screening until 30 days post surgery. Clinical Investigation data will be stored on a secure electronic trial database. The database will be managed by CEDAR researchers and will be secured by appropriate access control and password protection. Data entry will be permitted to delegated staff at each site and to Ceryx staff involved in calculating measures from the devices. Only those needing access for monitoring and regulatory purposes will have access to wider study data. The database will be stored on secure servers with password-protected accounts.

A Data Management Plan will be produced detailing the means of recording, extracting, and transcribing the study data into the CRF. This may be site specific, depending on local clinical equipment use.

Most data collection is performed whilst participants are inpatients. Most participants will be discharged between the Lead Removal (LR) and PP visits. Participants will be contacted prior to discharge to arrange a PP appointment and will be provided with travel expenses or transport to encourage retention. Elective patients will also be provided with travel expenses or transport for the baseline assessments if this is not conducted at the same visit as a standard clinic or pre-assessment appointment. For participants who may not be able to travel to hospital for the PP visit and who are

within a reasonable travel distance, a clinical researcher will visit the participant and conduct a subset of the assessments (section 4.7.5.5).

Some data will be entered directly onto the CRF, such as patient demographics, some patient history, route of admission, BP. Source documents include patient medical notes, routine blood tests, continuous clinical bedside monitoring systems, and other assessments that are standard of care (SOC). In addition, the following study recordings are source data: all continuous monitoring recordings on study devices (ECG, respiration, pacemaker output), echocardiograms for study purposes, and Uscom recordings. Participants will have a patient record on the Uscom device identified only by their study code. Local SOPs will describe how continuous monitoring data will be recorded and anonymised, depending on the clinical systems used.

All paper and electronic site documents will be stored securely at the study sites during data collection and only accessible by the clinical research team, appropriate individuals on the Study Delegation Logs, and authorised monitors or auditors. When completed, each CRF will be signed-off by the study PI/CI or designee.

4.9.2 Site initiation, monitoring and close down

CEDAR will be responsible for site initiation and trial monitoring. Before the trial starts at a participating site, a Site Initiation Visit (SIV) will take place to ensure that site staff are fully aware of the trial CIP and procedures. Checks will take place to ensure all relevant essential documents and trial supplies are in place.

A risk-based Trial Monitoring Plan (TMP) will be produced separately. On-site or remote monitoring visits will be conducted in accordance with the TMP and will be pre-arranged. On-site or remote monitoring will be an on-going activity from the SIVs until trial close-out, and will comply with the principles of Good Clinical Practice (GCP). The frequency and type of monitoring will be detailed in the TMP and agreed by the trial Sponsor.

Monitoring visits will check the accuracy of data entered into the CRF against the source documents; adherence to the CIP, GCP and relevant SOPs; the progress of patient recruitment and follow up; and device management. The PI or designee should ensure that access to all trial related documents including source documents are available during monitoring visits. The extent of source data verification (SDV) will be documented in the TMP. Appropriate checks will be made to enable cross validation against the original source data and ensure accurate data entry. Where clarification from site staff is required for data validations or missing data, site staff will respond to data queries ensuring that amendments are made as required. This will require CEDAR researchers to access personal identifiable data. Study participants will provide explicit consent to the use of all PID for the purposes of the study.

The close down procedure at each site will commence once the final patient enrolled there has completed all follow-ups required. Reports will be made to the TSC and DMC (if deemed necessary). The TSC will advise on the risk assessments and frequency of monitoring.

4.9.3 Access to data and data protection

All investigators, study site staff, and any subcontractors must comply with the requirements of the General Data Protection Regulation (GDPR) and Data Protection Act 2018 with regards to the

collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Each site will ensure that only staff identified in the Study Delegation Log will have access to study data.

Raw data from the bedside clinical monitors and the Ceryx RSA module will be extracted and analysed by Ceryx. This data will be pseudonymised, using the participant's study code, and Ceryx staff will not have access to the code list. Data transfer processes will ensure traceability, security and confidentiality of the data (e.g. logging and encryption of physical media). Participants will provide explicit consent for this. Ceryx analysts will enter the study variables from this analysis into the study database. Access to the database will only be given to designated individuals and no PID will be stored on the database.

