Solutions to the challenges of conduction system pacing

Version 6.1 29.09.2023

MAIN SPONSOR: Imperial College London
FUNDERS: British Heart Foundation
STUDY COORDINATION CENTRE: Dr Akriti Naraen
IRAS Project ID: 324395
REC reference: 23/WS/0122

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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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Imperial College - Research Governance and Integrity Team (RGIT) Website

Funder

This study will be funded by the British Heart Foundation.

This protocol describes the 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.

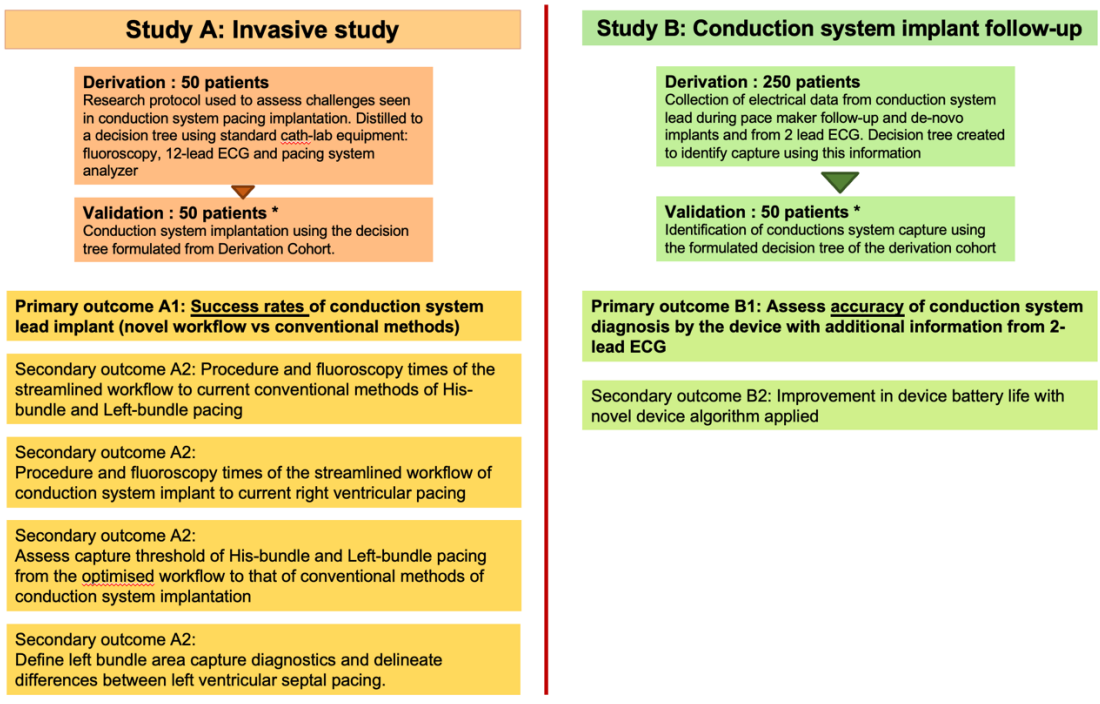
This study will adhere to the principles outlined in the **UK Policy Frame Work for Health and Social Care Research.** It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

Table of Contents

Glossary of Terms

CSP: Conduction system pacing
CT: Computed tomography
ECG: Electrocardiogram
EGM: Electrogram
HBP: His-bundle pacing
ICE: Intracardiac echocardiogram
LBBB: Left bundle branch block
LBP: Left bundle pacing
LBAP: Left bundle area pacing
LV: Left ventricle
LVAT: Left ventricular activation time
MRI: Magnetic resonance imaging
RV: Right ventricle
TOE: Transoesophageal echocardiogram
TTE: Transthoracic echocardiogram

Study Summary

TITLE	Solutions to the challenges of conduction system pacing
DESIGN	Cohort observational study and interventional at validation phase
AIMS	1. Provide a simplified standardised conduction system lead implantation protocol 2. Define capture diagnostics of left bundle pacing from left septal pacing
OUTCOME MEASURES	Primary Outcomes: A1: Success rates of conduction system lead implant (novel workflow vs conventional methods) B1: Assess accuracy of conduction system diagnosis by the device with additional information from 2-lead ECG Secondary Outcomes: A2: Procedure and fluoroscopy times of the streamlined workflow to current conventional methods *of His-bundle and Left-bundle pacing* A2: Procedure and fluoroscopy times of the streamlined workflow of conduction system implant to current *right ventricular pacing* A2: Assess capture threshold of His-bundle and Left-bundle pacing from the optimised workflow to that of conventional methods of conduction system implantation A2: Define left bundle area capture diagnostics and delineate differences between left ventricular septal pacing. B2: Improvement in device battery life with novel device algorithm applied  **Figure 1:** A illustration to demonstrate the primary and secondary outcomes of Study A and Study B. * Sample size calculations indicate 50 patients will provide >80% power (see Section 8, statistics and data analysis for more information)

POPULATION	Patients with any indication for a pacemaker
ELIGIBILITY	**Inclusion criteria:** 1. Indication for pacemaker implant **Exclusion criteria:** 5. Unable to give consent 5. Children age < 18 years or adults >100 years old 5. Pregnant patients
DURATION	3 years

1. Introduction

1.1 Background

Discovering how to clinically deliver conduction system pacing efficiently could be a paradigm shift. Early work on conduction system pacing focused on the His bundle, with right atrial mapping for the His signal and deployment of a lumenless pacing lead(1). Left bundle pacing (LBP) then emerged as an alternative, approaching via the basal right ventricular septum to deploy a lead through the septum to capture the left bundle on the left side of the septum(2,3)

Current literature report improved left ventricular function, heart failure outcomes and mortality in conduction system pacing(4,5). Additionally, LBP has a larger target area, can be done with low capture thresholds, has better threshold stability and large amplitude R waves(3). Widespread roll out of conduction system pacing clinically, however, faces three major challenges.

