

RIPCORT-CRT

Randomised Investigation of Physiological, Conventional and Optimised
Resynchronisation Therapy in Heart Failure with Prolonged QRS Duration

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Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

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Funder

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This protocol describes the RIPCORT-CRT study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the **UK Policy Framework for Health and Social Care Research**. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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Glossary of Abbreviations

AE	Adverse event
AF	Atrial fibrillation
ARI	Activation recovery interval
AVN	Atrio-ventricular node
BHCG	Beta-human chorionic gonadotrophin
BNP	B-type natriuretic peptide
BVP	Biventricular pacing
CMR	Cardiac magnetic resonance
CRT	Cardiac resynchronisation therapy
CSP	Conduction system pacing
CT	Computed tomography
ECG	Electrocardiogram
ESC	European Society of Cardiology
HF	Heart failure
HFH	Heart failure hospitalisation
HOT	His bundle optimised
ICD	Implantable cardioverter defibrillator
LBBAP	Left bundle branch area pacing
LBBB	Left bundle branch block
LBBP	Left bundle branch pacing
LOT	Left bundle optimised
LVAT	Left ventricular activation time
LVEDD	Left ventricular end diastolic dimension
LVESD	Left ventricular end systolic dimension
LVEF	Left ventricular ejection fraction
LVRG	Left ventricular repolarisation gradient
LVRT	Left ventricular repolarisation time
LVSP	Left ventricular septal pacing
KCCQ	Kansas City Cardiomyopathy Questionnaire
MLWHFQ	Minnesota living with heart failure questionnaire
NYHA	New York Heart Association
OMT	Optimised medical therapy
RVP	Right ventricular pacing
SCD	Sudden cardiac death
TTE	Transthoracic echocardiogram
UHF	Ultra-high frequency
VA	Ventricular arrhythmia
VF	Ventricular fibrillation
VT	Ventricular tachycardia

Keywords

Conduction system pacing, left bundle branch, heart failure, cardiac resynchronisation therapy, arrhythmia, LOT-CRT

Study Summary

Title	Randomisation Investigation of Physiological, Conventional and Optimised Resynchronisation Therapy in Heart Failure with Prolonged QRS Duration (RIPCORD-CRT)
Design	Double-blinded, randomised, 1:1:1 three-parallel-arm trial
Aims	1) To compare the clinical impact of conduction system pacing, conventional biventricular pacing and hybrid optimised cardiac resynchronisation therapy (LOT/HOT-CRT) on clinical heart failure (HF) and arrhythmia outcomes at six-months. 2) To explore the impact of these modalities on mechanistic contractility, arrhythmia and global function outcomes.
Outcome Measures	Primary outcome: • Daily ordinal symptom scale with clinical over-rides: 1) death, 2) intractable symptoms leading to trial exclusion/unblinding, 3) HF hospitalisation, 4) non-HF hospitalisation, 5) appropriate ICD therapy, 6) daily app-based symptom score to 6-months. Primary arrhythmia outcome: • Ordinal arrhythmia scale: 1) death, 2) appropriate ICD therapy, 3) sustained ventricular arrhythmia (VA), 4) sustained atrial arrhythmia, 5) non-sustained VA, 6) >10% ventricular ectopy on 24h ECG at 6 months. Primary contractility outcome: • Ordinal mechanistic scale: 1) death, 2) intractable symptoms leading to trial exclusion/unblinding, 3) HF hospitalisation, 4) non-HF hospitalisation, 5) LVEF at 6-month follow-up. Secondary outcomes: • QT dispersion from 24h digital ECG (at 6-months) • HF measures (at 6-months): LVEDD and LVESD (TTE), 6 minute-walk test, serum BNP, HeartQoL, KCCQ-12, MLWHFQ, NYHA classification • Device measures (at 6-months): Activity levels, AF burden, thoracic impedance • Non-invasive epicardial electrical mapping derived repolarisation heterogeneity (LVRT, LVRG) and activation parameters (LVAT, ARI) at 6-months • Blinding index • Safety endpoints: Device infections (requiring device extraction), pacing thresholds, need for lead revision or reimplantation, generator change, haematoma and pneumothorax
Population	• Patients referred for CRT; symptomatic heart failure (NYHA II-IV), LVEF $\leq 40\%$, QRS duration $\geq 130\text{ms}$ and left bundle branch block ECG morphology or $\geq 150\text{ms}$ and non-left bundle branch block ECG morphology, despite optimal medical therapy.
Eligibility	Inclusion criteria: - Clinically indicated CRT (+/- ICD) new implant or upgrade as per ESC guidelines (above) Exclusion criteria:

- Unable to provide informed consent
- <18 years old
- Pregnant patients

Duration 3 years

1 Study Objectives

Primary: To understand how cardiac resynchronisation therapy (CRT) delivered by conduction system pacing (CSP), left/His bundle optimised CRT (LOT/HOT-CRT) and biventricular pacing (BVP) impact on clinical measures of heart failure and arrhythmia.

Secondary: To understand the mechanisms and risk of developing ventricular arrhythmia in CRT delivered by CSP, LOT/HOT-CRT and BVP assessed by the impact on repolarisation heterogeneity in both the acute and long-term setting.