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

Under UK GDPR, the Sponsor is the Data Controller. CEDAR, each study site, and any subcontracted data services will act as Data Processors. The data extracted for the main analysis by Select Statistical Services Ltd will use anonymised data. If external service providers (such as ECG analysis) are used that require the transfer of PID for study purposes, the data transfer will be subject to an agreement that ensures suitable data protection and confidentiality. Participants will provide explicit consent for this where required. These entities will also be Data Processors. No other PID will be transferred to external entities. If database hosting is outsourced, the service will also adhere to GDPR safeguards.

Site staff will not have access to the full study dataset, only to their own site data. CEDAR will perform the basic descriptive analyses of the study data and Select Statistical Services Ltd will undertake the inferential analysis under the estimand framework. CEDAR will check, verify and clean the database data, and will provide Select with a blinded and anonymised data extract for the purposes of their analysis.

Any access to PID will be with documented consent by the participant. Fully anonymised data may be made publicly available following publication of the study results.

5 Safety reporting

5.1 Definitions

5.1.1 Adverse events/effects

Adverse Event (AE)	Any untoward medical occurrence in a participant, including occurrences which are not necessarily caused by or related to the trial procedures. For users, this is restricted to events related to the investigational device.
Adverse Device Effect/Event (ADE):	Any Adverse event which is possibly, probably or definitely related to the use of the investigational medical device or comparator device.

	This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the medical devices. This can also include any event that is a result of a use error or intentional misuse. It also includes the comparator, as the comparator is a medical device.
Serious Adverse Event (SAE)	• Resulted in death Or serious deterioration in the health of the subject, users, or other persons, as defined by one or more of the following: • Life threatening illness or injury • Permanent impairment of a body structure or body function, including chromic disease • In-patient or prolonged hospitalisation • Medical/surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or body function • Foetal distress, foetal death, congenital anomaly, or birth defect Or another important medical event. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Device Effect (SADE):	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated/ Unexpected Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk assessment.

5.1.2 Causality

The relationship of each adverse event to the medical devices, or investigational procedures must be determined by a medically qualified member of the research team, according to the following definitions. An event is ‘related’ if it is deemed possibly, probably, or definitely caused by use of the device or a study procedure. A ‘device-related’ event is an ADE, SADE, or USADE.

Causality	**Description**

Unrelated	The event is completely unrelated to the device or procedure.
Unlikely	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possible	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition and/or an effect of another device, drug or treatment).
Probable	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.
Causal	The serious event is associated with the investigational device or with procedures beyond reasonable doubt when: • the event is a known side effect of the product category the device belongs to or of similar devices and procedures; • the event has a temporal relationship with investigational device use/application or procedures; • the event involves a body-site or organ that ▪ the investigational device or procedures are applied to; ▪ the investigational device or procedures have an effect on; • the serious event follows a known response pattern to the medical device (if the response pattern is previously known); • the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); • other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; • harm to the subject is due to error in use; • the event depends on a false result given by the investigational device used for diagnosis, when applicable; In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

Complications of procedures are not related if that procedure would have been applied to the patient in the absence of the use/application of the investigational device.

If the event cannot be adequately assessed due to insufficient or contradictory information and/or the data cannot be verified or supplemented, and the sponsor remains uncertain about classifying the SAE, it should not exclude the relatedness and classify the event as “possible”.

5.1.3 Device deficiency (DD)

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. DDs include malfunctions, misuse or use errors, and inadequate information supplied by the manufacturer (including labelling). A DD may lead to an adverse event, or this may have been avoided due to action or chance. All DDs must be recorded.

5.2 Expected adverse events

These events will be recorded in the Adverse Event log, but do not require expedited reporting to the REC or MHRA (unless they meet the criteria for 'serious' – all serious AEs must be reported to the MHRA). Expected AEs and the main safety outcomes will be reviewed by the TSC and DMC at the interim analyses after 10 and 20 participants have reached PD6 assessments. The DMC will advise the TSC on continuation of the study, and whether additional expedited reporting of safety concerns to the Sponsor, REC, and/or MHRA are required.