Challenge A1: Identifying target area for lead deployment
Despite growing adoption, conduction system pacing implants remains challenging**.** Even experienced device consultants take time to learn the technique. Experienced centres achieve implant success of 95%, but centres with new conduction system implanters (but highly experienced pacemaker implanters) have rates as low as 56%(6,7).

Fluoroscopic interpretation is challenging, for several reasons. The target area is smaller than conventional right ventricular pacing, and can be even smaller when there is fibrosis in the septum. The chambers may well be dilated, which displaces not only the fluoroscopic position of the target, but also its orientation. The lead can also be difficult to advance, because of septal fibrosis, unrecognised lead entanglement and unclear trans-septal trajectory. Interpretation of surface ECG and lead data is not straightforward either: there are many levels in the conduction system at which block can occur and it is difficult to distinguish them confidently. Lead entanglement and mal-orientation may be detectable with elaborate equipment such as intracardiac echocardiography (ICE) but we do not know what fluoroscopic or electrical features might provide routine clinical operators with a timely warning. Previous approaches to address these issues have involved normal-heart cadaveric studies which do not give the electrical context of a clinical implant(8).

Challenge A2: Defining left bundle area capture.
Although there are various expert consensus' in the diagnosis of left bundle capture, the capture diagnostics has yet to be validated. In view of the limitations of left bundle capture confirmation, it remains difficult to establish confidently if there is left conduction system capture rather than left ventricular septal capture only. Furthermore, it is unclear if there is a clinically relevant advantage to left conduction system capture to left ventricular septum capture. This requires further investigation.

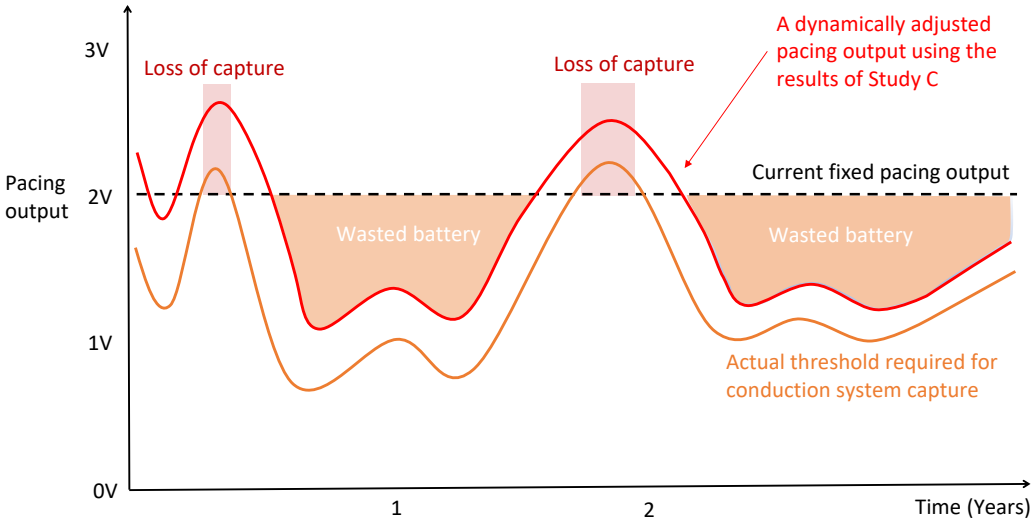
The paced activation patterns of the left ventricle during the lead deployment will be collected; at the left ventricular septal area (defined as more than half way beyond the septum) and the left bundle. At these points the electrical data from the pacing lead will be collected. The distal and proximal left bundle will be paced and restoration of physiological left ventricular activation will be assessed.

Challenge B: Reduced battery longevity due to high thresholds as result of limited conduction system capture discrimination by the device.
In conventional pacing, it is easy to describe to the device how to detect adequate capture, and therefore easy to have the device monitor adequacy of capture and adjust output to strike an efficient balance between ensuring capture and minimising energy consumption(9) (**Figure 1**). In conduction system pacing, we do not know how to check conduction system capture reliably using purely device-based information. Therefore, we cannot safely set the output to optimise battery life; instead, outputs are set unnecessarily high to ensure continued conduction system capture.

Checking correct capture is more difficult for conduction system pacing than conventional. It is not enough to detect capture: the device must confidently distinguish between several possible response patterns. Each patient may exhibit several patterns at different outputs. Misinterpreting the type of capture can cause harm. For example, in heart failure, if myocardium-only capture is mistakenly accepted as left bundle recruitment, patients would receive harmful right ventricular pacing rather than beneficial resynchronisation.

My aim is to develop an algorithm that can use the lead signals to reliably detect capture and classify the type of capture. I will augment the conventional lead signals with a 2 lead surface ECG from within the generator pocket. This may provide crucial additional information on type of capture.

