CLINICAL STUDY PROTOCOL

Study Title: AV optimisation delivered with direct His bundle pacing, in patients with heart failure, long PR without left bundle branch block: randomised multi-centre clinical outcome study.
The His Optimised Pacing Evaluated for Heart Failure Trial (HOPE-HF)

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ABBREVIATIONS (amend as necessary)

AE	Adverse Event
CI	Chief Investigator
CRF	Case Report Form
DMC	Data Monitoring and Ethical Committee
GCP	Good Clinical Practice
ICMJE	International Committee of Medical Journal Editors
ICTU	Imperial Clinical Trials Unit
REC	Research Ethics Committee
QA	Quality Assurance
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee

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TRIAL SUMMARY

TITLE
AV optimisation delivered with direct His bundle pacing, in patients with heart failure, long PR without left bundle branch block: randomised multi-centre clinical outcome study. The His Optimised Pacing Evaluated for Heart Failure Trial (HOPE-HF)

OBJECTIVE
To evaluate whether, a group of heart failure patients who are not currently targeted for pacing therapy for heart failure, will obtain benefit from pacing therapy delivered to allow optimisation of LV preload by shortening Atrioventricular delay.

DESIGN
This is a multi-centre, prospective randomised double-blinded cross over study, recruiting a sub-population of patients with heart failure.
All patients will be implanted with a CRT device with one of the leads positioned on the His bundle in order to obtain direct His-bundle capture. There will be a 2-month run-in period where the device will be programmed not to deliver His pacing therapy during this period.
A double-blinded cross-over design will then be employed to investigate the effect of His pacing. Patients will be allocated in random order to six month treatment periods in each of the following two states (1) No His pacing; (2) AV optimised His-bundle pacing. Endpoint measurements will be taken at baseline, 6 months and 12 months post randomisation. Treatment allocation will be blinded to the endpoint assessor.

SAMPLE SIZE
126 patients will be needed to detect the expected effect size on the primary endpoint with 90% power. A total of 160 patients will be randomised to allow for patient drop-out.

INCLUSION CRITERIA
- Aged 18 or above
- Ventricular Ejection Fraction (EF) ≤ 40%; BNP needs to be ≥250ng/L for patients with EF 36-40%
- New York Heart Association (NYHA) class II-IV
- PR interval ≥200ms
- Narrow QRS duration (≤140ms) or prolonged QRS duration with typical Right Bundle Branch Block (RBBB) morphology on 12 lead ECG and sinus rhythm

EXCLUSION CRITERIA
- Permanent or persistent atrial fibrillation (AF)
- Paroxysmal atrial fibrillation with history of sustained AF (more than 24 hours) in the 6 months prior to screening
- Patients who are unable to perform cardiopulmonary exercise testing
- Other serious medical condition with life expectancy of less than 1 year
- Lack of capacity to consent
- Pregnancy
- Contraindication to use of the relevant study device or leads (as per current manuals from manufacturer)

TREATMENT/MAIN STUDY PROCEDURES

Implantation of pacemaker or Implantable cardioverter defibrillator. In all patients leads will be positioned in the right atrium and at the His bundle. Participants who are not eligible for ICD implantation will have a lead positioned in a lateral ventricular branch of the coronary sinus. Those receiving an ICD will have an ICD lead positioned in the RV apex or RV septum.

AV delay optimisation will be performed using continuous non-invasive blood pressure measurements, with an algorithm to minimise the effect of noise.

PRIMARY ENDPOINT

The primary outcome measure will be exercise capacity, measured using peak oxygen uptake (VO_2).

SECONDARY ENDPOINTS

Secondary outcome measures will be echocardiographic measurement of left ventricular dimensions, quality of life scores, daily activity levels as recorded by the implanted device, cost effectiveness, changes in B-type Natriuretic Peptide (BNP), arrhythmia burden, pacing parameters (e.g. pacing thresholds, R Wave amplitude and lead impedance) and fluoroscopy time at time of device insertion.

1 INTRODUCTION

Heart failure is a major clinical problem, causing a high symptom burden and high mortality rates[1,2]. In the UK heart failure accounts for 1 million days of inpatient stay per year, this is ~ 2% of all NHS hospital inpatient days and 5% of emergency admissions[3].
Hospitalisation for heart failure is expected to rise by 50% over the next 25 years. Heart failure also causes significant mortality (35% mortality in the first year after diagnosis and then 10% thereafter). There are currently ~900 000 patients in the UK with heart failure[3].

Cardiac resynchronisation therapy (CRT) is an important treatment, which has been shown to improve symptoms, reduce hospital admissions[4,5] and decrease mortality[6].
However, CRT is only applicable to some patients with heart failure: those who have left bundle branch block[7]. Therefore a new method of pacing therapy that can benefit a group of heart failure patients not currently targeted for CRT would be a major advance.

