CLINICAL STUDY PROTOCOL

STUDY COORDINATION CENTRE: Imperial College London

Full Study Title: **PROTECT-HF: - Physiological vs Right ventricular pacing Outcome Trial Evaluated for bradyCardia Treatment**

Short Study title / Acronym: **PROTECT-HF**

Sponsor: Imperial College London

Version no: 9

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This protocol has regard for the HRA guidance

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This protocol describes the PROTECT-HF trial and provides information about procedures for enrolling participants to the trial. The protocol should not be used as a guide for the treatment of other participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study, but centres enrolling participants for the first time are advised to contact the Trial Coordination centre to confirm they have the most recent version. Problems relating to this trial should be referred, in the first instance, to the Trial Coordination centre.
This trial will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. It will be conducted in compliance with the protocol, the Data Protection Act 2018 and other regulatory requirements as appropriate.

ABBREVIATIONS

AE	Adverse Event
BVP	Biventricular Pacing
CI	Chief Investigator
CRF	Case Report Form
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
HBP	His Bundle Pacing
HRA	Health Research Authority
ICHNT	Imperial College Healthcare NHS Trust
ICMJE	International Committee of Medical Journal Editors
ICTU	Imperial Clinical Trials Unit
ITT	Intention to Treat
LBBP	Left Bundle Branch Pacing
LV	Left ventricular
PICM	Pacing Induced Cardiomyopathy
QA	Quality Assurance
REC	Research Ethics Committee
RSI	Reference Safety Information
RV	Right ventricular
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	Standard of Care
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee

Table of Contents

TRIAL SUMMARY

TITLE: PROTECT-HF: - Physiological vs Right ventricular pacing Outcome Trial Evaluated for bradyCardia Treatment

OBJECTIVES:

- Does physiological pacing reduce mortality and unplanned heart failure acute care (hospital admissions or ambulatory diuretic therapy)?
- Does physiological pacing improve daily patient activity and patient reported quality of life?
- Does physiological pacing reduce the need for later upgrade to biventricular pacemaker?
- Does physiological pacing better maintain cardiac function (Left Ventricular Volumes and Ejection Fraction)?

DESIGN: This is a multi-centre, patient blinded, randomised controlled (Physiological pacing vs Right Ventricular pacing) trial including approximately 40 hospital sites in England, Wales and Scotland together with approximately 6 international sites. Recruitment and pacemaker implantation will be carried out at each participating centre. The trial will include an initial Vanguard Phase to demonstrate safety and feasibility. The primary analysis will be intention to treat. We will also perform an on-treatment analysis.

SAMPLE SIZE: 2600

INCLUSION CRITERIA:

- Adults aged 18 or above with
- Left ventricular ejection fraction >35% from any clinical echocardiogram (including V scan and MRI if ECHO cannot be done) performed any time in the 12 months prior to study enrolment.
- And one or more of the following guideline based ventricular pacing indications:
    a) Permanent or intermittent 3rd degree AV block
    b) Permanent or intermittent Mobitz type II AV block
    c) First Degree AV block with a pacing indication
    d) Slow chronic Atrial Fibrillation or Proposed AV node ablation
    e) Bifasicular block with a pacing indication
    f) Trifasicular block with a pacing indication
    g) Wenckebach with a pacing indication

EXCLUSION CRITERIA:

- Patients who are likely to only need occasional ventricular pacing, i.e. those with isolated sick sinus syndrome
- Pregnant women
- Unable to provide informed consent
- Those with comorbidity leading to a life expectancy <1year

INTERVENTION:

A physiological pacing strategy will be compared with right ventricular pacing (apical or septal lead locations as per the implanting physicians' normal practice).

MAIN STUDY PROCEDURES

- Planned intervention:

  Physiological pacing will be compared with right ventricular pacing. The approach for physiological pacing will be either His bundle pacing or left bundle pacing at the operator's discretion, (biventricular pacing will be offered should both of these attempts fail).

  Following the implant, patients (or their nominated representative) will be contacted at 6 monthly intervals, for a median duration of 4 years (max 6.5 years, min 3 years). During each encounter, mortality and heart failure events will be collated together with data on participant's quality of life and general health.

  Information will also be collected remotely from the pacemaker relating to daily patient activity and arrhythmia.

  A 500-patient sub-study will assess within patient, and between groups, echocardiographic changes over a 24-month period to try and improve mechanistic understanding of PICM.

PRIMARY ENDPOINT:

- Death and unplanned heart failure acute care

SECONDARY ENDPOINTS

- Via the pacemaker and adjudicated by blinded endpoint committee:
  - Atrial fibrillation (duration >6minutes)
  - Ventricular arrhythmia incidence
  - Daily patient activity (hours stratified by device vendor)
- Patient quality of life assessed via questionnaires (EQ5D and SF-36)
- Monthly Symptom assessment
- Incidence of upgrade of pacing device
- Safety Endpoints

Sub-study Endpoint:

- Within group differences of Left Ventricular End Systolic Volume (>10mls)

BACKGROUND

1.1 Existing Research and rationale for the study

~40,000 people a year in the UK and ~1,000,000 worldwide, develop cardiac conduction system disease and require pacing therapy to prevent potentially life-threatening bradycardia.

For the past 60 years, ventricular pacing using a right ventricular (RV) lead has been routine practice. However, chronic right ventricular pacing can be harmful, leading to impaired ventricular function (Pacing Induced Cardiomyopathy, PICM). PICM develops in 12 - 37% of patients, as reported in RCTs over a mean follow up of 4 years. PICM is believed to result from the non-physiological sequence of activation of ventricular myocytes. The activation wave-front begins near the lead tip and spreads slowly from the RV to the left ventricle via cell-to-cell conduction, producing uncoordinated and inefficient ventricular contraction.

Physiological forms of pacing, which maximally utilise the heart's own natural high-speed conduction system, have been developed with the aim of reducing the abnormality of the activation wavefront and thereby preventing right ventricular pacing cardiomyopathy.
In this study we will assess whether physiological pacing reduces mortality and heart failure morbidity compared with RV pacing, in patients without severely impaired ventricular function (EF>35%) and conduction system disease requiring ventricular pacing.

The clinical impact of the health problem

Heart failure is a major clinical problem, causing a high symptom burden and high mortality. In the UK, heart failure accounts for 1 million days of inpatient stay per year, which is ~2% of all NHS hospital inpatient days and 5% of emergency admissions. Heart failure causes significant mortality (35% mortality in the first year after diagnosis and 10% thereafter). There are currently ~900000 patients in the UK with heart failure. This study will establish whether we can reduce the incidence of heart failure by preventing pacing-induced heart failure.

What is already known about the topic

Harm from standard pacing

Right ventricular pacing saves lives in the short term by preventing bradycardia, but can lead to left ventricular impairment in the longer term, increasing the rate of heart failure and death.

The MOST trial randomised 2010 patients with normal ventricular function and a bradycardia indication for pacing, between dual chamber pacing and VVI pacing. Both arms had the same programmed lower rate intervals and therefore the same amount of pacing, but the dual chamber group had the benefit of native conduction for times when atrial pacing was sufficient (i.e. sinus bradycardia). This difference was important enough that the VVI group, whose pacing was always RV, had substantially increased heart failure hospitalisations (HR 1.37; 95% CI 1.05– 1.79; P=0.02). Most startling was the observation that every 10%

increase in time spent receiving RV pacing, was associated with a 20% increase in heart failure hospitalisations.

Even more dramatic was the DAVID trial, where RV pacing in patients with left ventricular impairment markedly increased heart failure and death from 16.1% to 26.7% (HR 1.61; 95% CI 1.06-2.44).

Physiological pacing utilises the heart's natural conduction system to provide ventricular activation, using a pacing lead at either the His or left bundle. Biventricular pacing may also provide a method to deliver a more physiological pacing strategy than standard RV pacing.

1) *His bundle pacing:*
The pacing stimulus captures the specialised His-Purkinje conduction system, producing normal, rapid and coordinated biventricular activation and contraction. Many centres have avidly taken up conduction system pacing, producing an increasing body of observational data, which now has systematic reviews and meta-analyses. These data show that His bundle pacing can be safely delivered and will chronically in the main remain stable. Pacing thresholds are typically slightly higher than RV pacing (mean 1.3V versus 0.59V) and procedural times slightly longer (70 minutes versus 55 minutes), as seen in a recent 765-patient observational study. There is a ~7% lead reintervention rate which is similar to that reported for LV leads. However, these potential disadvantages appear to be offset by more physiological ventricular activation as evidenced by narrower paced QRS complexes (128ms versus 166ms with RV pacing) and subsequent improved cardiac function. In the mentioned observational study these physiological improvements, in patients who required more than 20% ventricular pacing, were associated with a lower rate of death and heart failure hospitalisations when compared with RV pacing (25.3% vs 35.6%, p = 0.02). Although promising, these findings need to be tested in an adequately powered randomised control trial.