Figure 2: Comparison of battery saving algorithms with fixed output



1.2 Original Hypothesis

Hypothesis A: A conduction system pacing protocol can be devised for use in any cath lab.
Hypothesis B: Lead data with a novel sensing vector can detect and categorise conduction system capture, which will allow automated conduction system capture discrimination on implanted devices.

1.3 Rational for Current Study

Currently conductions system pacing is undertaken by experts in tertiary centres with the support of specialised expensive equipment. However, most conventional pacemakers are implanted without this expertise and the advanced equipment. In order to facilitate a wider adoption of conduction system pacing a standardised and simplified implant protocol is required. Our study will devise a simplified, standardised conduction system implantation protocol in order to increase the access to the benefits seen in conduction system pacing.

2. Study Objectives

Primary Objective
The primary objective of this study is to simplify conduction system capture implantation thereby increasing accessibility of the procedure to more operators worldwide.

Secondary Objective
The secondary objectives will be

1. To reduce the overall procedure and fluoroscopy time with utilisation of targeted lead deployment.
2. Improve conduction system capture discrimination by the device and subsequently increase battery longevity, through development of a unique algorithm.

3. Recruitment

300 patients will be recruited to this study. 100 patients will be recruited to the invasive aspect of this study. These 100 patients will be divided into two-groups: patients 1-50 will be the derivation cohort and will undergo the tests in the derivation arms of Study A and Study B, patients 51-100 will be the validation cohort and will undergo the tests in the validation arms of Study A and Study B.

200 patients with a conduction system device in situ prior to commencement of this study, under pacing follow-up will also be recruited.

Invasive study recruitment
100 prospective patients with an indication for a pacemaker will be recruited from Imperial College Healthcare NHS trust. The direct care team will screen the records and identify patients that are suitable for the study. There will be two groups of patients:

1. Derivation cohort
These patients will undergo the research protocols of the studies. The data will be collated and analysed to develop our unique algorithms. This group will consist of the first fifty patients recruited (patients 1-50).

There will be three groups in this cohort

1. Group 1 (all 50 patient): These will undergo
    a. Preimplant: ECG, echocardiography, ultra-high frequency ECG and MRI
    b. Intra-implant: Right ventricular mapping, ultra-high frequency ECG and echocardiography
2. Group 2 (24 patients): These patients will undergo
    a. Preimplant: ECG, echocardiography, ultra-high frequency ECG, MRI
    b. Intra-implant: Right ventricular mapping, ultra-high frequency ECG, echocardiography **and ECGi**
3. Group 3 (15 patients): These patients will undergo
    a. Preimplant: ECG, echocardiography, ultra-high frequency ECG and MRI
    b. Intra-implant: Right ventricular mapping, ultra-high frequency ECG echocardiography and **arterial access for left ventricular mapping and invasive blood pressure monitoring**

2. Validation cohort

The step by step algorithms devised from the data collected from the derivation cohort to improve the conduction system lead implant will be prospectively applied on these patients and the outcomes will be assessed. This group will consist of the second fifty patients recruited (patients 51-100).

Conduction system implant follow-up recruitment

Prospective, pseudonymised electrical data from 200 patients with a chronic conduction system device in situ, that are under follow up will be collected. They will undergo the standard clinical pacing checks and manoeuvres.

The 100 prospectively recruited patients and the 200 patients with a chronic conduction system lead will undergo a consent process. The direct care team will obtain consent to share their information with the research care team. Once the patient has consented to their information being shared, a member of the research team will contact the patient and explain the details of the research study. Written consent will be gained prior to any procedures taking place.

Patients will be consented to take part in the ECGi (Derivation Cohort, Group 2), invasive blood-pressure monitoring and left ventricular mapping (Derivation cohort, Group 3) sub-studies at the time of recruitment, until recruitment target for these sub-studies are met.