Currently patients with narrow QRS duration or right bundle branch block are not routinely selected for treatment with CRT because, when tested in a bias-resistant manner, the results have not been favourable[8,9]. However, these studies did not specifically target the group who are most likely to derive benefit, namely those with a long PR interval. In addition classical CRT when applied to patients with good intraventricular conduction appears to induce a degree of iatrogenic intraventricular dyssynchrony, which may partly offset the benefits of PR interval shortening[10].

PR prolongation in heart failure is associated with poor outcomes (58% higher mortality) regardless of QRS duration[11]. Shortening a prolonged PR interval with pacing therapy appears to have beneficial effects. In CRT studies performed in patients with LBBB, longer baseline PR interval predicted greater benefit[12]. In COMPANION, patients with a long PR interval had a 17% greater risk reduction compared to those with a normal PR interval[13], an effect size on par with that of mandatory drugs in heart failure[14]. Similarly in the MADIT-CRT trial, participants with non-LBBB QRS broadening derived a prognostic benefit from CRT only when the PR interval was above 230 ms, whereas the opposite effect was found when the PR was shorter than 230 ms[15].

In our institution, patients with PR prolongation account for 30% of the non-left bundle branch block heart failure population. Therefore in the UK alone this group of patients is likely to represent ~180,000 patients.

1.1 Rationale for the study

Optimising left ventricular filling by shortening AV delay has been demonstrated to have a powerful effect on acute cardiac function, which is reflected by changes in LV dp/dtmax, stroke volume, coronary artery flow and systolic blood pressure[16,17,18]. We have developed a haemodynamic method for identifying optimal AV delay settings with pacing therapy for heart failure. The advantage of using systolic pressure is that this is an extra cardiac measure, which reflects the net change in cardiac function occurring as a result of adjustments in intra cardiac timing. In patients with heart failure, contrary to the general population, higher blood pressure is associated with lower mortality[19]. The increased blood pressure occurring with more optimal AV delays is reflected by a sustained increase in stroke volume[20].

We have previously shown that when haemodynamic measurements are used for AV delay optimisation it is essential to use a method that minimises the effect of noise. Noise occurs with all haemodynamic measurements, regardless of whether they are made

invasively or non-invasively[21]. The protocol we have developed for performing AV delay optimisation utilises several steps to ensure precise and reproducible measures are obtained. These include comparing each tested delay to a reference setting and using the mean value of multiple alternations to and from the reference setting[22]. We have shown that it is most efficient to sample immediately after a transition[21], to use a sampling window which includes the number of beats occurring in 1 respiratory cycle and to perform measurements at an elevated heart rate[23]. We have shown that this method is highly reproducible when used for AV delay optimisation[22,17].

As discussed above, improving LV preload by shortening AV delay appears to be an important mechanism through which CRT delivers its beneficial effect in patients with left bundle branch block and heart failure[13]. Patients with narrow QRS duration and PR prolongation may also be expected to obtain benefit from AV delay optimisation. However, applying CRT pacing to patients with good intraventricular conduction appears to induce a degree of iatrogenic intraventricular dyssynchrony which has the potential to partly offset the benefits of PR interval shortening[10].

In patients with an intact intraventricular conduction system, a special form of pacing called direct His-bundle pacing, offers the potential to stimulate ventricular contraction while preserving ventricular activation patterns[24,25,26]. Permanent direct His pacing has been shown to be feasible when it has been applied in patients who have a bradycardia indication for pacing[27] or to reverse proximal LBBB in patients who have failed a conventional LV lead implant[28].

Permanent direct His pacing has never been assessed as a method for delivering AV delay optimisation to patients with narrow QRS duration or RBBB and heart failure. We have assessed the acute haemodynamic effect in this patient population and found favourable results[29].

Therefore in this study we will evaluate whether, a new group of heart failure patients who are not currently targeted for pacing therapy for heart failure, obtain benefit from pacing therapy delivered to allow optimisation of LV preload by shortening AV delay.

Our study involves two novel aspects. Firstly, in order to reduce the risk of causing harm by inducing ventricular electrical dyssychrony, we will use a special form of pacing – direct

His bundle pacing- which has not previously evaluated in this context. Secondly, we will use a novel method for identifying optimal AV delay, which is designed to ensure precise and reproducible values are obtained.

1.2 Intervention details

All patients will be implanted with a Pacemaker or Implantable cardioverter defibrillator (ICD).
All participants will have pacemaker leads positioned in the right atrium (typically the right atrial appendage) and on the His bundle in order to obtain His-bundle capture. If it is not possible to successfully implant a His-bundle lead with selective direct His bundle capture or non-selective capture with < 40ms prolongation of the QRS duration, then a lead will be implanted in a lateral branch of the coronary sinus as an alternative approach.