2) *Left bundle pacing:*
The pacing lead is positioned on or near to the left bundle (i.e. slightly more distal than the His bundle site). This provides the advantage of coordinated left bundle activation even when His pacing is impractical due to high thresholds or a non-treatable infra-Hisian block, at the cost of slower right ventricular activation. Happily, experiments show that pacing the left bundle rather than the His bundle does not seem to impair left ventricular synchrony, even in patients with narrow intrinsic QRS). Implant success rates are high (>94%), pacing thresholds low (0.6V@0.5ms) and R wave amplitude large. Safety across 12 observational studies totalling 1162 patients has been demonstrated with a lead complication rate of only 2.8%, similar to the 2.6% of RV pacing.

3) *Biventricular pacing:*
BVP pacing delivers more physiological pacing compared to RV pacing, with more rapid ventricular activation time. However, activation still relies on slow cell to cell activation rather than physiological activation via the conduction system, as a result left ventricular activation time is prolonged compared to normal intrinsic activation. In the BLOCK-HF trial BVP was compared with RV pacing in patients with a bradycardia indication for pacing and an EF40% as an alternative to RV pacing. Finally, the ACC/AHA give 2a to denovo CRT or Physiological Pacing (despite no RCTs) for those with EF 35- 50% and ESC pacing guidelines advocate that His pacing is reasonable for those patients with an EF >40%. Our

proposed PIs agree there is clinical equipoise in this group of patients. Therefore, we are proposing including all patients with an EF greater than 35% in the PROTECT-HF trial which will provide the needed RCT evidence for future guidelines.

1.2 Need for RCT

Physiological pacing strategies may be associated with slightly longer procedural time, higher thresholds and slightly higher lead related complications than RV pacing which has been the standard of care of >60 years. However, whether these potential issues are offset by the potential benefit of improved cardiac activation and therefore function needs to be determined in an adequately powered RCT. This is what PROTECT-HF aims to do.

2. OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

- Does physiological pacing reduce mortality and unplanned heart failure acute care (hospital admissions or ambulatory diuretic therapy)?

2.2 Secondary Objectives

- Does physiological pacing improve objectively measured patient activity and quality of life?
- Does physiological pacing reduce the need for later upgrade to biventricular pacemaker?
- Does physiological pacing better maintain cardiac function (Left Ventricular Volumes and Ejection Fraction)?

2.3 Tertiary Objectives

- Determine whether endpoint data collection utilising wholly digital means (NHS digital data for patients residing in England) matches endpoint data collection utilising traditional methods, i.e. direct participant contact.
- Determine whether there are genetic variations which may accurately detect which patients are at highest risk of pacing-induced cardiomyopathy and whether the detrimental effect of a genetic variation can be offset with the improved cardiac activation patterns provided by a physiological pacing approach.

2.4 Primary Endpoint

- Death and adjudicated unplanned heart failure acute care (hospital admissions or ambulatory diuretic therapy i.e. diuretic lounge visit).

2.5 Secondary Endpoints (all adjudicated by blinded endpoint committee)

- Via the pacemaker:
  a) Atrial fibrillation (duration >6minutes)
  b) Ventricular arrhythmia incidence
  c) Daily patient activity (hours stratified by device vendor)

- Incidence of clinically indicated upgrade to conventional biventricular pacing (CRT device)
- Patient quality of life assessed via questionnaires (EQ5D, SF-36 and health resource every 6-months)
- Safety endpoints: Device infections (requiring device extraction), pacing thresholds, need for lead revision or reimplantation, generator change, haematoma and pneumothorax.

Echo Sub-study (optional)

- Within patient changes and between group differences in LV volumes and EF will be assessed for differences according to treatment allocation.

Genetics Sub-Study (optional)

Available only at certain sites depending on the availability of appropriate equipment/personnel. Please ask your local study team if this is sub-study is available at your participating hospital.

- Genetic variations which may accurately detect which patients are at highest risk of pacing-induced cardiomyopathy and whether the detrimental effect of a genetic variation can be offset with the improved cardiac activation patterns provided by a physiological pacing approach.

3. STUDY DESIGN

The PROTECT-HF study will be performed at approximately 40 investigational sites in England, Wales, Scotland, and Northern Ireland, together with approximately 6 international investigational sites. The study will be a multi-centre, prospective, 1:1 randomised, patient-blinded trial with an initial Vanguard Phase to demonstrate safety and feasibility. The primary analysis will be intention to treat. We will also perform an on-treatment analysis.

The trial will include an initial Vanguard Phase to demonstrate safety and feasibility in recruitment. This phase will last 24 months and will aim to meet pre-specified recruitment targets (>80%) with cross-over rate of less than 30% This will be reviewed within the trial steering committee and a decision taken at the time regarding continuation of the trial as is, activation of additional sites or consideration of early termination.

Patients will be identified from clinical services as those requiring cardiac pacing and then invited to participate.

If eligible, informed consent will be obtained. If patient is unable to sign the informed consent form themselves due to blindness or other disability which doesn't affect their understanding of the study/capacity, a witness can sign on behalf of the patient. Where verbal consent is used to consent patient to the trial, randomisation cannot occur until the patient or witness physically signs the informed consent form. Demographic data and medical history information will be collected at screening. Patients will then be randomised following written consent to either standard of care RV pacing - this pacing lead can be placed either apically or septally at the operator's discretion, or to a physiological pacing strategy. Patients will be blinded to the strategy they are allocated. If allocated to a physiological strategy – this can be either His or Left Bundle pacing at the operator's discretion. If physiological pacing cannot be appropriately delivered utilising the initial choice, approach operators must transition to

try the alternative conduction system pacing method i.e. if fail His pacing move to Left bundle pacing if they are trained in the alternate method as well. If neither are successful operators should implant an LV lead to deliver biventricular pacing as this delivers a more physiological approach than standard RV pacing. Crossover to the RV arm would occur if available physiological approaches were attempted and unsuccessful.

A CSP Capture adjudication committee will review all implant data at 6 monthly intervals to provide an assessment of whether CSP was achieved. If operators have high cross over rates or failure rates to deliver CSP they will be asked to undertake further training.

Device Programming: Programming is at the discretion of the clinical team. Pacing avoidance modes are advised, as per guidelines, with one modification. Unlike RV pacing, physiological pacing need not be avoided in patients with very long AV delays, (physiological pacing does not induce dramatic mechanical dyssynchrony which would otherwise be present with obligatory dual-chamber RV pacing[58]) therefore DDD modes with shorter AV delays are acceptable or utilising programming options that mode switch with prolonged AV intervals. Ultimately programming decisions are at the discretion of the implanting physician as the trial aims to test the implantation strategy.

Initial data will be collected on patients pacing indication, comorbidity and medication. Pacing data will be collected from implant including paced ECG and threshold data to demonstrate the type of capture delivered. This will be adjudicated by a core lab based at Imperial College London to confirm capture type for subsequent analysis by pacing type.

His Capture

1) One of:

(A) Selective Capture

- Isoelectric line on ECG in all leads
- Stim to onset of QRS >30ms
- Local ventricular distinct from pacing stimulus on EGM