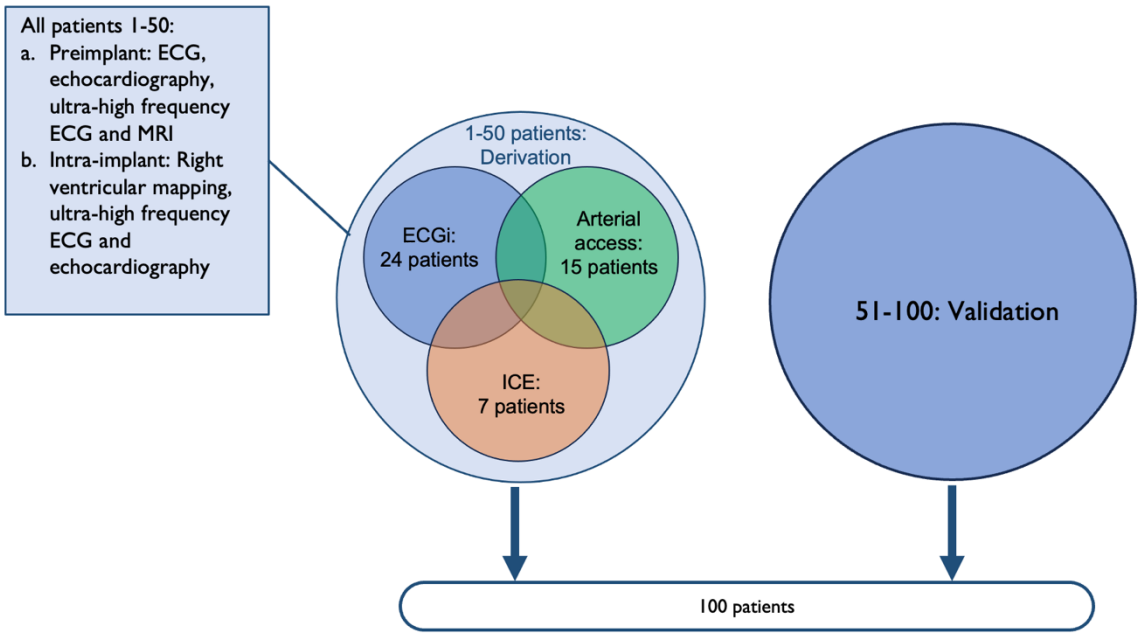


Figure 3: A diagram to illustrate patient recruitment for **Study A**. A total of 100 patients will be recruited. Patients 1-50 will be the derivation cohort and 51-100 will be the validation cohort. Within the derivation cohort, some patients will undergo ECGi, additional arterial access and intracardiac echo (ICE), some will undergo two of these additional tests, some will undergo one and some will not undergo any at all. All patients in the derivation cohort will undergo preimplant ECG, echocardiography, ultra-high frequency ECG (UHF ECG) and MRI, as well as right ventricular mapping, UHF ECG and echocardiography during the implant.

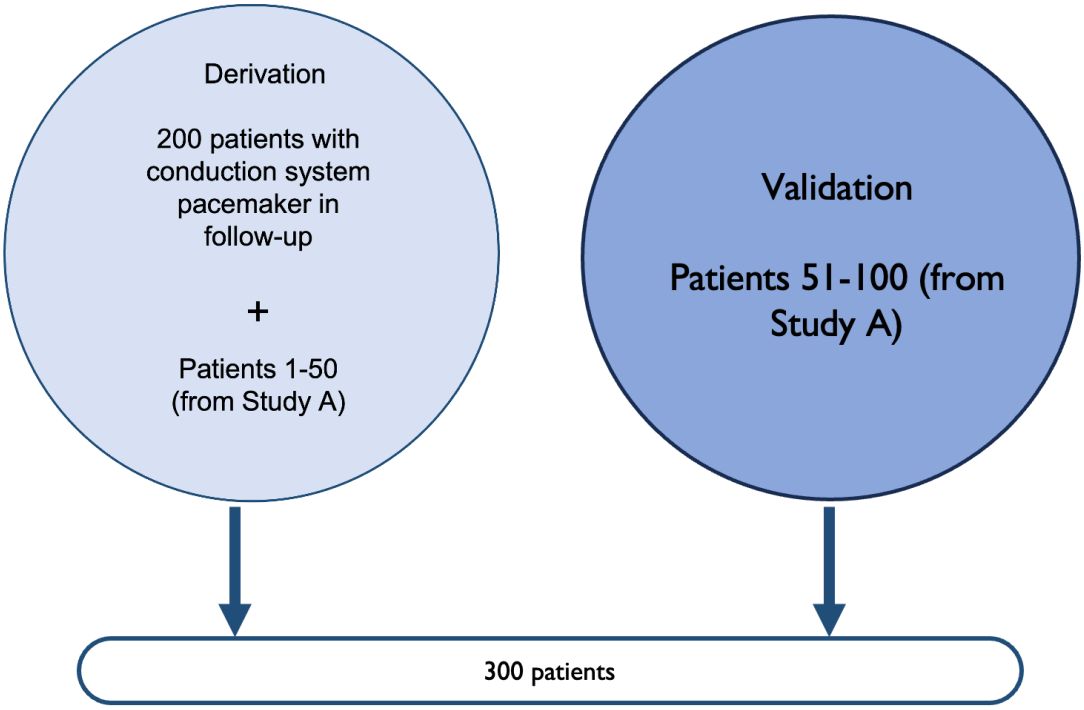


Figure 4: Recruitment of patients in Study B

4. Methodology

4.1 Derivation

Study A:
In Study A the derivation cohort will comprise of 50 prospectively recruited patients. These patients will undergo the research protocol. In these patients, we will attempt to implant a permanent conduction system pacing lead, in lieu of the RV or LV lead. The lead will be implanted by operators who have implanted more than 40 leads to overcome the learning curve.

The participants will undergo the following procedural steps after written informed consent is gained:

1. Pre-implant Cardiac MRI (Non-invasive)
   Patients will undergo cardiac MRI as part of their standard clinical care. As it is an MRI there will be no radiation exposure. Gadolinium contrast will be used to better define anatomy and to assess fibrosis.

2. Pre-implant 12-lead ECG
   Patients will undergo a surface 12-lead ECG as part of their standard clinical care.

3. Pre-implant echocardiogram
   Patients will undergo transthoracic echocardiogram as part of their standard clinical care.

4. Pre- and intra-procedural UHF-ECG (Non-invasive)
   UHF-ECG will be recorded with the aim of assessing the level of conduction system block (during intrinsic conduction) and to establish capture type and degree of correction of conduction system disease. This could potentially help in choosing between His-bundle pacing

and left bundle pacing. This is a non-invasive surface ECG, similar to a 12-lead ECG, that is collected over several heart beats.

5. ECGi (Non-invasive activation map)
   With pre-procedural CT
   A subgroup of patients will undergo non-invasive electrical mapping using a specialised vest with multiple electrodes called ECGi. The ECGi system involves a 252 electrode ECG vest to record activation of the entire heart in a single beat. Patients have a CT scan with the vest on, so the exact anatomical location of the electrodes relative to the heart can be determined. ECGi can provide electrical activation maps and can be used to calculate the left ventricular activation time (LVAT). This is an optional procedure and the patient can participate in the study without the ECGi map.

