Imperial College London

Clinical Trial Protocol

PROTECTUP

Physiological vs **R**ight ventricular pacing **O**utcome **T**rial **E**valuated for Brady**C**ardia **T**reatment **Up**grades

Version 5.0

SPONSOR: Imperial College London

FUNDER: Academic grant Heart Research UK

TRIAL COORDINATION CENTRE: Hammersmith Hospital London

NRES reference: NRES Committee Greater Manchester West

Clinicaltrials.gov reference: NCT06052475

Protocol authorised by:

Name & Role	Date	Signature
Daniel Keene (CI)		

Trial Management Group

Chief Investigator	Dr. Daniel Keene
Co-investigators:	Dr Nandita Kaza
	Dr. Matthew Shun-Shin
	Dr. Zachary Whinnett
	Professor Darrel Francis
Statistician	Professor Darrel Francis
Trial Manager	Miss Aya Khalil

Clinical Queries

Clinical queries should be directed to Dr Daniel Keene (d.keene@imperial.ac.uk)

Sponsor

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

Research Governance and Integrity Team
Imperial College London and Imperial College Healthcare NHS Trust
Room 215, Level 2, Medical School Building
Norfolk Place
London, W2 1PG
Tel: 0207 594 1862
Imperial College - Research Governance and Integrity Team (RGIT) Website

Funder

This Trial is funded by an academic grant from Heart Research UK.

This protocol describes the Trial ('Physiological vs Right ventricular pacing Outcome Trial Evaluated for bradyCardia Treatment Upgrades IRAS ID 323165) 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 trial. Problems relating to this trial should be referred to the Chief Investigator in the first instance.
This trial will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition).

It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

Imperial College London

Table of Contents:

TRIAL SUMMARY

TITLE	**P**hysiological vs **R**ight ventricular pacing **O**utcome **T**rial **E**valuated for brady**C**ardia **T**reatment Upgrades
DESIGN	It is a double-blind, randomized multi-centre trial. A total of 155 participants, considered for clinical pacemaker upgrade (placement of an additional pacing lead aiming to deliver more physiological ventricular activation; either within the coronary sinus (biventricular pacing) or at the Bundle of His or Left Bundle Area (Conduction System Pacing) undergo randomised crossover periods of 1 month and 6 months in either RV pacing (continued original pacing strategy) or with the more physiological pacing strategy. The crossover periods will enable assessment of the utility of clinically performed device upgrades.
AIMS	This trial will aim to study the utility of upgrading patients to physiological pacing from right ventricular (RV) pacing focusing on patients with mild or moderate impairment of cardiac function.
OUTCOME MEASURES	The primary outcome measure will be SF36 quality of life questionnaire physical component summary score
POPULATION	The trial will recruit 155 participants scheduled for clinical device upgrade either at the time of generator replacement or at any other timepoint.
ELIGIBILITY	Adults with an LVEF 35-50% AND >40% RV pacing AND at least one of the following: (1) EF reduced by >5% or increase in LVESV by 10ml since implant (2) NT-proBNP >250ng/L in sinus rhythm (3) NT-proBNP >750ng/L in Atrial Fibrillation (4) Left Atrial Volume index >30ml/m^2 (5) Regular loop diuretics prescribed (6) Decline in daily patient activity by >1hour per day since implant (7) Decrease in device measured thoracic impedance (8) Patient reported decline in functional class / exercise tolerance
DURATION	○ 18 months for patient recruitment ○ 15 month follow up period. ○ 3-month analysis and provisional reporting **Total duration: 36 months**

GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects
DSMB	Data Safety Monitoring Board
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HFrEF	Heart Failure with reduced Ejection Fraction
IB	Investigator's Brochure
IC	Informed Consent
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
LVEF	Left Ventricular Ejection Fraction
LBB	Left Bundle Branch
LBBB	Left Bundle Branch Block
LBBP	Left Bundle Branch Pacing
NYHA	New York Heart Association functional class
(S)AE	(Serious) Adverse Event
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a trial but does not commission it is not regarded as the sponsor but referred to as a subsidising party.
SUSAR	Suspected Unexpected Serious Adverse Reaction

KEYWORDS

Cardiac Resynchronisation

HIS Bundle Pacing

Left Bundle Branch Pacing

Device Upgrade

1. INTRODUCTION

1.1 BACKGROUND AND RATIONALE FOR CURRENT TRIAL

Today, patients who are scheduled to receive a pacemaker for the first time and are expected to have high burden of RV pacing (>20/40%), with any (i. e., mild, moderate, or severe) degree of LV impairment are guideline recommended to receive a physiological pacing strategy rather than RV pacing. RCTs, observational studies and meta-analysis data provide strong evidence that this improves patient symptoms, echocardiographic markers, morbidity and even mortality.