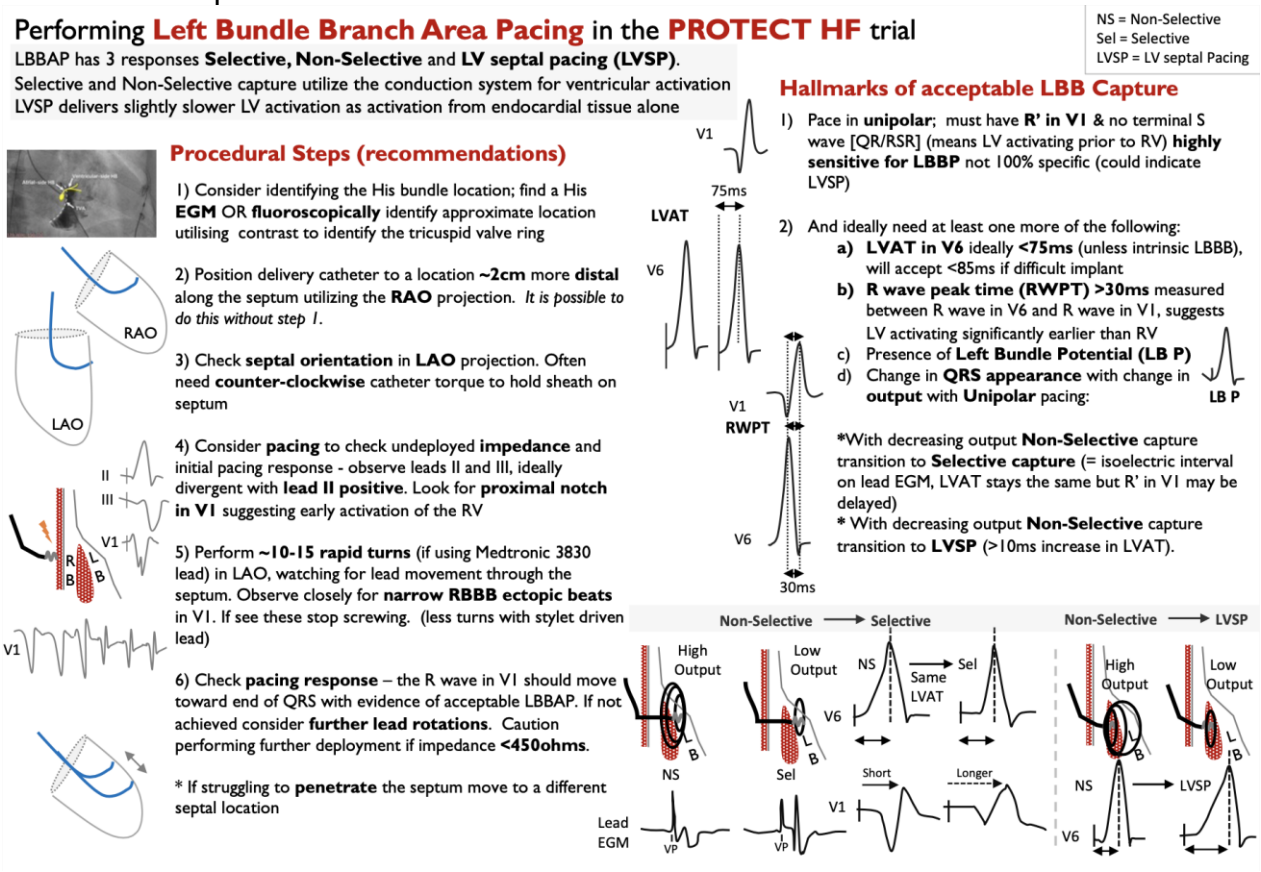
(B) Change in paced QRS morphology with change in pacing output or programmed stimulation

- Non-selective to selective capture (loss of delta wave, step out of local ventricular electrogram)
- Non-selective to myocardial capture (increase in QRS duration and change in QRS morphology)

(C) If neither of above:

- His to end of intrinsic QRS = Stim to end of QRS (within 10ms) if narrow QRS
- Mid to end QRS: paced QRS = intrinsic Morphology (pattern matching)

Left Bundle Capture:



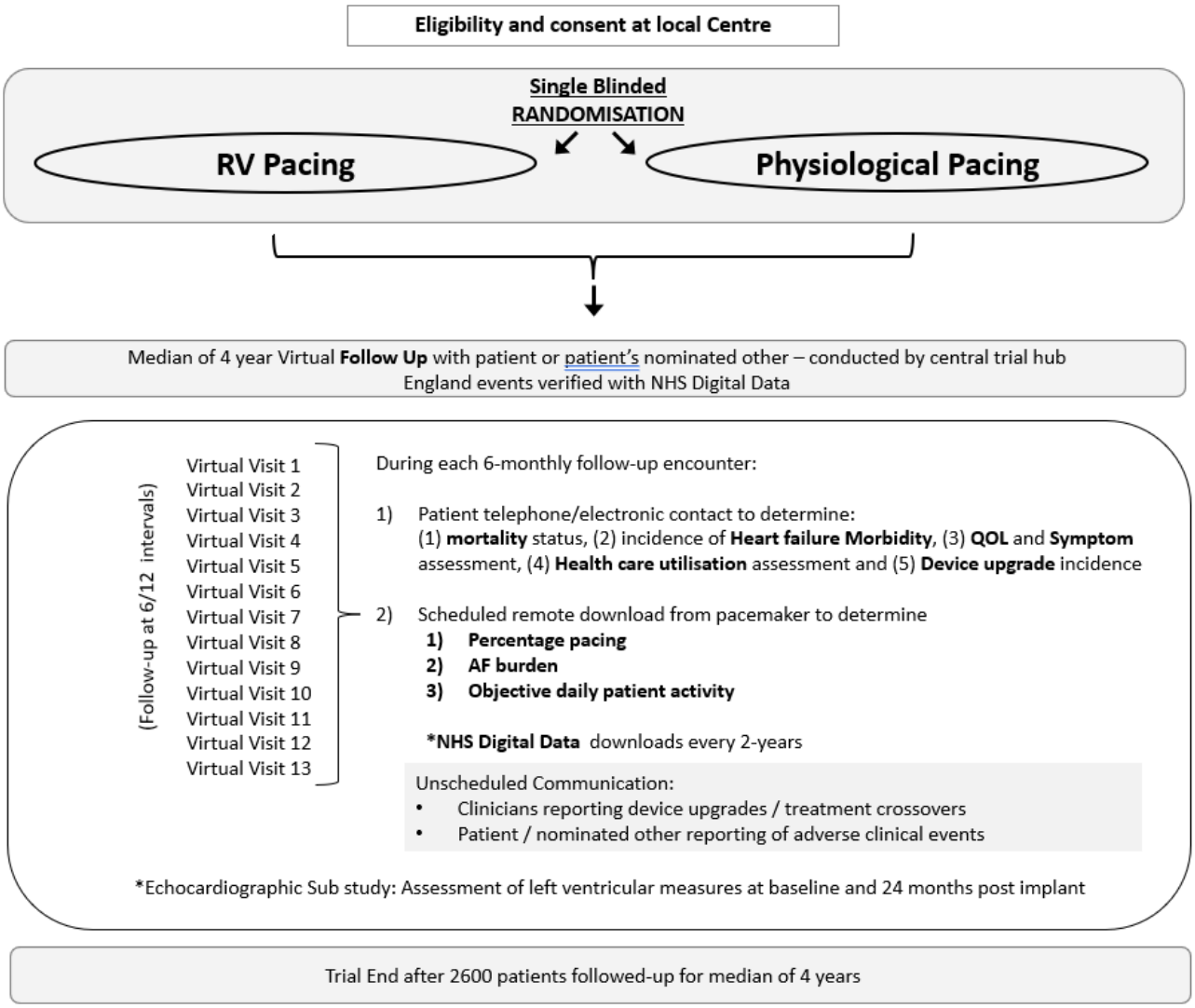
Patients or a nominated representative will then be contacted every 6 months to ascertain end point data – this will be remotely from the central trial hub at Imperial for mortality, heart failure events, and QOL. If events have occurred source data will be obtained for adjudication as to cause of events.

In some international centres, patients will be contacted by their local site teams instead of the central trial hub. Some international centres may conduct streamlined follow-up, collecting data on HFH and mortality only. Some international centres may also conduct 1-yearly follow-up instead of 6-monthly follow-up and this may be based on data from a national registry instead of via telephone calls to participants directly.

Furthermore, for patients living in England, NHS digital data downloads will be collected at two year intervals for data on mortality and hospital acute care. We will compare the reporting of events between the standard approach and via the NHS digital route thus allowing us to gain insight into future trial design.

For patients recruited to the echo sub study (optional) an echocardiogram will be performed at the local centre within 6 weeks of initial pacemaker implantation and then after 24 months. All echocardiograms will be analysed by a core lab based at Imperial College London.

For patients recruited to the genetics sub-study (optional), a blood sample of 3mls (in a EDTA tube) will be taken for gene sequencing and analysis by a laboratory based at Imperial College London Pseudonymised samples will additionally be sent to an external lab for specific analyses.



PARTICIPANT ENTRY

3.1 Study setting and population

We will recruit patients who are referred for clinically indicated pacemaker implantation

(i) Inclusion criteria

- Adults aged 18 or above with
- Left ventricular ejection fraction >35% from any clinical echocardiogram (including MRI and V scan if ECHO cannot be done)performed any time in the 12 months prior to study enrolment.
- And one or more of the following guideline based ventricular pacing indications:
    a) Permanent or intermittent 3rd degree AV block
    b) Permanent or intermittent Mobitz type II AV block
    c) First Degree AV block with a pacing indication
    d) Slow chronic Atrial Fibrillation or Proposed AV node ablation
    e) Bifasicular block with a pacing indication
    f) Trifasicular block with a pacing indication
    g) Wenckebach with a pacing indication

(ii) Exclusion criteria

- Patients who are likely to only need occasional ventricular pacing, i.e. those with isolated sick sinus syndrome.
- Pregnant women.
- Unable to provide informed consent.
- Those with comorbidity leading to a life expectancy <1year.