6. Electro-anatomical 3D mapping (Invasive)
   As standard, an infraclavicular incision will be made and access to the venous system gained.

   a. Right ventricular map

The mapping catheter will be passed into the right ventricle via a sheath through the same venous access site used for the pacemaker leads. Once the anatomical and electrical maps are collected of the right heart, the mapping catheter will be removed and the conduction lead will be placed in the same sheath.

We will then pace from multiple sites during the process of endocardial mapping. The lead will not be deployed at these sites. The lead tip will be in contact with the myocardium. This form of electrical pace mapping is standard clinical practice during pacemaker implantation. I will collect the electrical information from the lead, ECGs and EGMs at these sites in order to identify reliable hallmarks to guide lead deployment at the target site. Through this process I will identify areas of successful and unsuccessful implantation and areas to avoid lead deployment.

The anatomy maps will be correlated with fluoroscopy and cardiac MRI to characterise the appearance of the lead in relation to the the structures of the heart, not only within normal chamber dimensions but also abnormal chamber dimensions.

In the event of difficult lead implantation and lead deployment in unconventional areas, cardiac MRI will be used retrospectively to identify areas of septal fibrosis and variations in anatomy. The electrical hallmarks of fibrosis will be identified using EGM, lead parameters and 12-lead ECG.

   b. Left ventricular map

If the patients consent, 15 of the 50 participants will undergo left ventricular electro-anatomical mapping to assess ventricular activation patterns when a left bundle lead is deployed through the septum. The patients will have additional access from the right femoral artery in order to access the aortic circulation. The mapping catheter will be delivered to the left ventricle through a retrograde approach. The left ventricle will be mapped at two points of lead deployment

1. Lead in deep septum
2. Lead at left bundle

The lead will pace at each of these points of deployment and the activation maps will be collected.

Haemodynamic outcomes of left septal and left bundle pacing, using invasive and non-invasive blood pressure monitoring will be assessed. Invasive blood pressure will be collected from the femoral arterial access already obtained for the mapping catheter, where the sheath will be connected to a pressure inducer. Non-invasive blood pressure will be collected using a high precision beat by beat blood pressure cuff that is placed on the index finger (Finometer).

These patients will undergo additional consent in which the risks and benefits of the arterial access and the left ventricular maps will be explained. This is an optional procedure and the patient can participate in the study without undergoing a left ventricular map or invasive blood pressure monitoring.

5. Echocardiogram (Invasive and Non-invasive)
   During lead deployment we will visualise lead-septum interaction from echo and fluoroscopic imaging. Echocardiography directly visualises lead orientation, entanglement and progression. Characteristics of successful and unsuccessful deployment, lead progression and lead trajectory will be identified and how this is seen on fluoroscopy. The aim is to use this data to develop the algorithm to inform us whether deployment is progressing well or not well and if so, what is the reason for failure of lead progression.

   In a subgroup of patients, we will perform intracardiac echo to visualise the lead, if patients consent to this test. This will involve access from the right femoral vein for these patients. These patients will be additionally consented on implications and benefits of intracardiac echo to the procedure. This is an optional procedure and the patient can participate in the study without undergoing intracardiac echocardiogram.

   Those who do not undergo an intracardiac echocardiogram, will have their leads visualised by transthoracic echocardiography (if there are adequate windows) or paediatric transoesophageal echocardiography (TOE), which will eliminate the need for sedation. Participants undergoing TOE will have additional consent.

The right heart mapping will add 10 minutes to the overall procedure time. Left ventricular maps, will add a total of 14 minutes (7 minutes per map). The echocardiography will add 5 minutes to the overall procedure time which will include gaining additional access in ICE, visualisation of the lead and removal.

The aim is that the protocol we will develop will use information which can be acquired from the pacing lead, surface ECG and fluoroscopy without the need for pre-procedure MRI scans, electro-anatomical mapping or intra-procedure echocardiography (we will use these systems in our study to help develop and validate the algorithm in addition to understanding and correcting mechanisms of failure).

The ECG, lead parameters (seen on the pacing system analyser (PSA), a machine used to test the pacemaker leads) and fluoroscopic hallmarks of optimal initial deployment positions and optimal lead-septum interactions will be converted to a step-by-step guide for implanters without the need of specialised EP equipment, to achieve conduction system pacing in a systematic and reliable way. The diagnostic characteristics on 12-lead ECG and lead parameters will be analysed by software that can be integrated into the PSA.

<u>Study B:</u>
In patients 1-50 undergoing implantation of conduction system pacemakers, I will collect a 2-lead surface ECG alongside conventional lead data. A surface 12-lead ECG will be collected as well. The patients will undergo the standard pacing manoeuvres for conduction system pacing. The patient will be paced using the PSA and a 12-lead ECG and 2-lead ECG will be collected via Bard, a computer software that is able to collect highly accurate ECG traces of the heart using mapping catheters placed inside the heart and the surface ECG.

I will also collect prospective data from 200 patients with a chronic conduction system lead implant under device follow-up to obtain EGM, 12 -lead ECG and the 2-lead ECG recordings of multiple pacing and sensing configurations. These patients will be attending for routine appointments. The pacing and sensing configurations are undertaken as part of routine checks. The direct care team will identify the patients that are suitable and obtain consent for participating sharing their information with the research team. The research team will contact the patients and obtain informed written consent.