5.2.1 CABG surgery risks

CABG surgery is associated with risks such as infection, excess bleeding, temporary arrhythmias, temporary renal impairment, stroke, and persistent arrhythmias requiring permanent pacemaker implantation. Participants in this study will have surgery as per SOC - there are no additional surgical risks to patients from participating in this study. Patients who experience any significant negative surgical outcomes will most likely meet the withdrawal criteria (Section 4.7.6.1), either before randomisation or during pacing.

5.2.2 Pacing risks

Participants in this study will have temporary epicardial pacing wires attached during CABG surgery as per SOC. There are small risks associated with these wires, including migration of the tips, retention of the wires, and bleeding or tamponade when the wires are removed (Lazarescu et al. 2014; Cote et al. 2020b). The wires are normally removed around 4 days post-surgery, and the patient is kept under observation for at least 6 hours before they are allowed home. However, some patients may have wires in place for 10 days or longer if required (Lazarescu et al. 2014). Participants in this trial will have pacing wires in situ for several days post-surgery. Longer implantation duration may be associated with higher risk of complications upon removal, but most published data does not support this (section 3.5.1). Pacing- and lead-related AEs are included as a study safety outcomes.

Following CABG surgery, patients may require cardiac pacing to correct or prevent temporary AF or bradycardia. Multiple studies have investigated the proactive use of different pacing modalities post-CABG (section 3.3). An increase in the rate of arrhythmias due to cardiac pacing has not been reported in these studies and is included as the primary outcome measure for this trial.

Additional information is listed in the Investigator's Brochure.

5.2.3 Assessment risks

Most of the assessments in this study are passive or are conducted as SOC. There are no known complications associated with the use of the Uscom device, echocardiograms, or the measurement of air pressure to record respiration.

There is a theoretical risk of a cardiovascular event due to the static handgrip exercise at baseline, which occurs before revascularisation of the heart has been conducted. However, there are no published data to support this, and patients often have treadmill exercise tests prior to CABG. This risk has been reviewed by the clinical advisers to the study. The static handgrip test is not considered to be more demanding than a treadmill test.

5.3 Recording and reporting of adverse events

Adverse events (AEs) will be recorded for each participant from the screening/enrolment visit until 30 days post surgery (D30). Participants will be provided with contact details for reporting AEs following discharge and up to D30. Participants will be telephoned by a clinical investigator on, or soon after D30, to report any AEs.

AEs considered possibly, probably or definitely related to the investigational or comparator medical device, as judged by a medically qualified investigator or the Sponsor, are an ADE. These will be followed either until resolution, or the event is considered stable. It will be left to the Investigator's clinical judgment to decide whether or not an ADE is of sufficient severity to require the participant's removal from the study. A participant may also voluntarily withdraw from the study due to an intolerable ADE.

In the event of a SADE, the decision to cease pacing, change to a standard pacing mode (using a non-investigational device), or to remove the pacing wires, will be made by the clinical team after weighing risks and benefits. If the investigational device is stopped due to an ADE or SADE, the Investigator will quarantine the device as soon as possible. Until the MHRA has been given the opportunity to carry out an investigation, the device should not be discarded, repaired, or returned to the manufacturer/Sponsor. All material evidence, i.e. devices/parts removed, replaced or withdrawn from use following an incident, instructions for use, records of use, repair and maintenance records, packaging materials, or other means of batch identification must be:

- clearly identified and labelled
- stored securely
- evidence should not be interfered with in any way except for safety reasons or to prevent its loss.

Where appropriate, a record should be made of all readings, together with any photographic evidence and eyewitness reports. All further supplies of the device should be quarantined as a precaution until further advice is sought.