2 Experimental Protocol

Visit 1

Informed consent
Baseline: ECG, CMR, TTE, 6MWT, BNP, questionnaires, UHF-ECG
Daily symptom scoring app begins (lead in)

Visit 2

Stratified randomisation (Strauss criteria)
Implant procedure
AVd + VVd optimisation
Manual HR drivetrain (shortening S2)
ECGi activation + repolarisation, haemodynamics
ECG
Programming to randomised allocation

Visit 3

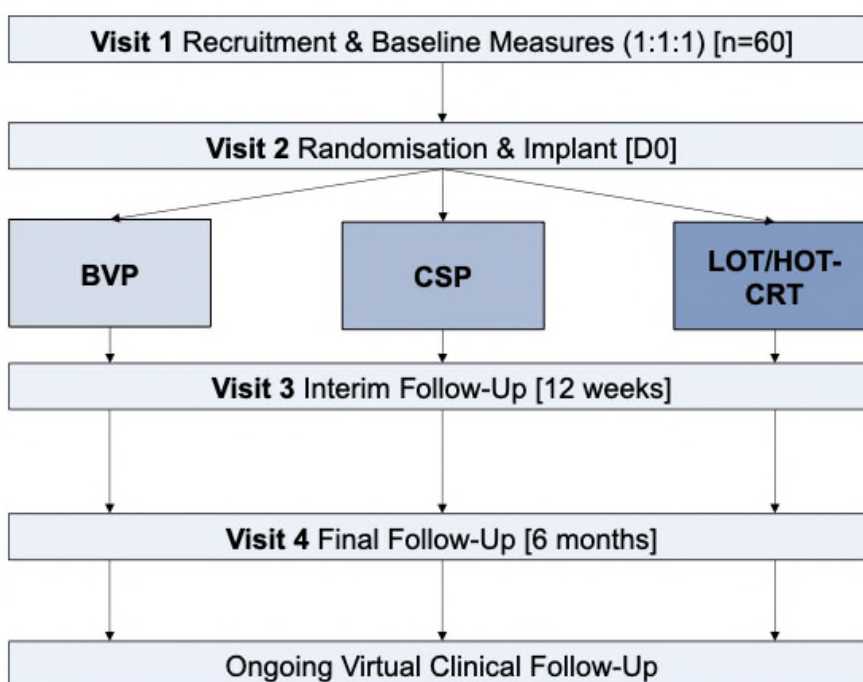
Post implant device check
Repeat: ECG, TTE, 6MWT, BNP, questionnaires, UHF-ECG
12-lead 24h digital Holter monitor fitting

Visit 4

Repeat device check
Repeat ECG, TTE, 6MWT, BNP, questionnaires, UHF-ECG, ECGi activation + repolarisation, haemodynamics
Natural HR - 24h Holter monitor return
Daily symptom scoring via app stops

Study Exit

Programming to clinically optimal settings
After maximum 3y, patients exit the study



Primary outcome: Daily ordinal symptom scale with clinical over-rides: 1) death, 2) intractable symptoms leading to trial exclusion/crossover/unblinding, 3) HF hospitalisation, 4) non-HF hospitalisation, 5) appropriate ICD therapy, 6) symptom score
Primary arrhythmia outcome: Ordinal arrhythmia scale: 1) death, 2) appropriate ICD therapy, 3) sustained ventricular arrhythmia (VA), 4) sustained atrial arrhythmia, 5) non-sustained VA, 6) >10% ventricular ectopy on 24h ECG
Primary contractility outcome: Ordinal mechanistic scale: 1) death, 2) intractable symptoms leading to trial exclusion/crossover/unblinding, 3) HF hospitalisation, 4) non-HF hospitalisation, 5) LVEF

Figure 2: RIPCORT study flow chart. Secondary outcomes: QT dispersion from 24h digital ECG (at 6-months); HF measures (at 6-months): LVEDD and LVESD (TTE), 6 minute-walk test, serum BNP, HeartQoL, KCCQ-12, MLWHFQ, NYHA classification; Device measures (at 6-months): Activity levels, AF burden, thoracic impedance; Non-invasive epicardial electrical mapping derived repolarisation heterogeneity (LVRT, LVRG) and activation parameters (LVAT, ARI) at 6-months, blinding index.

2.1 Trial Design

This is a prospective randomised clinical study. Patients will be blindly randomised in a 1:1:1 fashion to one of the three arms (CSP, LOT-CRT or BVP). Based on power calculations for the primary symptom outcome, we primarily aim to recruit 60 patients, but with additional funding we will recruit a further 40 (total 100) to improve precision on the primary contractility outcome. The study will run for a maximum of 3 years. Primary outcome follow-up will be at 6 months, with virtual clinical event follow-up being between 6-36 months depending on the time of individual patient recruitment.

2.2 Patient Screening

Patients referred for either a new implant CRT device or an upgrade of an existing pacing system (either bradycardia pacing device or an ICD) on a heart failure indication as per current clinical guidelines will be screened for recruitment (fully specified in *inclusion criteria* section below).

Patients will be identified and approached from clinical encounters via their standard NHS care givers.

