TITLE PAGE

This protocol has regard for HRA guidance

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The Leeds Teaching Hospitals
NHS Trust

Study protocol

Title:	**OPTimising a screening program to detect pacemaker-associated heart failure using Artificial Intelligence (OPT-AI)**
Chief Investigator:	**Dr Sam Straw (s.straw@leeds.ac.uk; 0113 3928240)**
Sponsor:	**The University of Leeds**
Protocol version:	**1.1**
Date:	**05/09/2025**
IRAS number:	**347225**
Sponsor number:	**2025-NCT11**

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirements.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose than the evaluation or conduction of the investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator:

Signature: 

Date: 01/12/2024

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Name: (please print): Dr Sam Straw

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LIST OF CONTENTS

KEY STUDY CONTACTS

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STUDY SUMMARY

Study title:	OPTimising a screening program to detect pacemaker-associated heart failure using Artificial Intelligence (OPT-AI)
Study design:	Prospective, observational, pilot study
Study participants:	Patients with pacemakers for bradycardia.
Planned sample size:	150 participants.
Follow up duration:	Not applicable.
Planned study period:	July 2025-June 2026
Aims:	To determine whether new technologies can improve the detection of pacemaker-associated heart failure.

FUNDING

Leeds Hospitals Charity: Research and Innovation Funding.

ROLE OF STUDY SPONSOR AND FUNDER

The University, when acting as Sponsor assumes overall responsibility for the initiation and management of the study.

Neither Sponsor or the Funder have any role in the study design, data analysis and interpretation, manuscript writing, conduct, and dissemination of results, nor have final decision regarding any of these aspects of the study.

STUDY PROTOCOL
OPTimising a screening program to detect pacemaker-associated heart failure using Artificial Intelligence (OPT-AI)

1. BACKGROUND

1.1 PACEMAKERS FOR THE TREATMENT OF BRADYCARDIA

Permanent pacemaker implantation for the treatment of bradycardia (slow heart rates) improves quality of life and normalises life expectency.[1,2] Around 600,000 people undergo implantation of a pacemaker device each year, and there are around 3 million people currently living with pacemakers worldwide. Typical pacemaker devices for bradycardia consist of a generator implanted into a pre-pectoral pocket, with a lead in the right ventricular (RV) apex, with or without a second lead in the right atrial appendage. Usually, battery life is around 8-12 years, after which time a generator replacement is required.

1.2 RIGHT VENTRICULAR PACING AND HEART FAILURE

Although pacemakers can transform a patient's quality of life, there are some disadvantages. Compared with intrinsic electrical conduction, RV apical electrical stimulation results in electrical and mechanical dyssynchrony, leading to acute changes in LV performance, and over the long-term adverse left ventricular (LV) remodelling, progressive systolic dysfunction and, in some, the clinical syndrome of heart failure. Patients with pacemakers for bradycardia often have co-morbidities, such as ischaemic heart disease or hypertension which can make this problem more likely. Pacemaker-associated heart failure is the most common long-term complication of device implantation, however this is often unrecognised, and although certain patient characteristics make it more likely, it is not currently possible to identify individuals who might develop heart failure in the future.[3]

1.3 ALTERNATIVE STRATEGIES TO PREVENT HEART FAILURE

The burden of RV apical pacing is positively correlated with the risk of HF hospitalisation. RV pacing avoidance algorithms can reduce this burden ,[4] however, this is often unavoidable for patients with high-degree atrioventricular (AV) block.[5] Alternative strategies such as the implantation of devices capable of delivering biventricular pacing (cardiac resynchronisation therapy), septal or conduction system pacing are available. However, each had its own limitations including longer procedure times, premature lead failure, financial costs, the higher risk of upfront complications, and more fundamentally, that none of these strategies have not been proven to improve clinical outcomes.[6] The RV apical position continues to be far and away the most common site for ventricular lead implantation for patients implanted with pacemakers for bradycardia.

1.4 THE PACEMAKER CARE PATHWAY AND THE OPPORTUNITY TO INTERVENE

The implant procedure itself is only one aspect of the pacemaker pathway of care. Following implantation patients are required to have ongoing follow-up to assess device functionality and battery longevity. Standard practice is for patients to attend a clinic in person, even for those who now benefit from the provision of remote monitoring. Additionally, towards the end of a device's lifespan, patients are required to undergo a day case procedure to undergo generator replacement. Both of these offer the opportunity to assess for pacemaker-associated heart failure during a patient's routine hospital contact.