4. PROCEDURES AND MEASUREMENTS

4.1 Identification and recruitment of participants

We will recruit patients who are referred for clinically indicated cardiac pacemaker procedures. Patients who potentially fulfil the study inclusion criteria and none of the exclusion criteria will be identified and approached by members of their direct healthcare team to discuss study participation. Many patients will be identified by clinical teams during acute admissions to hospital with bradycardia. Clinical teams will alert the study teams within the hospital to facilitate trial enrolment.

4.2 Screening and pre-randomisation evaluations

Written informed consent will be obtained before the participant undergoes any screening procedures. If patient is unable to sign the informed consent form themselves due to blindness or other disability which doesn't affect their understanding of the study/capacity, a witness can sign on behalf of the patient. Where verbal consent is used to consent patient to the trial, randomisation cannot occur until the patient physically signs the informed

consent form. All subjects will be assigned a study-specific subject number at the screening visit and the following tests/assessments will be performed:

- Medical History
- Review of clinical echocardiographic data
- Review of clinical ECG and pacing indication
- Concomitant medication
- Pregnancy test (where required) as per standard of care

4.3 Randomisation and Blinding

Randomisation will take place using a fully validated, high quality, real-time electronic data capture system (OpenClinica database). Randomisation will be 1:1 between receiving ventricular myocardial pacing from a lead in the Right Ventricle versus a Physiological Pacing approach. Randomisation will occur once a patient has signed the informed consent form. The randomisation list will be programmed by the statistician using variable block length and stratified by site. Patients will be blinded to treatment allocation in a single blinded fashion. All endpoints will be adjudicated by blinded committee of clinicians with expertise in heart failure.

4.4 Visit Schedule

	Local Sites				Central Trial Hub		
	Screening	Implant	ECHO Sub-study (500 pts)		Follow Up Virtual Visits		
Visit/Timepoints	-6 weeks to 0 Day	0	0-6 weeks post implant	24 months (± 1month)	Monthly[A] (± 7 days)	6 Monthly[B] (± 7 days)	Final Visit[C]
ENROLMENT:							
Informed Consent	x						
Eligibility Criteria	x						
Demography	x						
Randomisation/Allocation		x					
INTERVENTION:							
Device Implantation		x					
ASSESSMENTS:							
Medical history	x						
Echocardiography	x[$]		x	x			
ECG	x[£]	x[*]					
Heart rate and cardiac rhythm	x	x					
Concomitant medication	x	x	x	x		x	x
Pregnancy test where required	x						
Post implantation chest radiograph		x					
Pacing check		x				x[#]	x
Vital Signs		x					
PRIMARY ENDPOINTS:							
Mortality Status						x	x
HF Morbidity						x	x
SECONDARY ENDPOINTS:							
EQ-5D	x					x	x
SF-36	x					x	x
Healthcare Utilisation Assessment						x	x
AF burden						x	x
Percentage Pacing						x	x
Daily Patient Activity						x	x
Patient Reported Symptoms					x	x	x
Device Upgrade						x	x
Adverse Events		x	x	x		x	x
Study End of Visit Form							x

$ Taken at screening or within the past 12months
* Pre and Post Implant ECG (1)
£ Taken at screening or any point prior to implant
A The monthly visits are defined as follow-up visits that occur once a month (within ±7 days window) from implant
B The 6-monthly visits are defined as follow-up visits that occur every 6 months (within ±7 days window) from implant
C The final follow-up visit ranges from minimum of 3 years (LPLV)
Including in-house pacing checks done as per routine SOC, do not have to necessarily coincide with 6 monthly follow-ups, but should be collected and entered onto eCRF when occurring.
(1) for RV pacing implants, post-implant ECG can occur at any time post-implant

4.5 Interventions

Participants will attend the catheter laboratory for their clinically indicated procedure.

Intervention and comparator: Physiological pacing will be compared with right ventricular pacing (apical or septal lead locations as per the implanting physicians' normal practice). The approach for physiological pacing will be either His bundle pacing or left bundle pacing at the operator's discretion.

His bundle pacing: Conduction system capture will be confirmed using previously defined criteria (see above). If there is evidence of infra-Hisian block during the resting state or whilst pacing at higher heart rates (up to 130 bpm) then either a more distal His pacing position will be attempted or left bundle pacing will be performed.

Left bundle pacing using the technique described by Huang previously defined criteria will be used to confirm left conduction system capture (see above).

An acute pacing threshold of >1.5V @1ms, or unsatisfactory R wave sensing (less than 1.5 mV) will not be accepted and the lead will be repositioned or an alternative approach for conduction system pacing will be attempted.

In patients in whom conduction system pacing is not possible or pacing parameters are not acceptable a lead should be placed in the coronary sinus to reduce cross-over rates to RV pacing.

Evidence of the achieved physiological pacing response must be submitted for adjudication as to the type of capture achieved. The minimum required data set will include upload of the paced QRS with the pacing output shown, the lead EGM at the final position and evidence of a manoeuvre that demonstrates a transition in capture morphology demonstrating conduction system capture.

All patients will undergo a post-procedure chest radiograph to confirm lead position and rule out a pneumothorax if this is standard of care at the site. An AP image of this will need to be uploaded to the trial hub.

4.6 Assessments

<u>Implant Visit</u>

At the implant visit, after randomisation the following procedures will take place: -

- ECG
- Concomitant medication collection

- Device Implantation
- Post implant chest radiograph (if this is standard of care at the site)
- Pacing Check
- Vital signs

ECHO Sub study

For patients recruited to the echo sub study echocardiography will be performed at the local site within 6 weeks of the initial implant. Multiple recordings of apical 4 chamber and 2 chamber windows will be obtained for determination of blinded assessment of chamber dimensions, volumes and function. Atrial size and valvular function will be reported too.

ECHOs should be submitted via your site specific OneDrive link. All ECHOs should be identified by patient ID and timepoint.los

Genetic Sub-study

For patients recruited to the genetics sub-study (optional), a blood sample of 3mls (in a EDTA tube) will be taken for gene sequencing and analysis by a laboratory based at Imperial College London.

The samples will be stored and transported to the central trial hub for analysis. They will be stored in -80 freezers at Imperial College and tracked on the appropriate tracking software (LabVantage or equivalent) according to local governance. Sample tubes will be barcode-labelled with the StudyID and aliquot number. Imperial College Laboratory space is only accessible by security access.

For those participants in the optional genetic sub-study, 3mls of blood will be drawn at either the screening or implant visit. If not taken at this stage, they will be drawn at any other point in the trial.

4.7 Follow Up

Follow up at all UK centres will be conducted by a central trial hub utilising:

1. Online questionnaires and/or telephone contact with the participant or their nominated representative completing questions onto the OpenClinica ePRO database. This will occur every 6 months starting from device implantation.
2. Remote follow-up from a participant's pacemaker where available, downloads will be scheduled every 6 months. Where possible data will be transferred from device companies to the trial team either directly or via the implanting/recruiting centre.
3. For participants residing in England – mortality and hospital statistics will be obtained by data draws every 24 months from nationally held records.

Additionally, the central staff will contact participants if made aware by local study team or by the participant of an adverse events and will follow this up accordingly.

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

In some international centres, patients will be contacted by their local site teams instead of the central trial hub. Some international centres may conduct streamlined follow-up, collecting data on HFH and mortality only. Some international centres may also conduct 1-yearly follow-up instead of 6-monthly follow-up and this may be based on data from a national registry instead of via telephone calls to participants directly.

Participants can withdraw from questionnaire and where this is noted, the applicable participants will be followed up on their medical records only, if participants consents to this. A protocol deviation should be raised where participants want to withdraw from questionnaires.

4.8 Follow Up: In Person Pacing Checks

While in most centres, virtually all follow-up will be coordinated by the central trial hub, we would like to capture the in-house pacing check data. In-house pacing checks are to be performed as per routine standard of care. Frequency of the pacing checks to be done as per local site standard of care (do not have to coincide with 6 monthly follow-up visits). Information from these pacing checks should be collected and entered onto the OpenClinica database as they occur. If this is not possible, ventricular paced ECG and/ or in-house pacing check report, is to be sent to the central trial hub via NHS email or SharePoint.

4.9 Follow Up Period

The trial has a planned 3.5 year recruitment window followed by a 3 year follow up period. This means the first recruited participant will have 6.5 years of follow up and the last patient 3 years with estimated median follow up of 4 years for the trial.

For participants residing in England, NHS digital data draws will occur every two years in October. This will continue until the formal end of the trial.