2.3 Methodology

2.3.1 Visit 1 – Recruitment, Baseline & Clinical Measurements

Clinical teams at Imperial College Healthcare NHS Trust will identify patients who meet the study's eligibility criteria at routine clinical appointments. If the patient has an existing ICD with a DF-4 lead insitu which has been listed for upgrade to CRT, the clinical team will need to determine whether explant/extraction of that lead is clinically appropriate, as randomisation to LOT-CRT would necessitate a DF-1 lead implant.

A member of the research team will approach these patients, with a verbal explanation of the study and dissemination of the relevant patient information sheet and invite them to attend research visit 1 for recruitment.

Patients will have an opportunity to discuss any questions regarding the study before signing written informed consent forms. If happy to proceed patients will be made aware that all their data will be pseudonymised and they can retract their consent at any time.

Baseline measurements will be undertaken:

- Urinary beta human chorionic gonadotropin (BHCG) (if female and <65y)
- Cardiac magnetic resonance (CMR) scan
- 6-minute walk test (6MWT)
- HeartQoL questionnaire
- Kansas City Cardiomyopathy Questionnaire-12 (KCCQ-12)
- Minnesota Living with Heart Failure Questionnaire (MLWHFQ)
- New York Heart Association (NYHA) symptom classification
- Ultra-high frequency ECG

* Serum B-type natriuretic peptide (BNP), 12-lead ECG and Transthoracic echocardiogram (TTE) will be repeated if referral investigations are distance from recruitment time

If BHCG is positive, pregnancy must be excluded to continue in the study.

At visit 1, recruited patients will be helped to install a custom symptom (NATURE-DCM ORBITA) application (see **Appendix 11.1** for details) onto their smartphone. They will be on-boarded by a member of the research team. The research team member will train patients on how to use the application, including example cases. Patients without smartphones will be asked if they can suggest a proxy who owns a smartphone who can record their symptoms on their behalf. If patients do not own a smartphone, nor have anybody who can input data by proxy, a blinded member of the research team will call them daily and input data into the application as a remote proxy. Starting from Visit 1 onwards, patients will be asked to record symptom severity daily using the application.

2.3.2 Visit 2 –Randomisation, Implant & Baseline ECGi Measurements

We will aim for all implants to be scheduled >2 weeks post Visit 1, to allow for a lead-in phase of symptom scoring data to be collected.

Unless practically not possible, patients will be randomised to a study arm using custom randomisation software on the day of their procedure. Randomisation will be stratified by Strauss LBBB classification (positive vs. negative) performed using computerised randomisation software by a member of the primary research team. Patients will be blinded to their randomised allocated modality of CRT.

Immediately before the device implant procedure patients will be fitted with the 252-lead ECGi vests before undergoing a low dose CT scan to attain the required anatomical data for the non-invasive ECGi mapping. Before implantation, patients who have consented to undergo radial arterial monitoring will receive a radial arterial catheter inserted under local anaesthetic – which will be removed at the end of the procedure.

Biventricular Pacing (BVP) Arm

In this arm, which is standard of care, patients will undergo a local anaesthetic procedure where the following leads are implanted:

- Right atrial lead (unless permanent atrial fibrillation or clinical team decide this is not in the patient's interests)
- Conventional right ventricular myocardial lead (either septum or apex as per operator preference/feasibility)
- Conventional coronary sinus branch lead for left ventricular epicardial pacing

This is a standard BVP implant. In patients with a defibrillator indication the right ventricular lead will be a defibrillator lead (DF-4 or DF-1 as per operator preference). Patients will be programmed to receive biventricular pacing via their right ventricular

and coronary sinus branch lead. The ventriculo-ventricular timing between the two leads will be set as per operator discretion.

If the operator is unable to site a coronary sinus LV lead, they may choose to implant a conduction system pacing lead (with capture criteria and back-up options as specified below). If this option is taken, this CSP lead will remain switched off for the 6-month duration of follow-up until unblinding. At this point, programming should be dictated by the clinical team.

If the operator is unable to site a coronary sinus LV lead and they do not have the training to site a CSP lead, they may choose to implant a dual chamber pacemaker system, with a biventricular generator (with the LV port plugged). This would allow for a re-do procedure with the option of re-attempting an LV lead or a CSP lead. If the latter occurs before the primary outcome analyses at 6 months, the CSP lead is to be programmed off until unblinding.

Conduction System Pacing (CSP) Arm

Patients will undergo a local anaesthetic procedure where the following leads are implanted:

- Right atrial lead (unless permanent atrial fibrillation or clinical team decide this is not in the patient's interests)
- Left bundle branch lead with the aim of resynchronising the left ventricle

In patients with a CRT-D indication, a right ventricular defibrillator lead (DF-1 or DF-4 as per operator preference) will also be implanted.

In patients where LBB capture cannot be achieved as per contemporary guidelines¹, but left ventricular septal capture can be achieved this will be accepted (as left bundle branch area pacing, LBBAP). If LBBAP cannot be achieved, His bundle pacing will be attempted. If neither LBBP nor His bundle pacing can be achieved, mid-septal pacing will be accepted.

In the cases where LBB or His capture is not achieved, operators can implant a coronary sinus LV lead, but this will remain switched off for the 6-month duration of follow-up until unblinding. At this point, programming should be dictated by the clinical team.