1.5 THE ROLE OF CARDIAC ULTRASOUND IN DIAGNOSIS AND CLASSIFYING HEART FAILURE

Cardiac ultrasound, or echocardiography, is fundamental to the diagnosis and management of heart failure. A diagnosis of heart failure requires assessment of cardiac structure and function, and although alternative imaging modalities are available, cardiac ultrasound is almost always the initial imaging modality used to make the diagnosis. Furthermore, heart failure is currently classified by left ventricular ejection fraction (LVEF) into heart failure with

reduced (HFrEF) or preserved ejection fraction (HFpEF). Optimal care for people with HFrEF now includes four classes of medications proven to reduce hospitalisation and mortality risk.[7] Each of these pharmacological therapies result in incremental benefits to patients, and guidelines now recommend these are initiated in parallel, as soon as possible following the discovery of heart failure.[8] This is unlike the situation in HFpEF, where these therapies have either proven neutral, or have resulted in marginal improvements to outcomes. An assessment of LVEF with echocardiography is therefore essential. Until recently the effect of these agents for pacemaker-associated heart failure was unknown, and most phase III clinical trials of medical therapy for HFrEF did not report the effect of these agents for patients with pacemakers. Additional strategies to improve outcomes include device 'upgrade' procedures, in which an additional LV lead is implanted to deliver biventricular pacing (cardiac resynchronisation therapy), with or without a defibrillator.

2. PILOT DATA

2.1 RIGHT VENTRICULAR PACING RESULTS IN IMMEDAITE ADVERSE EFFECTS ON LEFT VENTRICULAR FUNCTION, AND ADVERSE REMOLLING IN THE LONG-TERM

We performed a single-centre, observational study of patients previously implanted with pacemakers for bradycardia and used cardiac magnetic resonance (CMR) imaging to determine the immediate effects of RV pacing on LV systolic function. We recruited 84 patients with an LVEF ≥40% into two observational studies. In 34 patients with preserved atrio-ventricular conduction, we programmed two pacing modes to deliver asynchronous atrial pacing (with intrinsic conduction) or asynchronous dual chamber pacing (forced RV apical pacing) during CMR. In a second study, patients with high degree AV block underwent a CMR at baseline and then again after 6-months

2.2 SCREENING FOR AND TREATING HEART FAILURE IN PATIENTS WITH PACEMAKERS IMPROVES OUTCOMES

OPT-PACE (OPTimising PACEmaker therapy) was a multi-centre, randomised controlled trial enrolling people with pacemakers implanted for bradycardia. Participants were randomised 1:1 to echocardiography screening or usual care. For participants in the screening arm found to have LVSD (LVEF <50%), we then compared patients managed by their primary care physician with those managed in a combined heart failure and devices clinic. The primary outcome was the time to death or first hospitalisation due to heart failure. We randomized 1201 participants were randomised, 600 to echocardiography screening and 601 to usual care. Patients in the echocardiography screening arm who were managed within a combined heart failure and devices clinic had better optimisation of medical therapy for heart failure and were at around a third lower risk of the combined primary endpoint (hazard ratio 0.67 [0.46-0.98]).

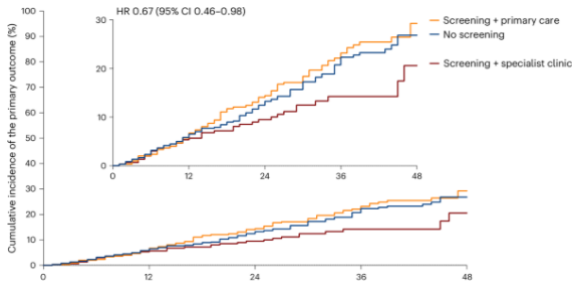

Figure: Screening for heart failure reduces the risk of all-cause mortality or heart failure hospitalization (Paton et al. *Nat Med*. 2024

2.3 SUMMARY AND LIMITATIONS OF THE AVAIABLE EVIDENCE

Pacemaker-associated heart failure with the most common long-term complication of pacemaker implantation. We now have robust evidence that show that echocardiography screening identifies heart failure in one third of patients attending routine pacemaker follow up, and that where this is identifies and then treated clinical outcomes are improved. However, this approach has limitations. First, an echocardiogram takes approximately 45 minutes to perform, analyse and report. Second, the technicians running the pacemaker clinics are not usually skilled in echocardiography. Third, each scan costs around £120, or approximately £540,000 to assess all 4,500 patients currently under the care of Leeds Teaching Hospitals Trust. A new approach is needed.