Patients with existing RV pacemakers, are frequently upgraded clinically using this same rationale, existing observational data sets and meta-analysis data that physiological pacing strategies are less damaging to cardiac function than ongoing RV pacing. RCTs currently though have only evaluated upgrade procedures in patients with severe LV impairment.

The trial aims to provide high-quality RCT evidence for upgrading patients to physiological pacing strategies for those patients with mild or moderate LV impairment. This represents a large patient cohort susceptible to morbidity and mortality from continued RV pacing. RV pacing saves lives in the short-term by preventing bradycardia but can lead to LV impairment in the longer term, increasing rates of heart failure and death. Two RCTs have demonstrated the harm of RV pacing.

In the DAVID trial, patients with an impaired LV were randomised to back-up pacing (minimising RV pacing), or obligatory RV pacing (maximising RV pacing). The group that received a high percentage of RV pacing had markedly higher rates of heart failure and death from 16.1% to 26.7% (HR 1.61). We have previously a meta-analysis of randomized controlled trials (RCTs) and observational studies assessing device upgrades. We analysed studies of biventricular (BiV) pacing (6 RCTs of 161 patients, and 46 observational studies of 2,795 patients) and Conduction system pacing (CSP) upgrades (7 studies of 197 patients) separately.11-68 RCTs of BiV pacing upgrade showed LVEF improvement of +8.4% from 34.4%, and observational studies showed LVEF improvement of +8.5% from 25.7%. Observational studies of CSP upgrade showed LVEF improvement of +11.2% from 38.4%. LVESV decreased significantly by -25.4mls, -23.7mls, and -19.8mls in BiV RCTs, BiV observational studies and CSP observational studies respectively. NYHA class improved by -

0.4, -0.8 and -1.0 respectively. RCTs of BiV pacing upgrade found improvements in Minnesota Heart Failure Score (-6.9 points) and peak oxygen uptake (+1.1ml/kg/min,). This was also seen in observational BiV upgrade studies (-19.7 points and +2.6ml/kg/min respectively).

2. TRIAL OBJECTIVES

We aim to test whether the positive effects of upgrading to physiological pacing strategies translate into benefit for patients with mild, or moderate impairment to their ventricles as a result of RV pacing.

We hypothesise that upgrade to physiological pacing strategies even when the extent of cardiac impairment is only mild or moderate will result in significant symptomatic and physiological benefit.

Primary Objectives:

This trial will evaluate, in patients with existing RV pacemakers and only mild or moderate LV impairment, whether clinically used modern physiological pacing strategies rather than continued RV pacing improve quality-of-life as measured by SF-36 questionnaire physical component summary score under double-blinded conditions?

Secondary Objectives:

1. In patients with RV pacemakers and existing mild to moderate LV impairment, what is the effect of modern physiological pacing strategies rather than continued RV pacing on:
    (a) Left ventricular ejection fraction.
    (b) Left ventricular end systolic index.
    (c) Quality of life questionnaires as measured by the Minnesota Living with Heart Failure Questionnaire, EQ5D5L and SF-36 questionnaire overall score.
    (d) Six-minute walk test
    (e) Atrial fibrillation
    (f) Patient preference based on blinded symptomatic preference
2. Is upgrading to physiological pacing more beneficial at time of generator change or at an earlier timepoint?
3. What are the complications associated with upgrade procedures?

3. TRIAL DESIGN

3.1 Trial protocol

Eligible patients will be those considered clinically for a device upgrade by their clinical team. Patients will be invited to participate in the trial before their planned clinical procedure.

All participants will undergo an upgrade procedure and receive either Conduction System Pacing (His or Left Bundle pacing) as first line approach or Biventricular Pacing if Conduction System Pacing cannot be delivered. An experienced operator will carry out the procedures.

Participants will be allocated in blinded random fashion to pacing periods using randomisation software (sealed envelope). They will be randomised to either having their 'physiological pacing strategy active OR continued RV pacing. Participants will undergo two one-month crossover periods and then two six-month crossover periods. Participants undergo the same evaluations at each visit.

At baseline and at the end of each period the participants will have the following assessed:

- Validated Quality-of-Life Questionnaire SF-36 questionnaire
- Minnesota Living with Heart Failure
- EQ5D5L questionnaires.
- 6-min walking test
- blood tests including NT-proBNP
- Echocardiography
- data collection regarding any heart failure hospitalisations
- medication list
- Pacing parameters: arrhythmia burden, pacing percentages, daily patient activity.

After the 2x 1-month periods and after the 2x 6-month periods, blinded patient preference will be asked on a 7-point preference scale. Again, at the end, they will be asked for their symptomatic preference. Participants will be invited to participate in the trial before their planned clinical investigation. Each participant will have a run-in period of 1 month, and then be followed-up at one-monthly intervals by a central trial hub followed by six-monthly intervals.