During the follow-up appointment, a member of the research team will apply the 2-lead ECG and the direct care team will perform the manoeuvres. The research team will collect data.

I will work with my team to develop algorithms to reduce the impact of local muscle noise. I will improve device diagnosis of conduction system capture using standard lead data, plus the 2-lead ECG. I expect this to be achievable by identifying EGM features that are highly discriminant and organising these into a systematic algorithm with a defined sensitivity and specificity for each capture type.

1.2 Validation

Study A:
A further 50 patients will be prospectively recruited that will make up the validation cohort for Study A. These patients will undergo a conduction system pacemaker as standard clinical practice. We will prospectively apply the step-by-step algorithm derived above to implant the conduction system lead using standard equipment alone; fluoroscopy, PSA and 12-lead ECG. We will assess the success rate, conduction system capture threshold, procedure time and fluoroscopy time. Although all operators will be highly experienced device implanters, these implants will include operators who are new to conduction system lead implantation.
The outcomes will be assessed against patients undergoing conventional methods of conduction system implantation (50 patients) and right ventricular pacing (50 patients).

Study B:
I will run the device algorithm to discriminate capture on patients 51 to 100. Through this I will establish my algorithm's accuracy with the addition of the 2-lead ECG against the gold-standard of combined 12-lead ECG, EGM and pacing manoeuvre diagnoses. These are standard clinical practices. I will test whether inclusion of the pocket EGM contributes to the algorithm's accuracy.

Follow-up
Patients will be followed up 6 weeks after device implantation and again at 1 year. These follow-up appointments will include a wound check at 6 weeks and device interrogation at 6 weeks and 1 year.

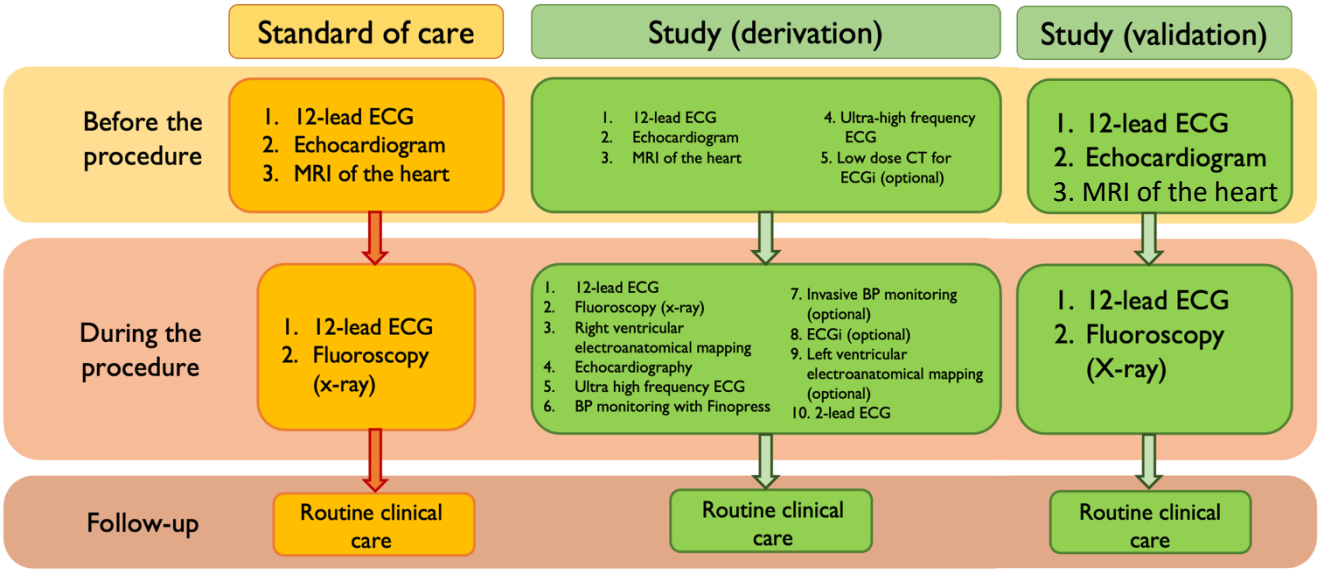


Figure 5: A flow diagram demonstrating the investigations the patient will undergo during the course of the Study A

1.3 Burden/Risk

The main burdens for the patient include:

1. The extra time taken to perform the experiments and experimental procedures during their scheduled clinical procedure due to the additional diagnostic investigations. The right heart electro-anatomical mapping will add 10 minutes. The echocardiography will add an additional 5 minutes. Those who consent to left ventricular maps will have an additional 14 minutes (7 minutes per map).
2. The extra access in the groin in those who consent to have an intracardiac echocardiography or left ventricular map (femoral vein and artery respectively).
3. The extra procedure of transoesophageal echocardiography in those who consent for this
4. Patients receiving unconventional therapy with conduction system lead implantation

The burden will be mitigated by the minimum extra time being used to complete the experiments, the use of local anaesthetic and the immediate removal of extra research related sheaths as soon as they are not needed

The main risks for the patient are:

A conduction system pacing wire is not known to have a higher complication rate compared to a conventional pacing wire. Conduction system pacing wires 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.

The additional risks of arterial tube placement include:

- 1% risk of bruising around the area
- 1 in 1000 risk of damage to the blood vessels requiring surgery
- Less than 1 in 500 risk of stroke

The additional risks of transoesophageal echocardiogram include

- 1% risk of damaging the food-pipe or wind-pipe including a 1 in 1000 risk of perforating the food-pipe.