5.3.1 Reporting process

All AEs occurring during the trial that are observed by the Investigator or reported by the participant will be recorded in the medical notes, the CRF, and the AE Log, whether or not attributed to the trial. AEs for each participant will be routinely recorded and reviewed at each assessment visit. The PI or other Investigator will inform CEDAR within 24 hours of becoming aware of a potentially serious AE.

The following information will be recorded:

- description,
- date of onset and end date,
- outcome
- seriousness
- causality - relatedness to the medical device or procedure
- action taken.

Follow-up information should be provided as necessary. Events will be followed up until the event has resolved or a final outcome has been reached.

The PI (or their delegate) will assess the AE for seriousness, relatedness/causality (section 5.1.2) and expectedness (section 5.2). If the event is deemed to be potentially serious the study safety form must be completed. The PI (or their delegate) must sign this, but another investigator may complete it. (This safety form is used for potentially serious AEs, and for DDs that may have led to a serious AE – see 5.3.3.)

All safety forms are collated by CEDAR with the Trial Master File. Copies must also be retained in the Investigator's Site File. CEDAR will inform all PIs as soon as possible of relevant information about serious events.

The CI is responsible for reporting of safety events to the REC, but these tasks will be delegated to CEDAR. This includes expedited reporting of USADEs and annual reports of all AEs.

Quarterly safety reports to the MHRA will be prepared by CEDAR, and reviewed and submitted by the Sponsor.

The TSC will review all AEs at each meeting. The DMC will review AEs periodically and will be informed of all events that require expedited reporting. The DMC will consist of two experienced physicians and a statistician who are independent of the trial. The DMC will:

- review unexpected events (USADEs), and take appropriate action
- seek additional advice or information from investigators where required
- evaluate the risk of the trial continuing and make recommendations as appropriate.

5.3.2 Expedited reporting

All potentially serious events (whether related or not) must be reported to CEDAR within 24 hours of the Investigator becoming aware of it using the study safety reporting form.

CEDAR can be contacted by email or by phone: susan.peirce@wales.nhs.uk
uhw.CEDAR@wales.nhs.uk
RSA.PACE.Cav@wales.nhs.uk
029 2184 4771

For all serious events, CEDAR will inform the Sponsor and CI as soon as possible and within 3 days at maximum. The Sponsor will review the seriousness and causality and report to the MHRA within 2 calendar days if there is an imminent risk of death or serious injury/illness and prompt remedial action is required, and within 7 days if not. If the Sponsor assessment is different to that of the Investigator, both opinions will be reported.

CEDAR will additionally report any USADEs (related and unexpected) to the CI for review. On behalf of the CI, CEDAR will report these to REC within 15 working days using the HRA 'non-CTIMP safety report form'.

If any serious and related events occur (SADE/USADE) the Sponsor must consider whether the risk analysis should be updated.

5.3.3 Reporting of device deficiencies

All device deficiencies (DDs) of the investigational and comparator devices will be documented throughout the Clinical Investigation. DDs for the investigational devices will be reported by CEDAR

to the Sponsor who will manage them in accordance with written procedures for the control of a non-conforming product. Where applicable, the Sponsor will take appropriate corrective and preventive actions to protect the safety of subjects, users, and other persons.

Any investigational device that is related to a DD will be withdrawn from the study and quarantined (if possible). The Sponsor will arrange for the safe return of an investigational device that is related to a device deficiency (unless required by the MHRA).

The PI must consider whether a DD that did not lead to an AE, could have led to a SADE. If so, the safety reporting form should be completed and sent to CEDAR within 24 hours. CEDAR will forward this to the CI and the Sponsor, who will report this to the MHRA. In case of disagreement between the Sponsor and the PI, both opinions will be sent.

If any DDs occur that could have led to an SADE, the Sponsor must consider whether the risk analysis should be updated.

5.4 Urgent safety measures/serious health threat

The Sponsor or Investigator may take appropriate urgent safety measures in order to protect research participants against any immediate hazard to their health or safety, without prior authorisation from a regulatory body. The measures taken and reasons must be reported to CEDAR immediately. On behalf of the CI, CEDAR will inform the Sponsor and REC within 3 days. The Sponsor will report these to the MHRA. Where an amendment to study documents is required, this will be submitted as a substantial amendment as soon as possible. Information should be provided to the REC using the current 'HRA non-CTIMP safety reporting form'.