4.10 Endpoints

Mortality Status and HF morbidity

This will be determined by direct contact with patient or their nominated representative at 6 monthly intervals. Additional notification may come from reporting of adverse events by the participant or the local study teams. Furthermore, for patients residing in England, mortality and hospital events will also be assessed and confirmed using NHS digital records.

Local study teams may be contacted to request further information from participant medical records, regarding adverse events, reported to the central team.

Questionnaires

Quality of Life and healthcare utilisation assessments will be performed by telephone/online/post questionnaires. The EQ5D, SF36 and a health resource use questionnaire will be completed at baseline and then every 6 months. The custom health resource utilisation form will enquire about change in employment status due to ill health as well as collate number and type of hospital visits.

Device Upgrade

Incidence of clinically indicated upgrade to conventional biventricular pacing will be obtained either from direct contact with the participant or their nominated representative at the 6 monthly contact or if reported by local study teams. Clinical adjudication of appropriateness will be considered by a blinded committee, they will meet every 12 months. The committee will review and agree these criteria but will include EF drop to ≤35% or a ≥10% drop from baseline, a raised BNP or a Hospitilisation for Heart Failure.

Pacemaker Reported Endpoints

Pacemaker parameters, Pacemaker-derived (remotely transmitted) objective metrics including atrial fibrillation (duration >6minutes) and ventricular arrhythmia incidence and daily patient activity (hours/day stratified by device vendor) will be collected as will percentage pacing. For those participants without remote monitoring a percentage pacing as a minimum will be obtained at least annually from clinical in-office reviews.

For patients with remote monitoring enabled devices we will aim to establish a “trial patient clinic” for read-only access of their data. Alternatively, the device manufacturers including Medtronic, Boston Scientific, Biotronik and Abbott will supply periodic spreadsheets of data for trial patients to the local PIs to be passed to the trial team. A trial patient clinic is a virtual read-only space within each manufacturers’ clinical device platform (CareLink for Medtronic, Merlin for Abbott, Latitude for Boston Scientific and Biotronik Home Monitoring for Biotronik) used as standard of care for remote monitoring of devices. The pacemaker parameters which are transmitted to the device manufacturers’ platforms as part of standard of care will be viewable within a dedicated virtual space on the platform to the research team. Clinical teams will access this information as per routine standard of care and there will be no change to this process. Where this workflow is not enabled, we will rely on the local PIs to pass information on where collected.

Medication Information

Medication information will also be collected at each contact with study participants so that changes in medication can be tracked.

Safety Endpoints

Device infections (requiring device extraction), pacing thresholds, need for lead revision or reimplantation, generator change, haematoma and pneumothorax. These events will be regularly reviewed by the trial Data Safety Monitoring Board.

5. EARLY DISCONTINUATION OF PARTICIPANTS

5.1 Withdrawal from study

Withdrawal from the study, which is different to withdrawal from QOL, qolrefers to discontinuation of study follow-up and can occur for the following reasons:

- Participant decision
- Loss to follow-up – where patient has been contacted multiple times during the follow-up over a period of time and unable to get in touch with them and/or hasn't been attending any appointments

5.2 Permanent discontinuation of trial intervention

Participants may discontinue trial intervention for the following reasons:

- At the request of the participant
- Due to an Adverse Event / Serious Adverse Event
- If the investigator considers that a participant's health will be compromised due to adverse events or concomitant illness that develop after entering the trial.

5.3 Procedures for permanent discontinuation or withdrawal from the trial

- If a participant permanently discontinues the trial intervention, they will be invited to continue to attend trial visits if possible to allow for collection of key outcome and safety data.
- If the participant withdraws consent to further be contacted at all for the study purposes, this will be documented on the electronic case report form (eCRF) and in the medical notes. No attempts of further contact will be made.
- Participants who have discontinued the trial intervention and/or have withdrawn from the trial will not be replaced.

6. SAFETY REPORTING

6.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical trial subject. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, whether or not considered related to the trial protocol.

6.2 Causality

Definitions for assessment of causality:

Unrelated: No evidence of any causal relationship
Unlikely: There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after device implantation. There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible: There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable: There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definite: There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

6.3 Severity of Adverse Events

Definitions for assessment of severity:

Mild: Awareness of event but easily tolerated
Moderate: Discomfort enough to cause some interference with usual activity
Severe: Inability to carry out usual activity

6.4 Adverse Event recording

For the purposes of this trial, only adverse events related to the study, defined medically important events and cardiac events and conditions after consent has been obtained will be recorded and reported on the database. Please see the complete list below of adverse events that must be reported. All related and unexpected serious adverse events must be reported as stipulated in the Safety Reporting instructions, regardless of whether they are in the list of defined reportable adverse events. Expected AEs in this population of patients with Heart Failure will include hospitalisations related to arrhythmia, worsening shortness of breath and chest pain. Other expected events include those that are related to known complications of pacemaker insertion. This includes, but is not limited to, lead displacement +/- revision, wound or device infection, pneumothorax, haematoma and deep vein thrombosis. For the purposes of this trial, AEs, both serious and non-serious, as described above, will be followed up according to local practice until the event has stabilised or resolved, or the Follow-up Visit, whichever is the sooner. *This may require the central team to contact local teams, to provide further information from the participant medical records, regarding an adverse event.*

All other adverse events, both serious and non-serious will not be reported and recorded on the study database; however, they must still be documented in the medical notes and followed up as per local practice by clinical teams. They will not be monitored for the purpose of this study.

Adverse Events that must be reported are:

- Heart Failure Hospitalisation (HFH)
- Ambulatory Heart Failure events (e.g., Ambulatory diuretic therapy)
- Suspected Heart Failure Hospitalisation (HFH)
- Device issues:
    - Device infection (requiring device extraction)
    - Device infection (requiring antibiotics, with or without device extraction)
    - Significant rise in pacing thresholds
    - Lead displacement or perforation
    - Lead revision or reimplantation
    - Generator change
    - Haematoma
    - Pneumothorax
    - Inappropriate pacing function
- Device upgrade
- Major bleeding or haemorrhage related to device implant
- Any cardiac related hospital admission
- Any cardiac related events, including but not limited to:
    - Myocardial Infarction
    - Arrhythmia events
        - Atrial Fibrillation
        - Ventricular Arrhythmia
    - EF changes
        - EF drop to ≤35% OR
        - EF drop to ≥10% drop from baseline
    - Shortness of breath
    - Worsening peripheral oedema
    - Lung atelectasis
    - Pericardial effusion
    - Pleural effusion
    - Chest Pain
    - Changes in cardiac blood markers (BNP, Troponin)
- Any cardiac related Accident & Emergency visit, day-case admission, or unplanned outpatient event or procedure
- Loss of capacity
- Delirium
- Dementia
- Stroke
- Non cardiac death
- Sudden cardiac death (Ventricular Tachycardia / Ventricular Fibrillation arrest)
- Cardiac death

6.5 Serious Adverse Events (SAE)

(i) Definition of SAE

An SAE is defined as any event that

- Results in death;
- Is life-threatening*;
- Requires hospitalisation or prolongation of existing inpatient's hospitalisation**;
- Results in persistent or significant disability or incapacity;
- Is a congenital abnormality or birth defect;

* "Life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

** "Hospitalisation" means any unexpected admission to a hospital department. It does not usually apply to scheduled admissions that were planned before study inclusion or visits to casualty (without admission).

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

(ii) Reporting of SAEs

Reporting of all SAEs, occurring during the study must be performed as detailed in the study-specific Safety reporting instructions.

Active monitoring of participants after the end of the trial is not required.

All SAEs will be reviewed by the Chief Investigator or a designated medically qualified representative to confirm expectedness and causality.

Expected AEs in this population of patients with Heart Failure will include hospitalisations related to arrhythmia, worsening shortness of breath and chest pain.

Reporting of SAEs and review by the CI will be via the trial data collection system (OpenClinica).

(iii) Related SAEs

Related: resulted from administration of any of the research procedures

(iv) Unexpected SAEs

Unexpected: type of event is not listed in the protocol as an expected occurrence

(v) Reporting of SAEs that are related and unexpected

SAEs that are *related and unexpected* should be notified to the relevant REC and the Sponsor in accordance with local requirements. For Imperial-Sponsored studies related and unexpected SAEs must be reported to the Sponsor within 15 days of the investigator becoming aware of the event.

Follow up of participants who have experienced a related and unexpected SAE should continue until recovery is complete or the condition has stabilised. Reports for related and unexpected SAEs should be unblinded prior to submission if required by national requirements.

(vi) Annual reporting of Serious Adverse Events

Annual Progress reports will be submitted to the Sponsor and the Ethics Committee in accordance with local requirements. The Annual Progress Report will detail all SAEs recorded.