3. HYPOTHESIS

Artificial intelligence (AI) can detect pacemaker-associated heart failure with similar levels of accuracy compared to echocardiography.

4. RESEARCH QUESTION

4.1 PRIMARY RESEARCH AIM

To determine the accuracy of AI derived LVEF compared to standard cart-based echocardiography with left ventricular ejection fraction (LVEF - the percentage of blood pumped during each heart beat) measured by biplane method, assessed by correlation coefficient.

4.2 SECONDARY RESEARCH AIMS

To determine the accuracy of AI determined abnormal left ventricular ejection fraction (LVEF <50%) compared to standard cart-based echocardiography measurement of LVEF <50% by biplane method, determined by sensitivity, specificity, positive and negative predictive values.
To determine the incremental improvement of a model to predict LVEF <50% in a population with pacemakers of the addition of AI derived LVEF, point of care NT-proBNP, or both.
To determine the proportion of participants in whom it was not possible to determine AI derived LVEF, LVEF measured by biplane method, or subjective visual estimation of LVEF.

5. STUDY SETTING

We will recruit potential participants from those attending routine pacemaker clinic follow-up at the Leeds Teaching Hospitals NHS Trust. All study procedures will be undertaken at the Leeds National Institute for Health and Care Research Cardiovascular Clinical Research Facility (CRF). The Leeds Cardiovascular CRF has facilities and equipment available for echocardiography and pacemaker interrogation, as well as appropriately trained staff to conduct the study procedures.

6 IDENTIFICATION OF POTENTIAL PARTICIPANTS

6.1 ELIGIBILITY CRITERIA

We require patients to have standard pacemakers implanted for the management of bradycardia, and for at least 20% of heart beats to be paced (right ventricular pacing burden >20%) as these patients are at risk of developing pacemaker-associated heart failure. Patients with specialised types of pacemakers which reduce the risk of developing heart failure (conduction system pacemakers) or have been implanted for the management of known heart failure (cardiac resynchronisation therapy pacemakers/defibrillators, implantable cardioverter defibrillators) are not eligible for inclusion.

6.2 INCLUSION CRITERIA

Adult patients aged ≥18 years.
Patients with existing pacemakers who have a RV pacing burden ≥20%.
Ability to provide informed consent.

6.3 EXCLUSION CRITERIA

Patients who are unwilling or unable to provide informed consent.
Patients known to have heart failure
Patients with any previous measurement of LVEF <50%.
Patients with conduction system pacemakers.
Patients with cardiac resynchronisation therapy pacemakers/defibrillators.
Patients with implantable cardioverter defibrillators.
Patients with leadless pacemakers.

7 RECRUITMENT PROCESS

7.1 PARTICIPANT IDENTIFICATION

To make participation as simple as possible, and to avoid unnecessary visits to the hospital, patients will be approached prior to their routine pacemaker clinic appointment. Patients who

have pacemakers attend the hospital every 6-12 months in person to undergo a check of their pacemaker's battery life and functionality. All potential participants will be identified by a member the patient's direct care team according to the study inclusion criteria. Potential participants will be sent an Invitation Letter and the Patient Information Sheet, offering them the opportunity to attend an appointment in the Leeds Cardiovascular Clinical Research Facility instead of their usual pacemaker clinic appointment. This will then be followed up by a telephone call from the direct care team, and only those who are potentially interested and confirm their agreement to have their information passed to the research team will be approached to arrange an appointment.

7.2 CONSENT PROCESS

The Chief Investigator retains overall responsibility for the conduct of research at this site, this includes the receiving of informed consent of participants at the site. They must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, training and compete to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki.

On the day of the appointment, a member of the research team will approach the patient, explain the study and offer the opportunity to ask questions. Participants will have already had at least one week to read the Participant Information Sheet and to consider whether they wish to take part. If willing to participate, they will then provide written consent to undertake the study procedures. All patients, regardless of whether they consent to participate in the research study, or not, will have a pacemaker safety check completed as part of their usual clinical care by an accredited cardiac physiologist.