3.2 Trial End

The trial ends when the last enrolled trial participant completes their last follow-up at fifteen months following their upgrade date. The trial end date is defined as the date the last

participant's second 6-month period comes to an end and all the research procedures occurring at this timepoint are completed.

Any procedures occurring as part of the research study will be reviewed in the Imperial College Healthcare NHS Trust weekly multi-disciplinary team meeting, which includes a group of consultant cardiologists. Any complications resulting from these research procedures will be formally presented, evaluated and discussed within the MDT. If any concerning trends are identified as a result of these research procedures, a decision will be made to end the trial early.

3.3 Trial outcome measures

Primary outcome measure:

The primary outcome is quality-of-life as measured by SF-36 questionnaire physical component summary score under double-blinded conditions. It is mandatory for participants to complete the SF-36 questionnaire physical component summary score at baseline, months 1, 2, 8, and 14 for essential data points. Additional submissions between these periods are optional, providing participants flexibility for more frequent updates on their quality of life.

Secondary outcome measure:

1. In patients with RV pacemakers and existing mild to moderate LV impairment, what is the effect of modern physiological pacing strategies rather than continued RV pacing on:
    (a) Left ventricular ejection fraction.
    (b) Left ventricular end systolic index.
    (c) Quality of life questionnaires as measured by the Minnesota Living with Heart Failure Questionnaire, EQ5D5L and SF-36 questionnaire overall score.
    (d) Six-minute walk test
    (e) Atrial fibrillation
    (f) Patient preference based on blinded symptomatic preference.
2. Is upgrading to physiological pacing more beneficial at time of generator change or at an earlier timepoint?
3. What are the complications associated with upgrade procedures?

4. PARTICIPANT ENTRY

4.1 PRE-REGISTRATION EVALUATIONS

We will recruit patients who are referred for clinically indicated cardiac resynchronisation therapy upgrade.

PIC sites will identify patients meeting eligibility criteria with high burden RV pacing who are clinically indicated for an upgrade procedure. These patients will then undergo their upgrade procedure at ICHT - Hammersmith Hospital (as these PIC sites do not offer the conduction system pacing upgrade procedure).

4.2 INCLUSION CRITERIA

Adults with an RV pacemaker and LVEF 35-50% who are clinically indicated for an upgrade procedure plus any of the following:

- EF reduced by >5% or increase in LVESV by 10ml since implant.
- NT-proBNP >250ng/L in sinus rhythm
- NT-pro BNP>750ng/L if AF
- Left atrial volume index >30 mL/m^2
- Regular loop diuretics prescribed.
- Decline in daily patient activity by >1 hour per day since implant.
- Decrease in device measured thoracic impedance.
- Patient reported decline in functional class / exercise tolerance.

4.3 EXCLUSION CRITERIA

- Inability to provide informed consent.
- Aged under 18
- Pregnant women.

5. ADVERSE EVENTS

Any complications resulting from these research procedures will be formally presented, evaluated and discussed within the Imperial College Healthcare NHS Cardiology MDT. If any concerning trends are identified as a result of these research, a decision will be made to end the trial early.

5.1 DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical trial 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 require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

5.2 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.

5.2.1 Non-serious AEs

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

5.2.2 Serious AEs

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

All SAEs should be reported to the REC (NRES Committee Greater Manchester West) 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 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
Please send SAE forms to: d.keene@imperial.ac.uk
Tel: 020 7594 1093 (Mon to Fri 09.00 – 17.00)

6. ASSESSMENT AND FOLLOW UP

Post-procedure, the participant will be followed up by their clinical team. Pacing checks will be undertaken as per clinical protocol and standard of care. All patients pacing notes will be marked as indicating the patient is involved in a clinical trial and clinical team should not disclose to the patient the pacing period allocation.

At every timepoint for research follow-ups following the participant’s pacemaker upgrade i.e. at the 1-month, 2-months, 8-months and 14-month timepoint – we will collect:

- Validated Quality-of-Life Questionnaire SF-36, Minnesota Living with Heart Failure, and EQ5D5L questionnaires.
- 6-min walking test
- blood tests incl. NT-proBNP
- Echocardiography
- data collection regarding any heart failure hospitalisations
- medication list
- Pacing parameters: arrhythmia burden, pacing percentages, daily patient activity.

Patient’s Quality of life will be assessed monthly via the SF36 validated quality of life questionnaire and this will be done either electronically or via telephone, according to patient’s preference. Patient symptoms will also be assessed monthly via custom symptom

questionnaires (non-validated) in the one-month crossover periods and then monthly in the six-month crossover periods. Participants can choose whether to participate in monthly questionnaires, and it's entirely optional for those who are willing to take part in the monthly assessment.