6.6 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant REC of the measures taken and the circumstances giving rise to those measures.

Contact details for reporting SAEs
Please send SAE forms to: protect-hf@imperial.ac.uk
Tel: 07749576830 (Mon to Fri 09.00 – 17.00)

7. STATISTICAL ANALYSES

7.1 Sample Size and power considerations

Event rate. We used a conservative 27.5% rate of death or unplanned Heart Failure acute care at four years. For context, BLOCK HF saw 39% in the RV pacing mild/moderate LV impairment group, and Abdelrahman et al saw 36% rate in the patients with significant RV pacing.

Effect Size detectable. We plan to be able to detect a 19% relative risk reduction, which is an effect size which would change clinical practice. For context, Biventricular pacing in the BLOCK HF trial delivered a relative risk reduction of 27%1. Observational data comparing conduction system pacing with RV pacing shows a 35% lower rate in the physiological pacing group.

Assuming 3.5 years recruitment and 3 years follow up, a conservative survival probability at 4 years of 0.725 (event rate of 27.5%) in the control group and a Hazard Ratio of 0.78 (relative risk of 0.81), 2048 patients would give 85% power with a two-sided α level of 0.05.

Adjusting for a slower recruitment rate in the first 12 months, a 7.5% cross over from physiological pacing to RV pacing and 7% drop-out, we would need 2539.

7.2 Planned recruitment rate

We will recruit 2600, as a total across both UK and international centres. We expect sites to recruit approximately 2.5 patients per month once activated.

Planned recruitment timelines are as below:
0 to 24 months: ***Vanguard recruitment:***
0 to 6 months: ≥ 12 sites active,
6 to 12 months: ≥ 24 sites active,
12 to 24 months: 36 sites active.
Expected 1296 patients recruited by 24 months
24 to 42 month: ***Main recruitment phase:*** 36 sites. Reach 2600 patients.
42 to 78 month: ***Follow up phase:*** Follow-up will range from 36 to 78 months

7.3 Statistical analysis

Data will be entered into a validated eCRF developed by ICTU. Continuous variables will be presented as means and standard deviations if normally distributed, and as medians and inter-quartile ranges for skewed data, whilst categorical variables will be presented as frequencies and percentages. Normality will be checked, and appropriate transformation performed if not normally distributed. All statistical tests will be two-tailed with a 5% significance level.

A detailed description of all the analyses will be given in the statistical analysis plan (SAP) that will be prepared and finalised prior to database lock. Any deviations from the SAP will be justified and documented in the final report.

(i) Analysis populations

The primary analysis will be performed according to the intention to treat principle, including all participants who are randomised to a study arm, according to their allocated arm, regardless of treatment received.

Per-Protocol (PP) populations will also be defined:
Those who received CSP as per adjudication
Those who received His bundle pacing as per adjudication
Those who received Left bundle pacing as per adjudication
Those who received selective His bundle pacing as per adjudication
Those who received non-selective His bundle pacing as per adjudication
Those with an EF <50% at enrolment
Those with an EF >50% at enrolment
Those with an mean pacing percentage >20% during the trial
Those with a mean pacing percentage >40% during the trial
Those with a mean pacing percentage >80% during the trial
Those with AF at baseline

Those with complete AV block at baseline

(ii) Primary Endpoint Analysis

Survival curves for primary endpoint will be estimated by Kaplan and Meier and the log-rank test methods. 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.

(iii) Secondary Endpoint Analysis

Secondary outcomes will be analysed using the appropriate generalised linear model depending on the distribution of the outcome, like linear regression for continuous and logistic regression for binary outcomes. When measurements are collected at multiple time points, repeated measurements mixed models will be used. All implant pacing parameters will be recorded including X-ray time as a surrogate for procedure time and pacing thresholds, sensed R wave, impedance and pacing amplitudes. These metrics will be compared between arms.

Quality of life will be assessed over time and treatment groups compared using longitudinal analysis with appropriate recognition for informative dropout, using joint modelling to account for events.

Our planned subgroup analyses will be performed by adding the interaction term between treatment and the subgroup variable into the model.

Planned Subgroup / Sub-study Analyses

i. *Mechanistic Echocardiographic Sub-study of 500 patients.* At trial enrolment, 500 patients will enter the Echo sub-study, with echocardiograms at baseline (within 6 weeks of implant) and 24 months later. The sub-study will analyse group mean effects and individual patient changes, focusing on LV volumes and ejection fraction. The data will be analysed using a core lab blinded to treatment allocation. We will also conduct an exploratory analysis using the AI technology developed and validated in our institution.

   We have chosen LV end systolic volume as the primary endpoint variable of this sub-study because was found to be a powerful predictor of heart failure hospitalisations and mortality in previous clinical trials. A 10ml increase in volumes in the BLOCK HF study was associated with a 7% increase in death and 10% increase in heart failure hospitalisations.

   The sample size is designed to detect a between-arm difference in change of LVESV of 10mls, with 90% power at the 5% significance level, assuming SD of differences is 27mls based on previous trials. We assume 7.5% cross over rate at implant but a dropout rate of 15% (because some patients may decline to attend for the follow-up echo when the time comes). This requires 426 patients. We plan to recruit 500 patients.

ii. *Effect of physiological pacing stratified by percentage of ventricular pacing.* Because randomisation is unlikely to affect the proportion of beats that require ventricular pacing, we will be able to validly analyse all the endpoints of the study with proportion of ventricular pacing as an input covariate. This means we may see a progressively larger difference between arms as the proportion of ventricular pacing increases. This will be a useful indicator for the mechanism of any effect seen.

iii. *By pre-implant LV function.* Similarly, we will test whether pre-implant (clinically documented without cost to the BHF) ejection fraction predicts the difference in outcomes between arms.

iv. *By pacing type.* On-treatment analysis is planned that will report outcomes for: selective His bundle pacing, non-selective His bundle pacing, selective left bundle pacing, non-selective left bundle pacing and pacing via the coronary sinus. Capture type will be adjudicated by blinded committee reviewing predefined manoeuvres designed to confirm the type of capture present. 12 lead ECG's and intracardiac electrograms will be collected at the time of implantation. 12 lead ECG's will also be collected during in person pacing follow up.

v. *NHS Digital follow up.* For England-recruited patients we plan to utilise NHS digital data to confirm mortality status and hospital episodes for the duration of the study. We anticipate ~1500 patients will be recruited from England.

vi. Cost Effectiveness analysis. Data as recommended by our health-economist for cost effectiveness analysis will be collected; health care utilization including number of hospital admissions, days in hospital, other unplanned visits to hospital, GP and outpatient visits.

8. REGULATORY, ETHICAL AND LEGAL ISSUES

8.1 Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformity with the 7th revision of the 1964 Declaration of Helsinki.

8.2 Good Clinical Practice

The study will be conducted in accordance with the guidelines laid down by the International Conference on Harmonisation for Good Clinical Practice (ICH GCP E6 R2 guidelines).

8.3 Research Ethics Committee (REC) Approval

(i) Initial Approval

Prior to the enrolment of participants, the REC must provide written approval of the conduct of the study at named sites, the protocol and any amendments, the Participant Information

Sheet and Consent Form, any other written information that will be provided to the participants, any advertisements that will be used and details of any participant compensation.

(ii) Approval of Amendments

Proposed amendments to the protocol and aforementioned documents must be submitted to the REC for approval. Amendments requiring REC approval may be implemented only after a copy of the REC's approval letter has been obtained.

Amendments that are intended to eliminate an apparent immediate hazard to participants may be implemented prior to receiving Sponsor or REC approval. However, in this case, approval must be obtained as soon as possible after implementation.

The trial team, in collaboration with the Sponsor will assess whether a proposed amendment is substantial or non-substantial/ For each proposed amendment, a revised version of the protocol will be prepared using tracked changes, a new version assigned and the revised document will be reviewed and approved by the Sponsor prior to submission to the REC and Health Research Authority *HRA). The amendment protocol will be sent to participating sites for local approval to be granted and the approved version will be shared with all staff involved in the trial.

(iii)Annual Progress Reports

Annual Progress Reports will be submitted to the Research Ethics Committee (REC) and the Sponsor in accordance with national requirements.

(iv)End of Trial Notification

The REC will be informed about the end of the trial, within the required timelines.
The end of trial notification will be submitted within 90 days of the end of trial definition being met. In the event of a premature halt of the trial, the timeframe is 15 days, and the reasons should be clearly explained in the notification.

8.4 HRA approval

Health Research Authority (HRA) approval will be obtained prior to starting the study. Each participating site will confirm capacity and capability prior to commencing.

The HRA and all participating sites also need to be notified of all protocol amendments to assess whether the amendment affects the institutional approval for each site.