In cases where a backup coronary sinus LV lead is implanted and a defibrillator function is required; operators will be mandated to use a DF-1 lead. The pace-sense branch of this lead will be capped and buried. The left bundle branch lead will be connected to the pace-sense port instead (**Figure 3**).

LOT/HOT-CRT Arm

Patients will undergo a local anaesthetic procedure where the following leads are implanted:

- Right atrial lead (unless permanent atrial fibrillation or clinical team decide this is not in the patient's interests)

- Left bundle branch lead with the aim of resynchronising the left ventricle. If left bundle capture cannot be achieved, the sequence of backup options will be followed as per the CSP arm.
- Conventional coronary sinus branch lead for left ventricular epicardial pacing

In patients with a defibrillator indication, a right ventricular defibrillator lead (DF-1 only) will also be implanted with header arrangement as per highlighted in the CSP arm section above.

In this arm, patients will be programmed to receive biventricular pacing via their left bundle branch lead and coronary sinus branch lead. The ventriculo-ventricular timing between the two leads will be set as per operator discretion.

If the coronary sinus LV lead cannot be sited, patients will have a CSP setup. These will remain in the LOT/HOT-CRT arm for intention to treat analysis, though can be considered CSP in any per protocol analyses.

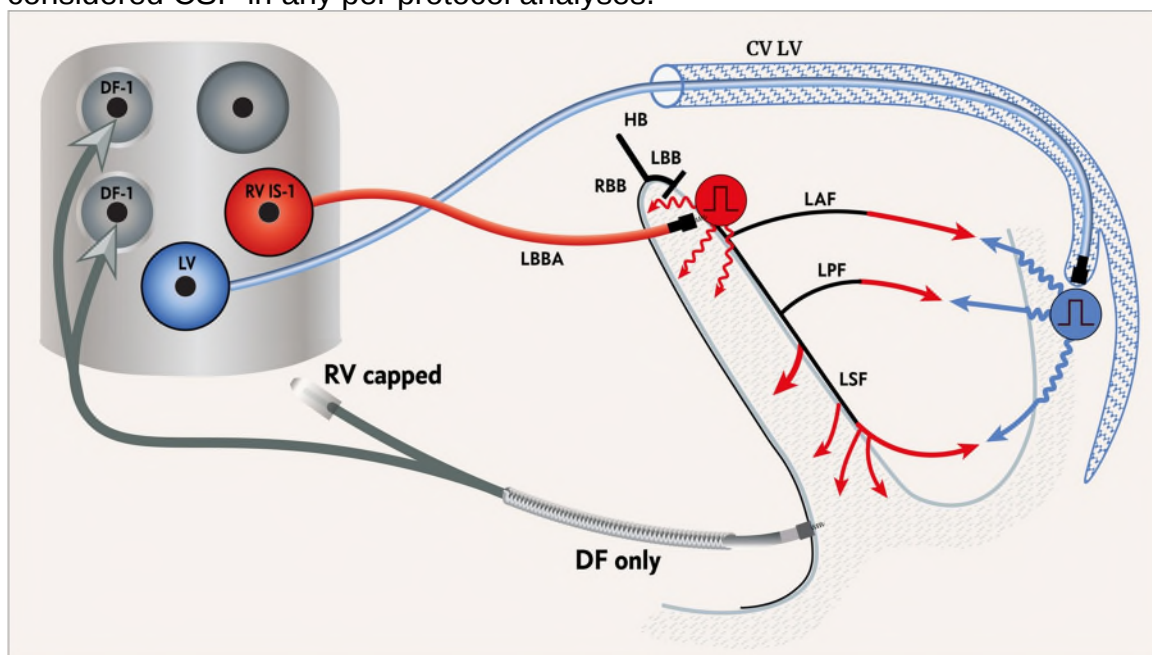


Figure 3 (above) Schematic of configuration of device capable of CSP +/- LOT-CRT + defibrillation². Those patients receiving CSP alone (i.e. without coronary sinus lead) who also have an indication for a defibrillator we will connect the CSP lead (red) to the RV IS-1 port of a CRT-D generator. These patients can receive DF-4 defibrillator leads (grey). For those patients receiving LOT/HOT-CRT, who also have an indication for a defibrillator we will connect DF-1 defibrillator lead to the defibrillator port of the generator, with the pace-sense branch capped and buried. The coronary sinus left ventricular lead will be connected to the LV port of the generator. Patients will be made aware, during the consent process, that these configurations render their system MRI non-conditional.

Once the device has been implanted, several measurements will be taken before the procedure has been completed.

- ECGi derived measures of left ventricular activation and repolarisation following a specified programmed stimulation protocol with varying coupling intervals (measurements detailed in **Appendix 11.2** and pacing protocol **Appendix 11.3**).

- Multiple blood-pressure measurements using a Finometer (a small blood pressure cuff attached to fingertips +/- an invasive measurement with a catheter in the radial artery).
- UHF-ECG

Whilst the research team member taking the measurements will be unblinded to the modality of the CRT device to undertake the pacing manoeuvres required, all data will be anonymised to the research team member for the analysis – thus protecting the blinding.

On all devices, atrio-ventricular delay will be set as per local optimisation protocol.