8. EXPERIMENTAL DESIGN

A single centre, prospective, observational study enrolling patients with existing pacemakers.

9. STUDY PROCEDURES

9.1 BASELINE STUDY PROCEDURES

Participants will attend an appointment at the Leeds Cardiovascular Research Facility. They will have already received the Participant Information Sheet at least a week prior to their appointment, if willing to participate they will provide informed written consent. We will then collect demographic and clinical data from the participant's electronic healthcare record prior to undergoing the study procedures. Participants will undergo a routine device interrogation by an accredited cardiac physiologist as per usual clinical care to confirm device functionality and RV pacing burden ≥20%.Participants will undergo point-of-care blood testing for NTpro-BNP, a hand-held echocardiogram and a standard cart-based echocardiogram. The appointment is expected to last around one hour. Following the appointment a member of the research team will arrange their next scheduled pacemaker clinic appointment with their usual care team.

9.2 POINT OF CARE NTPRO-BNP BLOOD TESTING

LumiraDx (LumiraDx Ltd, Cayman Islands) is a quantitative point-of-care, fingerpick blood test capable of measuring various biomarkers using a micro-sample of blood obtained from a finger prick. The LumiraDx can measure NTpro-BNP with only 20μL of blood, is highly portable, with a turn-around time of only 12 minutes – feasible within the time constraints of a standard pacemaker follow-up appointment. Their technology has been validated in a study of 659 samples compared to gold-standard commercially available laboratory equipment (Roche Cobas Elecsys proBNP II assay) and found to have comparable accuracy (slope 0.86, intercept -4.12, r 0.97).

9.3 STANDARD CART-BASED CARDIAC ULTRASOUND

participants will undergo a transthoracic echocardiogram by a senior cardiac physiologist accredited by the British Society of Echocardiography (or equivalent international body) using

a GE Healthcare Vivid E95 Ultra Edition Cardiac Ultrasound. A minimum dataset will be obtained with LVEF measured by the biplane method where possible, as well as assess for any (at least) moderate valvular disease or other finding which could result in a change to patient management.

9.3 HAND-HELD CARDIAC ULTRASOUND USING ARTIFICIAL INTELLIGENCE

Participants will undergo a focussed hand-held echocardiogram with AI derived LVEF using the Kosmos platform (EchoNous Inc., Redmond, USA) a point-of-care, hand-held ultrasound device capable of cardiac imaging, which uses US2.AI (Ultrasound Anyone Anywhere, Singapore) integrated AI driven software capable of automated measurement of LVEF. Existing data suggest the Kosmos platform is able to reliably detect abnormal LVEF in patients referred with suspected heart failure, however there are no data describing its use in a population with pacing-induced LV dysfunction. Hand-held echocardiography will be done by a specialist nurse or cardiac physiologist who does not hold accreditation in echocardiography.

10 OUTCOMES

10.1 PRIMARY OUTCOME

The accuracy of AI derived LVEF compared to standard cart-based echocardiography with LVEF measured by biplane method, assessed by correlation coefficient.

10.2 SECONDARY OUTCOMES

- The accuracy of AI derived LVEF <50% compared to standard cart-based echocardiography measurement of LVEF <50% by biplane method, determined by sensitivity, specificity, positive and negative predictive values.
- The incremental improvement of a model to predict LVEF <50% in a population with pacemakers of the addition of AI derived LVEF, point of care NT-proBNP, or both.
- The proportion of participants in whom it was not possible to determine AI derived LVEF, LVEF measured by biplane method, and subjective measurement of LVEF.

10.3 SAFETY OUTCOMES

- The proportion of patients with a new diagnosis of at least moderate valve disease, or any other echocardiography finding which resulted in a change to patient care.

11. STATISTICAL ANALYSIS

11.1 POWER CALCULATIONS

For this pilot study all analyses are exploratory, no statistical hypothesis has been prespecified and no formal sample size calculation has been performed. Based on previously published work assessing the accuracy of AI derived LVEF and sonographer determined LVEF we anticipate the inclusion of 150 participants would provide adequate statistical power to compare the two imaging modalities.

11.2 PRIMARY OUTCOME

The comparison of AI derived LVEF and sonographer measured LVEF will be determined by correlation coefficient.