6 Ethics and regulatory compliance

This Clinical Investigation will comply with the Declaration of Helsinki (2013) and Good Clinical Practice (GCP). It will be run in accordance with all applicable regulatory guidance. In the UK this includes, but is not limited to, the Medicines and Healthcare products Regulatory Agency (MHRA) guidance for Clinical Investigations of medical devices, BS EN ISO 14155 standard for Clinical Investigations of Medical Devices for Human Subjects, and the UK Policy Framework for Health and Social Care (2017).

The rights, safety, and well-being of human subjects are the most important considerations and prevail over interests of science and society. The study will respect the rights of participating patients and ensure confidentiality of patient information.

On behalf of the Sponsor and the CI, CEDAR will submit this CIP, informed consent form, and participant information sheets (PIS) to an appropriate Research Ethics Committee (REC) for approval. These documents will also form part of the notification of a Clinical Investigation to MHRA by the Sponsor.

No site will commence study procedures (including screening) until all national and local regulatory approvals have been achieved and the Sponsor's representative has completed and signed off the Site Initiation Visit.

6.1 Research ethics and regulatory review and reporting

The Clinical Investigation will not commence until approvals have been obtained from Health Research Authority (HRA) and Health and Care Research Wales (HCRW), an appropriate Research Ethics Committee (REC), and the MHRA. Any additional requirements imposed by the REC or MHRA shall be followed.

All correspondence with the REC and MHRA will be retained in the Trial Master File and Investigator Site Files (as appropriate).

The CI is responsible for notifying the REC and MHRA of the end of the trial, but can delegate the task to CEDAR. If the trial is ended prematurely, the CI or CEDAR will notify the REC and MHRA, including the reasons for the premature termination. Within one year of the trial end, the CI/CEDAR will submit a final report with the results, including any publications/abstracts, to the REC.

6.2 Peer review

The CIP has been developed with input from several cardiology clinicians, trial specialists, the Sponsor, statisticians, regulatory consultants, and physiologists. Prior to submission to REC/MHRA the CIP will be independently reviewed by the clinical members of the Data Monitoring Committee. The study will be assessed for governance and legal compliance by HCRW. Once all checks are satisfied, HCRW will issue HRA/HCRW approval. The study should not commence at a site until local NHS R&D confirmation of capacity and capability is also received.

6.3 Patient and public involvement (PPI)

Patient representatives have been sought via the independent HCRW public engagement process. Three representatives who have had a CABG procedure and/or cared for someone who has undergone this procedure have been engaged. Additional PPI recruitment may be required as the study progresses.

PPI representatives have been asked for their input on the design of the research, and specifically on the procedures and assessments that participants will undergo. They have also reviewed patient facing documents, such as the Participant Information Sheet (PIS) and the Informed Consent Form, and will review any lay summaries of the trial. Two representatives will also participate in the Trial Steering Committee to monitor trial progress and advise on any changes required. After the trial ends, a lay summary of the results will be produced in collaboration with the PPI representatives for participants who request this and for public access (e.g. CEDAR website).

6.4 Indemnity and funding

The Sponsor's indemnity will be detailed in the Clinical Research Organisation Model Clinical Investigation Agreement (CRO-mCIA). The Sponsor will indemnify the trial sites against claims of harm arising from the use of the investigational device or procedures required by the study that are not part of SOC. The Sponsor will not be liable for harms resulting from clinical negligence or wrongdoing by site staff, or from failure of the site to follow the CIP. In Wales, clinical negligence is covered by the Welsh Risk Pool and non-clinical negligence by the relevant Health Board.

The study is funded entirely by the Sponsor, Ceryx Medical Ltd. Agreements between the Sponsor, CEDAR and NHS sites will use the tripartite CRO-mCIA.