Immediate post procedure recovery, routine post procedure checks and blinding testing will take place on the cardiac day ward, before discharge home which should take place the same day.

2.3.3 Visit 3 – Post Implant Check and Interim HF Assessment

Patients will attend the pacing clinic at 12 weeks for their routine post-implant check. All patients will repeat all their assessments specified in Visit 1 – with identical blinding of research team members. At this point, they will be fitted with a 12-lead 24-hour Holter monitor which they will wear for 24-hours and bring with them for their 6-month follow-up at Visit 4. Serum BNP, 12-lead ECG and TTE will not be repeated if they have been performed within the normal clinical care <2 weeks before Visit 3.

2.3.4 Visit 4 – Follow-up ECGi and HF Assessments and Unblinding

After 6 months of pacing in the allocated modality, patients will attend the pacing clinic as part of the routine care for patients receiving CRT at Hammersmith Hospital. Patients will undergo routine pacing checks, alongside research outcome assessments. Patients will repeat all their heart failure assessments specified in Visit 1. Serum BNP, 12-lead ECG and TTE will not be repeated if they have been performed within the normal clinical care <2 weeks before Visit 4.

A repeat low-dose CT chest and ECGi assessment of activation and repolarisation will be done. Patients will cease symptom recordings via the NATURE-DCM ORBITA application at Visit 4 and delete the application at this point. Patients will have their blinding re-assessed before unblinding as to which treatment arm they have received. Further device programming decisions will be made on solely clinical grounds as per contemporary guidelines.

2.3.5 Ongoing Remote Follow-Up

All patients will then undergo remote follow-up of device parameters, heart failure status, arrhythmia status and mortality status via inspection of electronic health records until the end of the study period (maximum 3 years total). If this information is not available, patients will be telephoned every 6-months to collect this data or ask permission to speak to care providers who will have access to this (e.g. local pacing clinics). The end of the study period will be defined by as when the last patient undergoes their final visit.

2.3.6 Burdens & Risks

The main burdens for patients are:

- Visit 1 for returning of consent and baseline measurements will add a hospital visit compared to usual clinical care (65 minutes plus travel).
- No increase to the length of time of the visit to hospital for device implant beyond normal clinical care. Research measurements will be taken during the mandated pre/post implant time in hospital.
- Time taken for research measurements at Visits 3 (60 minutes) and 4 (100 minutes)
- Patients with defibrillator indications and randomised to LBBP and LOT-CRT will be fitted with a device configuration (see **Figure 3**) which will require specialised approval before MRI scans. This support will be provided by the pacing and cardiac imaging teams at Imperial College Healthcare NHS trust as required.

The main risks for the patients are:

- Radiation: The two low-dose CT scans required for the ECGi measurements will mean an increased dose of ionising radiation compared to usual clinical care. This increased radiation can increase patient's the risk of developing cancer by 0.03% (normal lifetime risk of approximately 50%).
- Arterial access for invasive blood pressure monitoring carries a small (<1%) risk of bleeding, bruising, pain or vascular injury. This will be reduced by it being performed by trained individuals using well established and safe protocolised techniques and specialist equipment.
- Conduction system lead implantation is not known to have a higher complication rate compared to a conventional pacing lead. Conduction system pacing leads have been shown to be as effective as conventional pacing wires at preventing slow heart rates and improving heart pumping. If a complication occurs and the conduction system pacing wire cannot be implanted or does not perform as expected during follow-up a procedure will be performed to convert your pacing system to a conventional pacing system.

2.3.7 Confidentiality of Records

All identifiable information will be securely held in NHS Trust computers and there will be held in strict compliance to NHS Data Protection and Confidentiality regulation. Identifiable patient data will only be stored at Imperial College Healthcare NHS Trust computers. Only pseudonymised data will be stored at Imperial College London computer. Participants will be assigned a unique number to further ensure confidentiality of patient identity. The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act. All data will be analysed pseudonymously.

2.3.8 Conflicts of Interests

None.

2.3.9 Dissemination of Results

The results will be disseminated to the scientific community through peer reviewed journal publications, internal reporting, publication on website and conference

presentations. Identifiable information will not be included in the publication. Depending on patient's preference we will either write, telephone or arrange to meet participants after the analysis has been completed. We will summarise the findings and details of how the results are relevant to them.

2.3.10 Study Outcome Measures

Primary

- Daily ordinal symptom scale with clinical over-rides to 6-months:
 - 1) Death
 - 2) Intractable symptoms leading to trial exit/unblinding
 - 3) HF hospitalisation
 - 4) Non-HF hospitalisation
 - 5) Appropriate ICD therapy (ATP or shock, deemed appropriate as per clinical care team interrogating device)
 - 6) Symptom score

Primary arrhythmia outcome

- Ordinal arrhythmia scale at 6-months:
 - 1) Death
 - 2) Appropriate ICD therapy
 - 3) Sustained ventricular arrhythmia (VA) (>30s of rhythm determined to be ventricular in origin by clinical team on device interrogation)
 - 4) Sustained atrial arrhythmia
 - 5) Non-sustained VA
 - 6) >10% ventricular ectopy on 24h ECG