11.3 SECONDARY OUTCOME

The comparison of AI derived LVEF <50% will be reported as the sensitivity, specificity, positive and negative predictive values comparing sonographer measurement of LVEF <50% by cart-based echocardiography. The improvement in the model will be reported as a comparison of the area under the curve comparing models with and without the addition of AI derived LVEF, alongside their 95% confidence intervals. The useable images and safety outcomes will be reported as proportions.

11.4 DEFINITON OF THE END OF THE STUDY

The end of the study will occur at the completion of the final participant's research visit.

12 ETHICAL AND REGULATORY CONSIDERATIONS

All investigators and study site staff will comply with the requirements of the Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

12.1 ASSESSMENT AND MANAGEMENT OF RISK

This study enhances usual clinical care, and it is likely that the intervention of echocardiographic screening will result in new findings and changes to patient management. One potential issue is the discovery of important heart muscle weakness, or other abnormal findings on echocardiography. All new findings will be reviewed by the Chief Investigator, or delegated to another Investigator in his absence, and managed according to current clinical practice recommendations. We will report as a safety outcome the proportion of patients with a new diagnosis of at least moderate valve disease, or any other echocardiography finding which resulted in a change to patient care - whether this be a change in treatment, or a referral for further tests. We will inform the patient's General Practitioner of any abnormal findings and the action we have taken as a result of this. Cardiac physiologists work within the National Health Service as technicians who perform echocardiography and as part of their role will interpret the images and measure heart structure and function. The Chief Investigator is a Cardiologist who is familiar with echocardiography and appropriately trained to interpret and action the results. Any changes to participant management will fall outside of this study, and the Chief Investigator will either action these changes himself, or refer to the clinical team within the National Health Service, as appropriate.

12.2 RESEARCH ETHICS COMMITTEE (REC) AND OTHER REGULARTORY REVIEW AND REPORTS

Before the start of the study a favourable opinion will be sought from a REC for the study protocol, consent forms, and other relevant documents. Substantial amendments that require review by NHS REC will not be implemented until that review is in place. All correspondence with the REC will be retained. It is the Chief Investigator's responsibility to produce the annal reports, as required. The Chief Investigator will notify the REC of the end of the study. If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination. Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any research outputs, to the REC. Before any patients are recruited, the Chief Investigator will ensure that appropriate approvals from participating organisations are in place. Specific arrangements on how to gain approval from participating organisations are in place and comply with the relevant guidance. For any amendment to the study, the Chief Investigator or designee, in agreement with the Sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. It is a decision for the Sponsor as to whether an amendment is substantial or non-substantial. The Chief Investigator will work with the study site so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

12.3 PEER REVIEW

The study rationale was reviewed by the Funder and externally by two independent, expert reviewers. The study protocol has been reviewed by the Sponsor, and independently by two members of the Leeds Cardiovascular Patient and Public Involvement and Engagement group.

12.4 PATIENT AND PUBLIC INVOLVEMENT AND ENGAGEMENT

The study rationale was presented to the Leeds Cardiovascular Patient and Public Involvement and Engagement (PPIE) group. The group found the project interesting and that the study design would be acceptable to patients. The PPIE group advised participants were

likely to wish to combine all study procedures within a single visit, although some may require a second visit if they did not have sufficient time on the day and should be offered this opportunity. The PPIE group agreed that the inclusion and exclusion criteria should be kept minimal to reflect the population with pacemakers. Two members of the Leeds Cardiovascular PPIE group agreed to review the Patient Information Sheet, Consent Form, and Invitation Letter in detail. Using their feedback, we ensured the information provided was succinct and easily understandable. The members suggested amendments so it was easily understandable to as wide a range of people as possible. In line with their guidance, we also provide large print versions of these documents and will make use of translation services available at the Trust where required.

12.5 PROTOCOL DEVIATION AND SERIOUS BREACHES

All protocols deviations will be reported by Dr Sam Straw to the study sponsor (goverance-ethics@leeds.ac.uk) within one working day of the research team's awareness. All serious breaches of the protocol or Good Clinical Practice (a breach likely to affect to a significant degree the safety or physical or mental integrity of participants, or the scientific value of the research) will be reported to the study sponsor within one working day, and to the Research Ethics Committee within seven days.

12.6 REPORTING OF ADVERSE EVENTS

An Adverse Event (AE) is an untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurres which are not necessarily caused by or related to that product.
An AE is therefore not anticipated to occur during this study, which is observational in nature.
A Serious Adverse Event (SAE) is an untoward occurrence that either:
- results in death
- is life-threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- consists of a congenital anomaly or birth defect
- is otherwise considered medically significant by the Investigator.