6.5 Breaches/deviations of GCP or CIP

CIP deviations are departures from the approved CIP. Prospective, planned deviations or waivers to the CIP must not be used, except to protect the rights, safety and well-being of human subjects. Accidental CIP deviations can happen at any time. Recurring deviations from the CIP are not acceptable, will require immediate action, and could potentially be classified as a serious breach. All deviations (serious or not) must be documented on the relevant study form by the PI or their representative, and reported to the CI and CEDAR immediately. Deviations may also be identified during trial monitoring visits. CEDAR will report all deviations to the Sponsor, who will report these to the MHRA.

A "serious breach" is a breach of GCP or the CIP which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

CEDAR will notify the Sponsor immediately of any potentially serious breach. The incident will be investigated by the Sponsor who will determine whether the breach constitutes a serious breach. CEDAR (on behalf of the Sponsor) will report serious breaches to the local NHS research governance department, and will inform the REC within 7 days. Communication of the same to the MHRA will be the responsibility of the Sponsor. Any corrective action required will be undertaken by the CI/CEDAR, and REC and MHRA informed. If necessary a CIP amendment will be submitted for review.

6.6 Amendments

It is the Sponsor's responsibility to classify amendments as being non-substantial or substantial. On behalf of the Sponsor and CI, CEDAR will obtain approval from the REC and HCRW/HRA for all substantial amendments to the original approved documents.
All changes to the Clinical Investigation (substantial and non-substantial) will be notified to the MHRA by the Sponsor. Amendments will not be implemented until all relevant regulatory organisations have granted a favourable opinion (or no objection), and local site R&D office approval has been received.

7 End of study

The end of the trial is defined as the end of follow-up (30 days post-surgery) of the final participant.

The trial may be terminated early if:

- new information determines that the potential risk to participants outweighs the potential benefits,
- the DMC and/or TSC deem the trial to be statistically or economically futile,
- supply of the investigational devices cease.

On behalf of the CI and Sponsor, CEDAR will inform the REC of the end of the trial, including the reasons for early termination if relevant. They will also submit a final report to REC within 1 year of this. The Sponsor will be responsible for communicating the same to the MHRA.

7.1 Post trial care

Participants will receive cardiovascular and wound care clinical follow-up as for SOC. Participants in this trial have increased levels of monitoring and follow-up up to 30 day post surgery, compared to SOC, and are therefore already receive a higher level of care than non-participants. We do not expect any long-term negative sequelae from participation in this trial.

7.2 Archiving and access to final dataset

Following publication of the final study report or journal paper, CEDAR will arrange archiving of electronic data and central paper documents using the Sponsor's preferred supplier. Pseudonymised study data from the study database will be exported, protected, and stored securely on an appropriate media. Sites will be responsible for archiving local essential documents. All essential documents, and electronic data will be kept for 5 years after completion of the study. A label stating the required retention time will be placed on the inside front cover of participants' medical records. Study records will be destroyed after the required storage duration, following agreement with the Sponsor.

If agreed by the Sponsor, an anonymous data set may be made available to site investigators and other researchers following the publication of final results.

7.3 Dissemination plan

The trial will be publicly registered on ClinicalTrials.gov before enrolment starts.

Ownership of the data arising from this study resides with the Sponsor. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared. The study will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guideline. The results will be made publicly available, which may include one or more peer-reviewed journal papers. The TMG and Sponsor will be responsible for approval of all manuscripts arising from the study prior to submission for publication.

At the end of the study, PPI volunteers will assist with preparing a lay summary for participants and members of the public. This will be sent to participants and made publicly available via the CEDAR and/or Ceryx websites.