Primary contractility outcome

- Ordinal mechanistic scale at 6-months:
 - 1) Death
 - 2) Intractable symptoms leading to trial exclusion/unblinding
 - 3) HF hospitalisation
 - 4) Non-HF hospitalisation
 - 5) LVEF

Secondary

- Each individual endpoint in composite outcome in isolation
- Change in repolarisation heterogeneity from baseline to 6-months (Δ LVRT ms, Δ LVRG ms/mm): Using non-invasive electrical mapping via ECGi (CardioINSIGHT™ software, body surface potentials and anatomical data from low dose CT scan are combined to produce epicardial electrograms).
- Change in ECGi activation parameters (Δ ARI, Δ LVAT)
- Repolarisation parameters from surface ECG via 24h digital Holter (at 6-month follow-up): QT dispersion.
- Change in heart failure measures (from implant to 6-month): left ventricular end diastolic volume and left ventricular end systolic volume (TTE), 6 minute-walk test, serum BNP, HeartQoL, Kansas City Cardiomyopathy Questionnaire 12 (KCCQ-12), MLWHFQ, NYHA classification
- Device measures (at 6-months): Patient activity levels, AF burden, thoracic impedance.

- Blinding index.
- Safety endpoints: Device infections (requiring device extraction), pacing thresholds, need for lead revision or reimplantation, generator change, haematoma and pneumothorax.

3 Participant Entry

3.1 Pre-registration Evaluations

- 12-lead ECG
- TTE
- Clinical review with NYHA symptom classification

3.2 Inclusion Criteria

Patients referred/scheduled for a CRT procedure (new implant or upgrade) who have:

- Symptomatic heart failure (NYHA II-IV)
- Reduced ejection fraction (LVEF $\leq$ 40%)
- Prolonged QRS duration ($\geq$ 130ms) and left bundle branch block ECG morphology or very prolonged QRS duration ($>$ 150ms) and non-left bundle branch block ECG
- Optimal medical therapy for HF

3.3 Exclusion Criteria

- Unable to provide informed consent
- $<$ 18 years old
- Pregnant patients (with female patients of childbearing age requiring a negative urine BHCG)

3.4 Withdrawal Criteria

The research protocol will be terminated early if:

1. Patients lose their capacity to consent or become clinically unstable
2. The patient chooses to withdraw from the study
3. The sponsor, the chief investigator or the research team review the data and decide to stop the study

3.5 Consent

Patients will be identified by members of their direct care team when they attend clinic appointments or are admitted as an inpatient to the hospital. Patient records may be reviewed to assess suitability, and this will be performed by members of the direct care team. Participation in the study will be discussed with the patients by their direct care team and information will only be passed on to the research team with the patients consent. Verbal consent will be gained by the direct care team for personal contact information to be shared with the research team. This will be documented in the patient notes.

The direct care team will make patients aware that participation is voluntary and that if they do not wish to participate it will not affect their usual care.

Consent for the study of the prospectively recruited patients will be obtained by a member of the research team; this will be a physician who is experienced in performing conduction system implantation. Patients will have details of the study discussed with them and any family members or friends the patients wish to be present. They will also be provided with written information (patient information sheets). Patients will be given as much time as they wish, with a minimum of at least 24 hours, to decide whether they wish to participate in the study and will be offered additional visits to further discuss the study if they wish. Patients can withdraw their consent from the study at any time. Patients will be made aware that their participation is voluntary and that if they do not want to take part it will not affect their usual care. Patients who agree to take part in the study will sign a consent form, a copy of the form will be given to the patients, and a second copy will be kept in their study record file. A copy will also be kept in the site file.

4 Adverse Events

4.1 Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject 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*
- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

4.2 Reporting Procedures

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

4.3.1 Non-Serious AEs

All such events, whether expected or not, should be recorded.

4.3.2 Serious AEs

An SAE form should be completed and faxed to the Chief Investigator within 24 hours. However, hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the GM South REC (reference 25/NW/0269, IRAS 342311) where in the opinion of the Chief Investigator, the event was:

- 'related', i.e. resulted from the administration of any of the research procedures; and
- 'unexpected', i.e. an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all related and unexpected SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs

RGIT@imperial.ac.uk

Prof Zachary Whinnett email: z.whinnett@imperial.ac.uk

Please send SAE forms to: Hammersmith Hospital, Du Cane road, London W12
OHS. Tel: 020 8383 4967 (Mon to Fri 09.00 – 17.00)

5 Assessment & Follow-Up

Please refer to section 2.2 for study follow-up details.

Incidental findings identified on any of the investigations undertaken as part of the study will be reported to either the clinical secondary care team responsible or the patient's primary care giver (i.e. general practitioner) depending on the urgency of the finding as per radiology report or judgement from clinical research team member.

6 Statistics & Data Analysis

6.1 Sample size calculation

Sample size calculations have been performed by the study's statistician based on the expected change between groups on the symptom application score. This has been informed by data using similar tools from the ORBITA-2, OBRITA-COSMIC and EMORI-HCM trials and pilot feasibility work using the NATURE-DCM ORBITA application. Based on this, 20 vs 20 two group comparison would be expected to show a significant difference.