8.5 Non-Compliance and Serious Breaches

All protocol deviations and protocol violations will be reported via the eCRF/CRF and reviewed by the Chief Investigator and reported to the ICTU QA manager on a monthly basis. Protocol violations will be reported to the Sponsor.

Due to the nature of this trial, occasional accidental unblinding of participants is expected. Unblinding of participants does not affect the trial's primary endpoint and should be reported as protocol deviation

An assessment of whether the protocol deviation/violation constitutes a serious breach will be made.

A serious breach is defined as:

A breach of the conditions and principles of GCP in connection with a trial or the trial protocol, which is likely to affect to a significant degree:

- The safety or physical or mental integrity of the UK trial participants; or
- The overall scientific value of the trial

The Sponsor will be notified within 24 hours of identifying a likely Serious Breach. If a decision is made that the incident constitutes a Serious Breach, this will be reported to the REC within 7 days of becoming aware of the serious breach.

8.6 Insurance and Indemnity and Sponsor

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trust taking part in this study. Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

8.7 Trial Registration

The study will be registered on clinicaltrials.gov in accordance with requirements of the International Committee of Medical Journal Editors (ICMJE) regulations.

8.8 Informed Consent

Patients who clinically require a pacemaker for slow heart rates will be screened and identified by a member of the trial study team in the patient's local hospital.

The patient will be approached either face-to-face or via telephone before any consent (whether electronic or paper) is signed, and the trial rationale and methods explained. A face-to-face approach will be adopted whenever possible. They will be given a written information leaflet which will detail the known risks and potential risks. They will be given time to consider whether they would like to participate in the trial and ask questions if they so wish.

If they decide they would like to participate, they will be asked to sign a consent form either paper or electronically sent via a link emailed by OpenClinica. The electronic consent method will comply to UK eIDAS Regulations (SI 2016/696). They will be made aware that they can leave the trial at any time and can withdraw consent at any time. They will be made aware that this will not affect their clinical care. Where verbal consent is used to consent

patient to the trial, randomisation cannot occur until the patient physically signs the informed consent form.

Only patients with capacity to consent will be considered eligible for recruitment. Subjects should be provided with a copy of the signed Subject Information Sheet/Informed Consent Form document. The original Informed Consent Form should be retained with the source documents. If patient is unable to sign the informed consent form themselves due to blindness or other disability which doesn't affect their understanding of the study/capacity, a witness can sign on behalf of the patient.

Some people with capacity will consent to take part in research, but then may lose capacity before the end of the study. We will assume capacity is present unless established otherwise; should concerns arise, members of our clinical team will take steps to assess capacity status. If we become aware that a participant has lost capacity prior to implant they will be withdrawn from the study at this time-point. If a participant has lost capacity after implant there are no risks involved in the follow-up as both arms are receiving guideline indicated therapies. Primary endpoint data will be collected via their healthcare records and when necessary liaising with local research and clinical teams. For participants who lose capacity and are consented to the echo sub-study, they will not have their echocardiograms, if they have yet to have one or both. The participant and nominated other will not be contacted in any way or for any reason to obtain information required for endpoint data, this includes stopping the 6-monthly telephone follow-up visits.

8.9 Contact with General Practitioner

It is the investigator's responsibility to inform the participant's General Practitioner *(*by letter that the participant is taking part in the study provided the participant agrees to this, and information to this effect is included in the Participant Information Sheet and Informed Consent. A copy of the letter should be filed in the patients' medical records.

8.10 Participant Confidentiality

The investigator must ensure that the participant's confidentiality is maintained. On the CRF or other documents submitted to the Sponsors, participants will be identified by a participant ID number only. Documents that are not submitted to the Sponsor (e.g., signed informed consent form) should be kept in a strictly confidential file by the investigator.

The investigator shall permit direct access to participants' records and source documents for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor, NHS, Regulatory Authorities and RECs.

8.11 Data Protection and Participant Confidentiality

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

8.12 End of Trial

For safety reporting and regulatory purposes, End of Trial will be when all study visits are complete, all data are captured on the database and the study database is declared clean and hard-locked.

8.13 Study Documentation and Data Storage

The investigator must retain essential documents until notified by the Sponsor, and for at least ten years after study completion. Participant files and other source data (including copies of protocols, CRFs, original reports of test results, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) must be retained. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

9. DATA MANAGEMENT

9.1 Source Data

Source documents include original documents related to the trial, to medical treatment and to the history of the participant, and adequate source documentation must be maintained to allow reliable verification and validation of the trial data. What constitutes the source data for this trial will be outlined in the trial Monitoring Plan.

Generic names for concomitant medications should be recorded in the CRF wherever possible. All written material to be used by participants must use vocabulary that is clearly understood and be in the language appropriate for the study site.

9.2 Database

Trial data will be collected on an electronic case report form (eCRF). The principal means of data collection from participant visits will be Electronic Data Capture (EDC) via the internet using the OpenClinica database. Data is entered into the EDC system by trained site personnel. All data recorded in the eCRF will be signed off by the Investigator or his/her appropriate designee. All changes made following initial submission of data will have an electronic audit trail with a date. Specific instructions and further details will be outlined in the study specific eCRF manual.

9.3 Data Collection

Data from all trial visits will be collected and entered on the trial eCRF built in the OpenClinica system. Details of procedures for eCRF/CRF completion will be provided in a study manual.

9.4 Archiving

All trial documentation, including that held at participating sites and the trial coordinating centre, will be archived for a minimum of 10 years (following the end of the study).

10. STUDY MANAGEMENT STRUCTURE

The trial will be managed by the United Kingdom Clinical Research Collaboration (UKCRC) registered Imperial Clinical Trials Unit (ICTU).

The following groups and trial committees will be established:

10.1 Trial Steering Committee

A Trial Steering Committee (TSC) will be convened including as a minimum an independent Chair, independent clinician, the Chief Investigator, a lay person and members of ICTU (Trial Manager, Operations Manager and Statisticians). The role of the TSC is to provide overall supervision of trial conduct and progress. Details of membership, responsibilities and frequency of meetings will be defined in a separate Charter.

10.2 Trial Management Group

A Trial Management Group (TMG) will be convened including the Chief Investigator, co-investigators and key collaborators, Senior and trial statisticians, Operations Manager and trial manager. The TMG will be responsible for day-to-day conduct of the trial and operational issues. Details of membership, responsibilities and frequency of meetings will be defined in separate terms of Reference.

10.3 Adjudication Committees

Endpoint Event Adjudication Committee – this will adjudicate primary and secondary endpoint events, including death, all unplanned heart failure acute care (hospital admissions or ambulatory diuretic therapy) events, atrial fibrillation episodes and ventricular arrhythmia incidences.

Capture Adjudication Committee – this will adjudicate all capture responses for patients assigned to the physiological pacing strategy.

Upgrade Adjudication Committee – this will evaluate all patients in the trial that receive an upgrade to conventional biventricular pacing to assess whether the upgrade was deemed clinically appropriate.

10.4 Data Monitoring Committee

A fully independent Data Monitoring and Ethics Committee (DMEC) will be set up to monitor progress, participant safety, blinding fidelity, operator variability and any ethical issues involved in this trial. They will review trial progress, recruitment rates, safety, and data emerging from other trials and make recommendations to the TSC as to whether there are any reasons why the trial should not continue.

A separate DMEC Charter will be drawn up defining their responsibilities, frequency of meetings and reporting to the TSC.

The DMEC are permitted to have access to the unblinded data for review and any comparisons between groups where appropriate.

10.5 Early Discontinuation of the Study

The DMC will define the criteria for early discontinuation and make recommendations to the TSC as required.

10.6 Risk Assessment

A study-specific risk assessment will be performed prior to the start of the study to assign a risk category of 'low', 'medium' or 'high' to the trial. Risk assessment will be carried out by the ICTU QA Manager in collaboration with the Study Manager and the result will be used to guide the monitoring plan. The risk assessment will consider all aspects of the study and will be updated as required during the course of the study.

10.7 Monitoring

The study will be monitored periodically by trial monitors to assess the progress of the study, verify adherence to the protocol, ICH GCP E6 R2 guidelines and other national/international requirements and to review the completeness, accuracy and consistency of the data.

Monitoring procedures and requirements will be documented in a Monitoring Plan, developed in accordance with the risk assessment.

10.8 Quality Control and Quality Assurance

Quality Control will be performed according to ICTU internal procedures. The study may be audited by a Quality Assurance representative of the Sponsor and/or ICTU. All necessary data and documents will be made available for inspection.

The study may be participant to inspection and audit by regulatory bodies to ensure adherence to GCP and the UK policy for health and social care research.