A Related Unexpected Serious Adverse Event (RUSAE) is an event that meets the definition of serious and in the opinion of the Chief Investigator is:
- related i.e. the event has occurred because of the research procedures
- unexpected, i.e. the type of event is not listed in the protocol as an expected occurrence.

The Chief Investigator will review all AEs occurring during the study visit within one working day to determine if they meet the definition of a SAE or RUSAE. Any SAE or RUSAE occurring in a research participant, where, in the opinion of the Chief Investigator the event was related to the administration of any of the research procedures will be reported to the Sponsor (governance-ethics@leeds.ac.uk) within one working day of the research team's awareness. All RUSAEs will be reported to the REC within their required timeline of 15 days.

The following information will be reported by the Chief Investigator to the Sponsor:
- the full details of the SAE/RUSAE in medical terms
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to research investigation), in the opinion of the Chief Investigator
- whether the event would be considered expected.

Untoward events which occur after the study visit has been completed or are not directly related to the study visit will not be reported. It is anticipated that during this study we will identify important heart muscle weakness, or other abnormal findings on cardiac ultrasound.

These findings, and any untoward event which occur as a consequence of new diagnoses/findings (such as hospitalisation) will not be reported to the Sponsor or REC as these are regarded as being part of the patient's usual clinical care.

12.7 DATA PROTECTION AND PATIENT CONFIDENTIALITY

All investigators and study site staff will comply with the requirements of the Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Identifiable patient data will be collected by members of the research team and stored on a secure NHS server for a maximum of 3-years. We will collect demographic information, as well as access the electronic healthcare record to obtain information of relevant past medical history and currently prescribed medications. Raw image files obtained from echocardiography imaging studies will be stored on a secure NHS server for a maximum of 3-years. The fingerpick blood test obtained a small quantity of blood, which is transferred to a barcode chip. Following analysis the barcode chip is disposed of (in an appropriate biohazardous waste bin) so that no human tissue samples are stored.

All potentially identifiable data will be accessible only to members of the study team. Where new diagnoses may result in changes to patient management, these data may be shared with other members of the clinical team at the Leeds Teaching Hospitals with the patient's agreement. We will create a pseudonymisation key which will be stored on a secure NHS service for a maximum perform of 3-years. Only pseudoanonymised data (with a unique identifier) will be transferred to the University system for the purpose of statistical analysis. Consent forms will be stored in the site file located within a secured cabinet in the Cardiovascular Research Facility, Leeds General Infirmary – only accessible by members of the research team and stored for a maximum period of 3-years. For this study we will not collect data on future outcome events. Fully anonymised data will be stored for a maximum period of 7-years to allow adequate time for analysis and publication.

12.8 ACCESS TO THE FINAL STUDY DATASET

The Chief Investigator and Co-Investigators will have access to the final study dataset.

12.9 SPONSOR INDEMNITY STATEMENT

The University, when acting as Sponsor, has insurance cover in force, which meets claims against it and where those claims arise from the University's own negligence in its role and activities relating to the study (and which is subject to the terms, conditions and exceptions of the relevant policy). Clinical negligence indemnification will rest with the participating NHS Trust under standard NHS arrangements.

13 EXPECTED VALUE

We now have evidence that where pacing-associated heart failure is discovered and then treated with standard therapies, patient outcomes are improved. However, there remain significant barriers to implementing a screening program including cost, time, and staff training and skills. AI promises to streamline healthcare delivery and facilitate a screening program to detect pacing-associated heart failure embedded within the existing follow-up schedule for patients with pacemakers.

14 DISSEMINATION POLICY

This is an investigator-initiated study. The protocol has been designed by the Investigators. No funders, industry partner or third party has been involved in the design of this study, nor will any third party have access to the data, contribute to manuscript preparation, or be involved in the decision to publish. On completion of the study, a study report will be prepared for dissemination at international cardiovascular conferences and submitted for publication in a peer-reviewed journal. Funding bodies will be acknowledged within the publication. All

participants will be informed of the results of the study, on completion, and will be forwarded a copy of the manuscript.

AMENDMENT HISTORY

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	1.1	05/09/2025	Dr Sam Straw	To specify that in the absence of the Chief Investigator, the actioning of urgent findings would be delegated to another Investigator.

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