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Appendix 1 – **Schedule of Events**

RSA-PACE study: Schedule of activities	**Pre-screening/**		**Baseline**	**Procedure**	**Pacing period & assessments (until leads removed)**										**Lead Removal additional tests**	**Follow-up**	
	Pre-op appt or by post	Day -14 to -1	Day -14 to -1	Surgery	Pacing Day 1	Pacing Day 2	Pacing Day 3	Pacing Day 4	Pacing Day 5	Pacing Day 6	Pacing Day 7	Pacing Day 8	Pacing Day 9	Pacing Day 10		7 days post-pacing	Day 30
Provide information to inpatients/urgent patients (24+hrs before consent)		X															
Provide information to outpatients/elective patients	X																
Consent signed			X														
Medical history			SOC														
BP			SOC		SOC	SOC		SOC		SOC		SOC		SOC	(SOC)	(X)	
Renal biomarkers			SOC		SOC										SOC	(X)	
Thyroid function			SOC / X														
Haemoglobin			SOC														
HbA1c			SOC														
Cardiac biomarkers			X		X										X	(X)	
Full/BSE echo			SOC / X#														
Uscom (VTI)			X		X	X		X		X		X		X	(X)	X†	
Hand grip maximum voluntary contraction			X														
Static hand grip - excercise recovery			X					X							X	(X)	
Intrinsic RSA (unpaced)			X		X										X	X†	
CABG procedure				SOC													
Implantation of epicardial wires				SOC													
Randomisation					X												
Initiation of /resetting study pacing					X	X	X	X	X	X	X	X	X	X			
Continuous Lead II ECG monitoring					SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC		X	
Limited echo															X	(X)	
Phone call to patient																	X
Review of medical records (safety events, length of stay)																	X
CRF entry	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
(Blue) - not all participants get this event, e.g. for home PP visits.			*# Study procedure for some*													*† Only these used for home visits*	

Appendix 2 - **Standard Arrhythmia Definitions**

Bradyarrhythmias:

Asystole	The absence of any electrical activity on an electrocardiogram (Bergum et al. 2016).
First degree AV block	PR interval > 200ms (Neumar et al. 2010)
Second degree, Mobitz I AV block	Progressive prolongation of the PR interval culminating in a non-conducted P wave (Neumar et al. 2010).
Second degree, Mobitz II AV block	Intermittent non-conducted P waves without progressive prolongation of the PR interval (Neumar et al. 2010).
Third degree AV block or Complete heart block	Bradycardia due to absence of AV conduction. It is defined as complete AV dissociation with independent atrial and ventricle rates (Neumar et al. 2010).
Sinus Bradycarda	Sinus rhythm with a heart rate less than 60 beats per minute (Neumar et al. 2010).

Tachyarrhythmias:

Atrial fibrillation (AF)	Supraventricular tachyarrhythmia with uncoordinated atrial electrical activation and consequently ineffective atrial contraction. The electrocardiogram features include: irregularly irregular R-R intervals; absence of distinct repeating P waves and irregular atrial activations, lasting for 30 seconds or an entire 12-lead ECG (Calkins et al. 2018 and Charitos et al. 2012).
Atrial flutter	Regular atrial activity at 300 beats per minute with flutter waves. These are best seen in leads II, III and aVF.
Atrial tachycardia	Regular atrial heart rate > 100 beats per minute and an abnormal P wave morphology axis (Neumar et al. 2010)
Sinus tachycardia	Sinus rhythm with a heart rate of greater than 100 beats per minute (Neumar et al. 2010)
Narrow complex tachycardia	Heart rate of >100 beats per minute with a QRS duration of <=120ms (Brugada et al. 2019).
Broad complex tachycardia	heart rate of >100 beats per minute with a QRS duration of >120ms (Brugada et al. 2019).
Ventricular fibrillation	Rapid heart rate with chaotic irregular deflections of varying amplitude with no identifiable P waves, QRS complexes or T waves (Resuscitation Council UK 2021).
Ventricular tachycardia (VT)	Broad complex tachycardia arising from the ventricles. It is defined as 3 or more consecutive broad complex beats of ventricular origin. 3 or more of the following ECG criteria are considered diagnostic of VT: Initial R wave in V1; Initial r > 40ms in V1 or V2; Notched S in V1; Initial R wave in aVR; Lead II R wave peak time (RWPT) > = 50ms; Lack of RS complex in leads V1 - V6; and Atrioventricular dissociation (Jastrzebski et al. 2016)
Non-sustained ventricular tachycardia	VT lasting less than 30 seconds. (Priori et al. 2015)
Sustained ventricular tachycardia	VT lasting more than 30 seconds (Priori et al. 2015).