10.9 Peer review

The trial has undergone independent peer review via the BHF funding programme. The trial has also been reviewed by senior members of ICTU and researchers at Imperial College London.

10.10 Patient and Public Involvement

PPI members were involved in reviewing the plain English summary in the grant and the REC application, and will be part of the Trial Steering Committee, supporting the creation of patient facing materials, identifying the most effective ways to share information with

potential participants in order to maximise recruitment, promoting the trial during the recruitment phase and disseminating the trial results.

10.11 Publication and Dissemination policy

We will seek to publish the results of the study in internal reports, scientific presentations and peer-reviewed scientific journals. All analysis and decisions to publish will be made the scientific team and will not be determined by funder.

Information concerning the study, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of the Sponsor. The investigator may use this information for the purposes of the study only.

A Clinical Study Report summarising the study results will be prepared and submitted to the REC within a year of the end of study.

11. APPENDIX

11.1 International Sites

University Medical Centre Ljubljana	Slovenia
Helsinki University Hospital	Finland
Beacon Hospital	Ireland
Rigsholpitalet, Copenhagen	Denmark
Zealand University Hospital, Roskilde	Denmark
Sherbrooke Hospital	Canada
University Hospital London Health Sciences Centre	Canada
University Hospital Antwerp	Belgium
Semmelweis University Hospital	Hungary
Sarawak Heart Centre	Malaysia
Queen Elizabeth II Hospital	Malaysia
National University Heart Centre	Singapore
Canberra Heart Rhythm Centre	Australia

Appendix Revision History

1.0	30 April 2024	Addition of 1) University Medical Centre Ljubljana 2) Helsinki University Hospital 3) Beacon Hospital
2.0	17 July 2024	Addition of 1) Rigsholpitalet, Copenhagen, Denmark 2) Zealand University Hospital, Roskilde, Denmark 3) Sherbrooke

		Hospital, Canada and 4) University Hospital London Health Sciences Centre, Ontario, Canada
3.0	04 December 2024	Addition of 1) Semmelweis University Hospital, Budapest, Hungary 2) University Hospital Antwerp, Antwerp, Belgium 3) Canberra Heart Rhythm Centre, Canberra, Australia 4) Sarawak Heart Centre, Sarawak, Malaysia 5) Queen Elizabeth II Hospital, Sabah, Malaysia 6) National University Heart Centre, Singapore

12. REVISION HISTORY

Version	Date	Summary of changes
1.0	02/Dec/2022	First version
2.0	14/Mar/2023	Second version, following initial submission to REC. Changes made: addition and clarification of Endpoint Event Adjudication Committee; removal of reference to Consultee, associated documentation and participant advanced directive in section “Informed Consent”; removed additional custom sentence from SAE section as not required; formatting changes. Change to what adverse events require reporting.
3.0	29/Jun/2023	Third version, related to NSA02. (1) Change to study design inclusion criteria (specifying indications more precisely to facilitate clinical interpretation) and (2) Removal of non-applicable abbreviations in protocol, (3) Amendment of typographical error in Protocol (UK written in error instead of England).
4.0	25/Jul/2023	Fourth Version, related to NSA03. (1) Change to study design, Echocardiogram baseline visit window (baseline echocardiogram visit now to be within 6 weeks of implant), and (2) Removal of non-applicable abbreviations in protocol, addition of monitor details to Contact List on protocol, correction to inclusion criteria lettering under Trial Summary and section 3.1, and addition of Northern Ireland to description of UK sites in protocol under Section 3 Study Design, (i) Inclusion criteria.
5.0	30/Aug/2023	Fifth version, related to NSA04. (1) Paragraph added to clarify differences in follow-up (timing, researchers and data collection) for international sites (this is to improve feasibility at these sites, and support recruitment + retention of participants but will not affect the scientific integrity of the study as it is powered for our primary endpoint which is heart failure hospitalisations and mortality). (2) Protocol: change in phone number for CI, change in name of study manager; (3) Change in researchers due to changes in staff for trial

		manager and trial statistician and (4) Change to study design at all NHS sites and international sites clarifying that monthly symptom questionnaires will be sent only if patients have provided an email address and that post-procedre chest x-rays will be done only if this is standard of care at the respective site. Clarified that patients will receive a monthly symptom questionnaire only if they have provided an email address at the time of enrolment and that post-procedure X-ray will be done only if standard of care. This will not affect the scientific integrity of the study as it is powered for our primary endpoint which is heart failure hospitalisations and mortality.
6.0	18/12/2023	Sixth version related to NSA05. Amendment of protocol to a) clarify switching to alternate method of physiological pacing if operator trained in this method, b) clarify that pregnancy tests to be administered pre-implant as per standard of care, c) state pre-implant ECG can be from an time prior to implant (previously 'within 2 months'). This revision is to align with clinical practise as ECG data preceding 2 months is often used and this doesn't affect study integrity or findings in any way d) state that RV pacing ECGs post-implant can be obtained at any time post-implant. A 12-lead ECG is asked for at time of implant as there are potently changes in the ECG from time of implant and during follow-up. However for RV pacing, tis is not the case.As such, the RVpaced ECG can be obtained at any time post-implant - this facilitates data collection for the trial and e) this is further clarification that X-rays to be undertaken post-implant if standard of care at that site. This was submitted as part of NSA04 but was not corrected throughout the protocol f) additional adverse event of protocol (inappropriate pacing function)
7.0	30/04/2024	Addition of Appendix to the Protocol detailing participating international sites.
8.0	28/08/2024	Reference SA 01 dated 28/08/2024. Pg 12 – new paragraph under tertiary objectives describing aims of the genetics sub-study to determine if genetic variants may detect patients at risk of pacing induced cardiomyopathy and if physiological pacing improves cardiac activation patterns in patients with identified genetic variants.

		Pg 13 – new sub heading and details for genetics sub-study Pg 13, 15, 20, 21, 32 – removal of sentences relating to monthly symptom scale as this is no longer a study assessment Pg 16 – additional detail relating to genetics stub-study explaining blood samples will be collected for gene sequencing and analysis Pg 8 & 17 Further explicit clarification of inclusion criteria that the source data which demonstrates a patient's ejection fraction is 35% or greater (key inclusion criteria of the trial) is from a scan within the last 12 months. Pg 18 – annotation to the schedule of events at bottom of table to clarify that baseline echo is taken from screening or within the last 12 months Pg 19 – sub-heading and detail relating to genetic sub-study under the assessments heading, stating how blood will be collected and stored. Pg 22 – paragraph updated to include all device manufacturers (Medtronic, Boston Scientific, Biotronik and Abbott) in the “trial patient clinic” work flow. Previously, this only included Medtronic. Pg 24 – additional wording under adverse event reporting to include known pacemaker complications as expected events in this cohort. Pg 31 – additional sentence stating that accidental unblinding of study participants is to be recorded as a protocol deviation only (and not a protocol violation)

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14. SIGNATURE PAGE 1 (CHIEF INVESTIGATOR)

The signature below constitutes approval of this protocol by the signatory, on behalf of the Protocol Development Group, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: **PROTECT-HF: - Physiological vs Right ventricular pacing Outcome Trial Evaluated for bradyCardia Treatment**

Protocol Number: 22HH7931

Signed: _____

Dr Daniel Keene
Clinical Senior Lecturer in Cardiac Electrophysiology and Devices
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Date: _____

Signed: _____

Dr Zachary Whinnett
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SIGNATURE PAGE 2 (SPONSOR)

The signatures below constitute approval of this protocol by the signatory.

Study Title: **PROTECT-HF: - Physiological vs Right ventricular pacing Outcome Trial Evaluated for bradyCardia Treatment**

Protocol Number: 22HH7931

Signed: _____

Becky Ward
Research Governance and Integrity Manager, Research Governance and Integrity Team (RGIT),
Imperial College London

Date: _____

SIGNATURE PAGE 3 (STATISTICIAN)

The signatures below constitute approval of this protocol by the signatory.

Study Title: **PROTECT-HF: - Physiological vs Right ventricular pacing Outcome Trial Evaluated for bradyCardia Treatment**

Protocol Number: 22HH7931

Signed: _____

Ms Emanuela Falaschetti
Research Fellow in Clinical Trial Statistics at the Imperial Clinical Trial Unit (ICTU), Imperial College London

Date: _____

SIGNATURE PAGE 4 (PRINCIPAL INVESTIGATOR)

The signature of the below constitutes agreement of this protocol by the signatory and provides the necessary assurance that this study will be conducted at his/her investigational site according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: **PROTECT-HF: - Physiological vs Right ventricular pacing Outcome Trial Evaluated for bradyCardia Treatment**

Protocol Number: 22HH7931

Address of Institution: _____

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_____

Signed: _____

Print Name and Title: _____

Date: _____