6.2 Statistical Analyses

The primary outcomes of the primary ordinal symptom scale with clinical overrides will be analysed within a Bayesian framework using a first order Markov model (Markov Ordinal State Transition [MOST] model). Other outcomes assessed at a

single follow-up timepoint will be assessed using either ordinal models or generalised pairwise comparisons as will be detailed in the statistical analysis plan.

7 Regulatory Issues

7.1 Ethical Approval

The Study Coordination Centre has obtained approval from the “GM South REC” and Health Research Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

7.2 Consent

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered, and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study, the clinician remains free to give alternative treatment to that specified in the protocol at any stage if the clinician feels it is in the participant’s best interest, but the reasons for doing so should be recorded. In these cases, the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

7.3 Confidentiality

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act. Data will be pseudonymised.

7.4 Indemnity

Imperial College London hold negligent harm and non-negligent harm insurance policies which apply to this study.

7.5 Sponsor

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

7.6 Funding

This study is funded by the British Heart Foundation (grant: FS/CRTF/25/24768).

7.7 Audits

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Framework for Health and Social Care Research

8 Study Management

The day-to-day management of the study will be co-ordinated by Dr Jack Samways.

9 Publication Policy

Our aim to publish in a major international cardiology journal and present at international cardiology conferences.

10 References

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11 Appendices

11.1 'NATURE-DCM ORBITA' symptom recording smart-phone application

We have developed our own smart-phone application for bespoke heart failure symptom reporting. This is an adapted application, from the angina focussed application used in previous ORBITA studies³.

Owing to the varied and non-specific nature of heart failure symptoms, the on-boarding process will ask patients to identify the single symptom that they identify most closely with their heart failure. The patient will then be asked to access the application on a daily basis where they will be asked 1) If their symptom limited them when performing their daily activities over the previous day 2) to grade the severity of this symptom over this day on a sliding scale (between 'not limited at all' and 'extremely limited' with points 0-600).

On a weekly basis, patients will be asked a single anchoring question to determine whether they feel their symptom has improved, deteriorated or stayed the same compared to the previous week (to allow for validation of the continuum derived symptom scoring).

The on-boarding and training process will be undertaken in person with a research team member at Visit 1 (see screenshots below). Once trained, patients will be asked to start recording data immediately after Visit 1. This will allow for a period of baseline data between recruitment and device implant. After implant, patients will be asked to continue inputting daily for 6 months whilst undergoing the allocated modality of CRT.

This process has been developed and honed from a series of preliminary observations and questionnaires undertaken on heart failure patients attending either pacing clinic with an existing CRT device or heart failure outpatient service as part of a Patient and Public Involvement and Engagement. Part of these observations included, small comparison studies, assessing patient's engagement in the application with and without prompts from the research team.

The application will be used solely as a research tool. Responses from patients will not be made available to the clinical teams and will not guide care.

The smartphone application is only available in the English language. The smartphone application was intentionally designed to be very simple. An ethnically and gender diverse patient focus group with lived experience of cardiovascular disease assisted in the design of the smartphone application. Whilst we expect most patients will be able to read, write and speak English, there may be a minority who cannot. These patients will be asked to be assisted by a contact who can translate. If patients do not have a contact who can offer this help, a blinded member of the research team will arrange daily data entry using a translator service.

Patients will have 24/7 access to a blinded member of the trial team for any queries about the smartphone application.

11.2 ECGi Measurements

ECGi is a validated method for converting surface ECG data to epicardial electrograms by combining surface electrode positions with cardiac anatomy acquired through low dose CT scans⁴⁻⁶. The CardioInsight system applies a mathematical solution to the inverse problem to reconstruct the epicardial waveforms (**Figure 4**). ECGi has been validated for spatio-temporal annotation of both activation and repolarisation⁷. The steepest negative QRS slope ($-dV/dt \text{ max}$) is annotated as local activation. The Wyatt method is used to annotate repolarisation time as the most positive T wave slope ($+dV/dt \text{ max}$)⁸. Our group has developed custom software for measuring and visualising both activation synchrony⁹ and repolarisation heterogeneity¹⁰ as well as activation recovery interval (ARI, the time from activation to repolarisation on each waveform) dispersion¹¹. Furthermore, epicardial propagation mapping allows non-invasive discrimination of left bundle recruitment from myocardial only capture^{12,13}. Finally, we have developed a method for measuring local repolarisation gradients in ms/mm by comparing neighbouring electrograms¹⁰.