The additional risks of intracardiac echocardiogram include

- 1% risk of bruising around the access area in the leg
- Less than 1 in 1000 risk of heart perforation

The additional risks of electro-anatomical mapping include

- Less than 1 in 1000 risk of heart perforation

Therefore, the overall risk of serious complications arising from taking part in the research study are less than 4 in 1000 (0.4%)

Participants in this study will have a chest CT scan which is not part of standard care. Pacemaker implantation involves exposure to ionising radiation to visualise lead implantation. Taking part in this study involves exposure to additional exposure to radiation above the standard clinical procedure due to the additional measurements that will be taken.

Ionising radiation can cause cell damage that may, after many years or decades, turn cancerous. We are all at risk of developing cancer during our lifetime. The normal risk is that this will happen to about 50% of people at some point in their life. Taking part in this study will increase the chances of this happening to you from 0.01% to 0.1%

1.4 Study Outcome Measures

Primary Outcome Measures

A1: Success rates of conduction system lead implant (novel workflow vs conventional methods)

B1: Assess accuracy of conduction system diagnosis by the device with additional information from 2-lead ECG

Secondary Outcome Measures

A2: Procedure and fluoroscopy times of the streamlined workflow to current conventional methods *of His-bundle and Left-bundle pacing*
A2: Procedure and fluoroscopy times of the streamlined workflow of conduction system implant to current *right ventricular pacing*
A2: Assess capture threshold of His-bundle and Left-bundle pacing from the optimised workflow to that of conventional methods of conduction system implantation
A2: Define left bundle area capture diagnostics and delineate differences between left ventricular septal pacing.
B2: Improvement in device battery life with novel device algorithm applied

5 Participant Entry

5.1 Pre-registration Evaluations

5.2 Inclusion Criteria

1. Patients with a ventricular pacing indication: high grade atrioventricular block and symptomatic trifasicular, bifasicular block or left bundle branch block LBBB for cardiac resynchronisation therapy
2. Adults willing to take part (ages 18 – 100 years old)
3. Able to give consent.

5.3 Exclusion Criteria

1. Unable to give consent
2. Children age < 18 years and adults > 100 years old
3. Pregnant patients
   As per standard of care, female patients of child-bearing age will have a urine pregnancy test prior to their procedure.

5.4 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

5.5 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 are able to 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.

6 Adverse events

6.1 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.

6.2 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.

6.3 Non serious AEs

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

6.4 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 West of Scotland (REC 4) where in the opinion of the Chief Investigator, the event was:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie 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
Dr Zachary Whinnett email: z.whinnett@imperial.ac.uk
Please send SAE forms to: Hammersmith Hospital, Du Cane road, London W12 0HS.
Tel: 020 8383 4967 (Mon to Fri 09.00 – 17.00)

7 Assessment and Follow-up

Patients will be followed up for a 1 year period. During this time they will undergo the device interrogation and wound check at 6 weeks as part of standard clinical care. One year after device implantation, patients will undergo a device interrogation follow-up appointment. Any incidental findings that we identify during the study will be reviewed by the research team and reported to the GP and also the cardiology team normally looking after the patient.

Definition of end of Study
The end of the study will be defined as completion of the 1 year follow-up of the 100 prospectively recruited patients for the invasive aspect of the study. This will be the date of the final visit of the last participant at 1 year.

8 Statistics and data analysis

The following statistical analysis has been reviewed and approved by our statistician, Prof. Darrel Francis.

In **Study A**, I want the validation cohort to be big enough to calculate the success rate percentage with an error margin (standard error) of <10 percentage points in line with primary outcome A1. Similarly, for **Study B**, I want the validation cohort to show the accuracy of my algorithm with an SE under 10 percentage points in line with primary outcome B1. The standard error of a proportion p, in a sample of n patients, is $\sqrt{[p(1-p)/n]}$, i.e. $n=p(1-p)/SE^2$. Applying SE=0.1 (worst-case proportion 0.5) reveals the bare-minimum n required is $0.5*0.5/0.1^2=25$. I will have 50, to ensure the SE <10 percentage points.