Appendix 3 – **Amendment history**

Amendment number	CIP version	Date issued	Author	Details
1	1.1	11/07/24	S Peirce	1. Add reference numbers for MHRA, REC and ClinicalTrials.gov 2. Removed named contacts for Select, PPI, DMC and TSC. DMC and TSC are replaced with descriptions of members. To avoid the need for amendments due to changes in personnel. (CIP contributors have not been removed.) 3. Replace specific biomarkers and echo parameters with generic descriptions in case of small changes in data collection for recorded observations. This includes the removal of Appendix 3 (echo parameters) and small changes to the Schedule of Events (Appendix 1) 4. The ability to assess respiratory signals at baseline may not be possible if the trial devices are being used for Pacing Day assessments. Therefore this criteria will only be measured where possible. 5. Replace 'gender' with 'sex'. 6. Replace data storage 'cards' with 'devices', to avoid need for amendments due to minor changes in data collection. 7. Change intrinsic RSA measurement from 10 mins of ECG and respiration to 3 mins of ECG. 8. Some ECG analysis may be conducted using commercial analysis services, depending on the resources available at each site. These services are used clinically in some hospitals and require that patient PID is attached to the data. Where this service is used, participants will be explicitly consented for this data transfer and agreements will ensure suitable data protection and confidentiality processes are adhered to. This is added to the PIS and the ICF. 9. The handgrip assessment has been shortened and simplified as it was deemed unnecessarily onerous for both participants and researchers. This is now a single assessment of 30% MVC with HR and BP assessed for up to 5 mins post exercise. 10. Intrinsic HR will be checked and pacemakers reset each evening as well as the morning. This is because overnight is the most likely time for patients to be resting and therefore for the pacemakers to be capturing the heart. 11. Remove the requirement to return equipment to the sponsor at the end of the trial. Disposition of the trial equipment is determined by the CRO-mCIA for each site.

				12. Remove the option for CEDAR to manage transport bookings, and to store the site file and PID for the Cardiff site. This has been deemed impractical. 13. The definition of an SAE has been updated to more closely match that in BS EN 14155. Device Deficiencies removed from the SADE definition. 'Risk analysis report' replaced with 'risk assessment'. Fuller description of causality assessment for AEs has been added. 14. Generic trial email address added to contacts for expedited reporting. 15. Remove requirement for annual reporting to REC as the intended recruitment period is less than 2 years.
2	1.2	27/05/25	S Peirce	1. Remove bleeding requiring surgery as a PD1 withdrawal criterion. 2. Remove persistent inability to obtain Uscom signals as a withdrawal criterion, at PD1 and during pacing. 3. Change the wording of the withdrawal criteria regarding AF/arrhythmias. Move AF from PD1 to 'during pacing' criteria and remove the word 'persistent'. Separate AF from other arrhythmias. Include all arrhythmias/conditions that prevent the heart being paced by the pacemaker for <72 hours. 4. Change inclusion/exclusion criteria to allow for patients having off-pump CABG. 5. Change inclusion criteria to increase upper limit of LVEF to 45%. 6. Change minimisation factors for LVEF to 20-24% and 35-45%. 7. Remove arrhythmia adjudication from DMC role. 8. Add pacing test for heart block daily during pacing period. 9. Participants take an ECG monitoring device home and use it to record ECG between LR and PP visits. 10. Reword recruitment section to clarify that patients can be contacted remotely by research staff. 11. Replace requirement for patients to have the information sheet for 24 hours with 'sufficient time'. 12. Allow for pre-determination of randomisation where patients are likely to require treatment allocation out-of-hours. 13. Correct the SOE in Appendix 1 – remove blood tests that were previously removed from the CIP text.

				14. Add handgrip MVC measurement before each handgrip recovery assessment. Clarify 10min rest between these.