Incidental findings identified as part of the research protocol will be reviewed and reported by trained clinical members of the research team. Any incidental findings identified will be communicated to the participant's clinical team as well as their GP as per standard protocol.

7. STATISTICS AND DATA ANALYSIS

7.1 Sample size calculations:

The sample size calculation for the PROTECT UP cross over RCT is as follows:
Assuming standard deviation of difference of sequential measurements of SF35 of 10 units, 136 patients (68 in each arm – on/off or off/on) would provide 80% power at the 5% significance threshold to detect a 3.5-unit difference in SF36 Physical Component Score between the upgraded physiological pacing strategy and standard of care RV pacing. To account to loss to follow-up of 12% we will recruit and randomise 155 patients. Patients will only be randomised after successful upgrade.

Our primary outcome will use the longest available comparable period, ideally the 6-month duration periods, but if participants have elected to withdraw because of overwhelming patient perceived blinded benefit/harm we will use their blinded QOL assessment from the longest available period. If participants wish to withdraw during a pacing period because of poor symptoms we will aim to perform endpoint assessment at that point in a blinded fashion and use that data.

7.2 Statistical Analysis:

Analysis will be performed according to the ITT principle and all statistical tests will be two-tailed with a 5% significance level.

The primary and secondary continuous secondary endpoints (SF-36 individual and global components, MLWHF, daily patient activity, LVEF, LVESI, 6-minute walk test and patient preference, BNP) will be analysed using a mixed-effect modelling approach, including the treatment and randomisation order as independent variables.

For time-to-event endpoints (death and hospitalisation for heart failure), the hazard ratio and respective 95% confidence interval will be computed using the Cox proportional hazards regression model, or appropriate alternative.

In secondary analysis the model will be adjusted for clinical important confounders that will be pre-specified in the statistical analysis plan. The underlying assumptions of any fitted model will be assessed as appropriate.

We will test the impact of relevant subgroups (time of upgrade (ERI vs Early upgrade), timing of improvement (one month vs 6 month) presence of AF, percentage pacing, BIV vs CSP pacing approach) by testing the interaction of these variables on the treatment.

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the trial, including the follow-up period.

8. REGULATORY ISSUES

8.1 ETHICS APPROVAL

The Trial Coordination Centre has obtained approval from the Greater Manchester West Research Ethics Committee (REC) and Health Research Authority (HRA). The trial must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the trial, or any research activity is carried out. The trial will be conducted per the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2 CONSENT

Consent to enter the trial must be sought from each participant only after a complete explanation, an information leaflet offered, and time allowed for consideration. Signed participant consent should be obtained. There will be no pre-specified window for consenting patients; patients can consent to take part in the trial up until the day of their procedure. The right of the participant to refuse to participate without giving reasons must be respected.

Patient consent for a referral to the research team and transfer of their data will be documented in patient notes.

After the participant has entered the trial, the clinician remains free to give alternative treatment to that specified in the protocol at any stage if they feel it is in the participant's best interest. Still, the reasons for doing so should be recorded. In these cases, the participants remain within the trial for follow-up and data analysis. All participants are free to withdraw from the protocol treatment at any time without giving reasons or prejudicing further treatment

8.3 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants participating in the trial and is registered under the Data Protection Act.

Data will be pseudonymised using a number code which can only be linked to personally identifiable information kept in a separate record. The code will replace all personally identifiable information in the primary records used for the trial.

8.4 INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies, which apply to this trial.

8.5 SPONSOR

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

8.6 FUNDING

The Trial is funded by an academic grant from the Heart Research UK Charity.

As we are requiring participants to attend hospital for reasons aside from their usual clinical care, we will be able to offer expenses for participant's travel and refreshments. All the trial visits will be undertaken at Imperial College London, Hammersmith Hospital. Neither the clinical team nor members of the research team will receive any financial incentives as a result of inviting participants to take part in this research.

8.7 AUDITS

The trial may be subject to inspection and audit by Imperial College London under their remit as the sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

An independent Data Monitoring Committee (DMC) will be set up to review data for safety and efficacy at regular intervals. The DMC will prepare a charter (in line with the DAMOCLES recommendations) outlining their responsibilities and reporting requirements.

An independent Data Monitoring Committee (DMC) will be set up to review data for safety and efficacy at regular intervals. The DMC will prepare a charter (in line with the DAMOCLES recommendations) outlining their responsibilities and reporting requirements.

9. TRIAL MANAGEMENT

The day-to-day management of the trial will be coordinated through Dr Daniel Keene (d.keene@imperial.ac.uk), Dr Nandita Kaza (n.kaza@imperial.ac.uk) and Aya Khalil (akhalil@ic.ac.uk).

10. PUBLICATION POLICY

We will seek to publish the trial's results in internal reports, scientific presentations and peer-reviewed scientific journals. The scientific team will make all analyses and decisions to publish and will not be influenced by the funder.