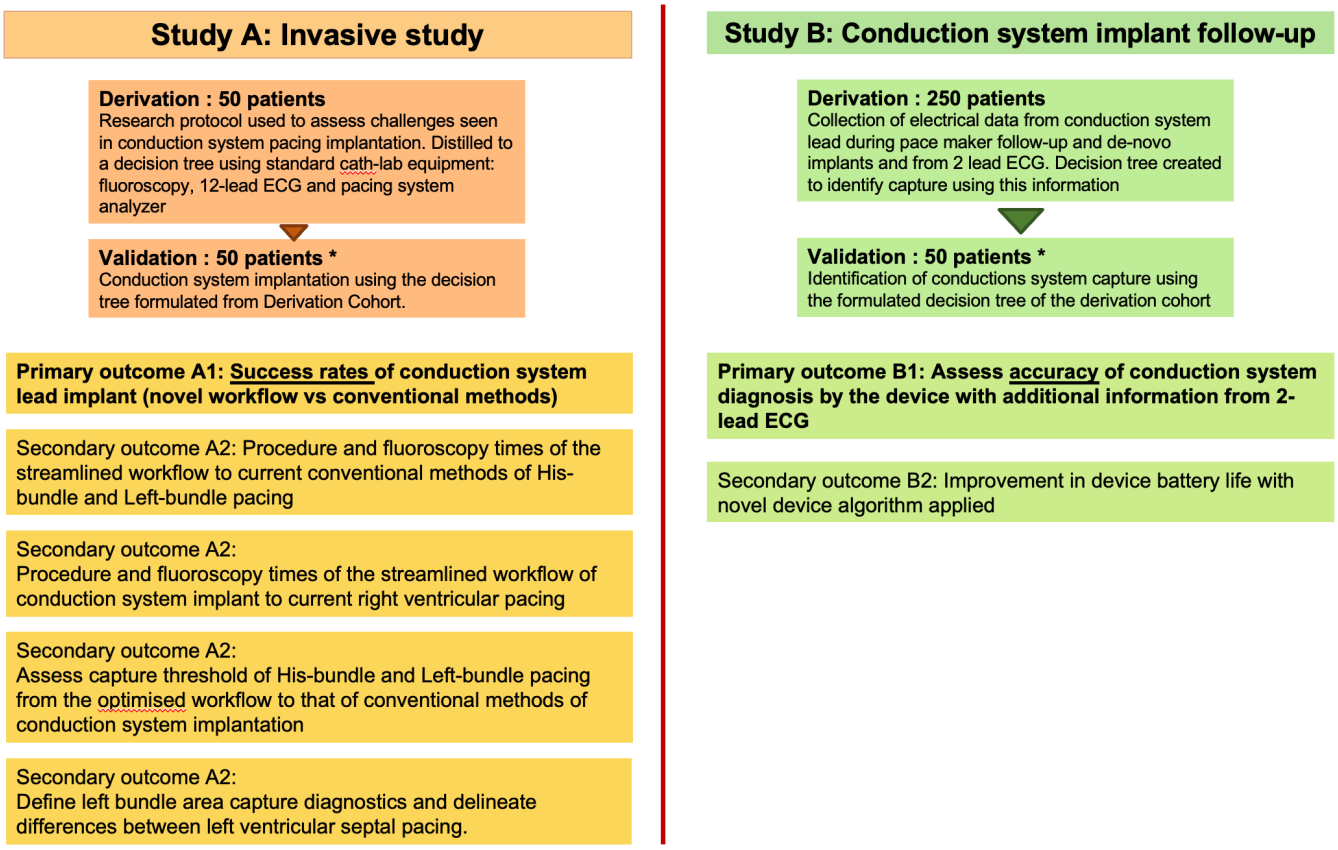


Figure 1: A illustration to demonstrate the primary and secondary outcomes of Study A and Study B. * Sample size calculations indicate 50 patients will provide >80% power (see Section 8, statistics and data analysis for more information)

9 Regulatory issues

9.1 Ethics approval

The Study Coordination Centre has obtained approval from the "Name of REC when allocated" 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.

9.2 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 he/she 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.

9.3 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.

9.4 Indemnity

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

9.5 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.

9.6 Funding

The British Heart Foundation.

9.7 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 Frame Work for Health and Social Care Research

10 Study Management

The day-to-day management of the study will be co-ordinated by Dr Akriti Naraen.

11 Publication Policy

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

12 Appendix

Table 1: Time consuming and complex criteria for conduction system capture. (1,11,12)

Intrinsic QRS	Degree of BBB correction	His Bundle Pacing	
		S-HPB	NS HBP
Normal QRS	Nil	Stim-QRS_{end} = H-QRS_{end} Paced QRSd = intrinsic QRSd Stim-vent = H-vent Single capture threshold	Stim-QRS_{end} < H-QRS_{end} +/- pseudodelta wave Paced QRSd > intrinsic QRSd Two distinct capture thresholds
LBBB	Full correction	Normal QRS appearance Stim-QRS_{end} < H-QRS_{end} Paced QRSd <120ms < intrinsic QRSd	Pre-excited normal QRS appearance Stim-QRS_{end} usually < H-QRS_{end} Paced QRSd > 120ms Paced QRSd usually < intrinsic QRSd
	Partial correction	LBBB morphology Stim-QRS_{end} < H-QRS_{end} Paced QRSd < instrinsic QRSd	LBBB QRS morphology Stim-QRS_{end} < / = H-QRS_{end} Paced QRSd >120ms Paced QRSd usually < intrinsic QRSd
	No correction	Stim-QRS_{end} = H-QRS_{end} LBBB morphology Paced QRSd = intrinsic QRSd	LBBB morphology Paced QRSd > intrinsic QRSd
	Myocardium only capture	LBBB morphology Stim QRSend usually > H-QRS_{end} Paced QRSd > intrinsic QRSd	
RBBB	Bundle recruitment	Normal QRS appearance Stim-QRS_{end} < H-QRS_{end} Paced QRSd < 120ms < intrinsic QRSd	Pre-excited normal QRS appearance Stim-QRS_{end} < H-QRS_{end} Paced QRSd </=/> intrinsic QRSd
	Resynchronisation	NS-HBP without right bundle recruitment Pre excited normal QRS appearance Stim-QRS_{end} < H-QRS_{end} /paced QRSd < intrinsic QRSd	
	No bundle recruitment or resynchronisation	S-HBP without right bundle recruitment RBBB morphology Stim-QRS_{end} = H-QRS_{end} /paced QRSd = intrinsic QRSd	
	Myocardium only capture	LBBB morphology Stim-QRS_{end} > H-QRS_{end} /paced QRSd >intrinsic QRSd	

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