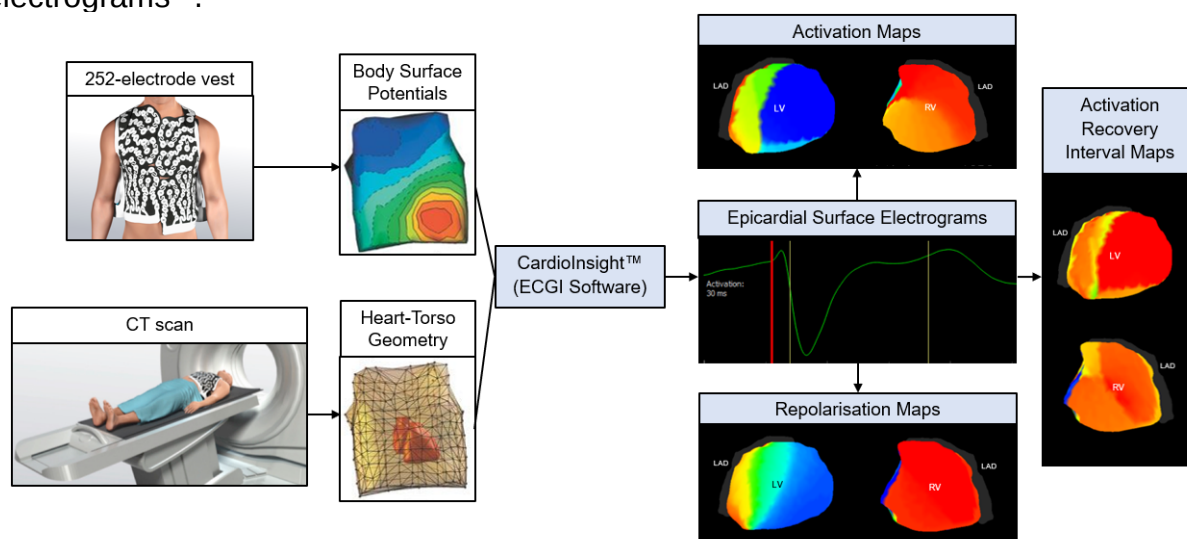
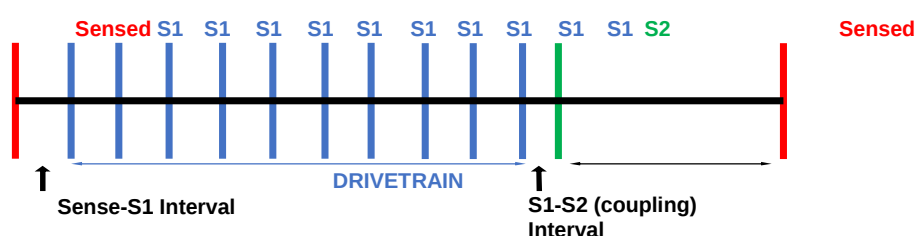


Figure 4 (above) Non-invasive Electrical Mapping Using ECGi: A 252-electrode vest is applied producing body surface potentials. A computed tomography scan shows heart contours and surface electrode positions. These are combined mathematically, producing epicardial electrograms, maps of activation, repolarisation and activation-recovery interval.

The primary ECGi measurements for our study are (i) the difference in left ventricular repolarisation time (LVRT) at 6-month follow-up between LBBP, LOT-CRT and BVP, (ii) the change in LVRT from baseline to 6-month follow-up in each arm and (iii) left ventricular repolarisation gradient (LVRG) for (i) and (ii). LVRT is the 95% central time from earliest to latest repolarisation on the LV measuring overall repolarisation heterogeneity. LVRG is the 95% centile of local repolarisation gradient steepness, measuring peak repolarisation heterogeneity. Secondary analyses will include LVRT and LVRG comparison between other configurations, whole heart repolarisation measures (VRT - ventricular repolarisation time, VRG – ventricular repolarisation gradient), ARI dispersion measurements and visual analysis of repolarisation patterns.

11.3 Programmed Heart Rate Variation Protocol

For each pacing configuration, I will perform a programmed stimulation protocol to vary coupling interval. By recording continuous ECGi, I will assess restitution effects on repolarisation heterogeneity for each modality. Arrhythmogenesis often requires both arrhythmogenic substrate *and* a triggering change in coupling interval. The change in heart rate itself affects the arrhythmogenicity of the substrate. 'Restitution' describes the impact of coupling interval on action potential duration. In other words: the effect of sudden heart rate change on repolarisation. I will plot repolarisation heterogeneity (LVRT) and activation-recovery interval dispersion (ARI) against coupling interval to determine the impact of pacing modalities on peak restitution slope (steepest gradient of the repolarisation-dispersion – coupling-interval relationship: where greatest repolarisation dynamism occurs in response to fixed heart rate changes).



Schematic of a ten-beat 'drivetrain' of paced beats at identical coupling intervals (drive cycle length, DCL – S1) will be delivered. This will be at 600ms S1. The eleventh beat will be delivered at a shorter coupling interval (S2); starting at 400ms. This eleven-beat sequence will be repeated with shorter S2 (in 10ms intervals) until the S2 stimulation does not capture. This entire process will be repeated three times for each pacing modality for reproducibility assessment.

11.4 Blinding Index Assessment

Whilst measures will be taken in each step of the protocol to prevent unblinding of patients, clinical care givers and researchers measuring outcome assessments and analysing data, we will assess for accidental unblinding.

Each caregiver who has had contact with the patient outside of the catheter will be asked to guess the treatment arm at the point of discharge from the implant visit.

Each caregiver or research team member who has contact with a patient will be asked to guess the treatment allocation before any follow-up visits

Patients will be asked to guess one of the following options:

- 1) Biventricular pacemaker (BVP)
- 2) Conduction system pacemaker (CSP)
- 3) Left-bundle optimised cardiac resynchronisation therapy (LOT-CRT)
- 4) Don't know

A follow-up question will be to grade their state of certainty (1-5) with 5 being most certain.

Statistical analysis of the blinding index will be performed using previously described methods.