In patients who do not have an indication for an Implantable cardioverter defibrillator (ICD) a second ventricular lead will be implanted in a lateral branch of the coronary sinus. If His pacing has not been successfully achieved then a further lead will be positioned at the RV apex. In patients who have an indication for an Implantable cardioverter defibrillator the ICD lead will be positioned in the right ventricle (either RV apex or RV septum).

Implantation procedure:

Implanters will undergo training in His bundle pacing and will be provided with detailed guidance regarding the device implantation protocol. In brief the implant process will include the following steps.

Venous access will be obtained in the standard way and an atrial lead will be implanted in the right atrial appendage. In patients receiving Implantable cardioverter defibrillator the ICD lead will next be implanted in the conventional way targeting the RV apex or RV septum.

His bundle pacing: a Medtronic Select Secure 3830 pacing lead will be positioned at the His bundle using a 9 French delivery sheath (either the Medtronic C315 fixed shaped catheters or the Medtronic SelectSite C304 deflectable catheter). His capture will be confirmed using the criteria previously described by Deshmukh et al[18]. In brief these consist of confirming the following: a) 12 lead ECG morphology match with direct His bundle pacing compared with intrinsic conduction, b) similar time delay between the stimulation artefact and the onset of the QRS complex compared with the intrinsic His to QRS time, c) His bundle capture in an all or none-fashion, demonstrated by the absence of QRS widening at a lower pacing output.

If selective His bundle pacing cannot be achieved then non-selective His bundle pacing will be accepted. Non-selective His pacing is defined as the direct capture of the basal ventricular myocardium in addition to His bundle capture.

Patients will be randomised to 6 months of the following:

1) *Active treatment*: His bundle pacing with the AV delay programmed to the optimal sensed and paced delays identified during the optimisation process

2) *No His pacing treatment:* pacemaker programmed to avoid pacing as per the implanting physicians discretion utilising the non His ventricular lead (suggested modes are VVI 30, DDD/I 30 etc). His pacing should only be programmed on active treatment.

Dynamic AV delay will be programmed off throughout the study.

1.3 Risk / Benefit Assessment

The risks associated with pacemaker implantation include:

- ~1% of developing pneumothorax
- ~1% of infection of pacemaker
- ~1% of lead displacement or device malfunction
- < 1% risk of pericardial effusion
- ~ 3% risk of haematoma
- ~2% risk of access vein clot

In order to minimise these risks, procedures will be carried out by highly experienced, high volume pacemaker implanters. All procedures will be carried out in centres which have the facilities and expertise available to manage complications should they occur.

Potential benefits of pacing in this population

- Improvement in heart failure symptoms
- Prevention of bradycardia (while this population do not have a pacing indication for bradycardia they are at increased risk of developing higher degrees of conduction

block or sinus bradycardia). The pacemaker will prevent bradycardia from occurring and symptoms occurring as a result of this.

- Patients with prolonged PR interval and heart failure are at higher risk of adverse outcomes including death. While this study is not powered to assess for a mortality benefit it is possible that the risk of death will be reduced with pacing therapy.

The Data Monitoring Committee will meet regularly and will review adverse event rates. If they are found to be higher than expected then appropriate action will be taken.

2 OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

To evaluate whether, a group of heart failure patients who are not currently targeted for pacing therapy for heart failure, will obtain benefit from pacing therapy delivered to allow optimisation of LV preload by shortening Atrioventricular delay.

2.2 Secondary Objective

To assess direct His pacing characteristics in this population (including acute and chronic pacing thresholds).

2.3 Primary Endpoint

The primary outcome measure will be exercise capacity, measured using peak oxygen uptake (VO_2).

2.4 Secondary Endpoints

Secondary outcome measures are:

(1) Echocardiographic measurement of left ventricular function and remodelling

(2) Changes in B-type Naturietic Peptide (BNP)

(3) Changes in Quality of Life Scores

(4) Changes in daily activity levels recorded using objective metrics from the pacemaker device

(5) Cost effectiveness analysis

(6) Percentage pacing will be recorded, as will arrhythmia burden (atrial fibrillation, atrial flutter and ventricular arrhythmias), pacing thresholds, R wave amplitude and lead impedance. Fluoroscopy time during device insertion will also be reported.

3 STUDY DESIGN

3.1 Design

This is a multi-centre, prospective randomised double-blinded cross over study, recruiting a sub-population of patients with heart failure from multiple investigational sites in the UK. Recruitment is expected to take place over about 2 years.

All patients will be implanted with a Pacemaker or Implantable Cardioverter Defibrillator with one of the leads positioned on the His bundle in order to obtain His-bundle capture. There will be a 2-month run-in period where the device will be programmed not to deliver His pacing therapy during this period. Patients will be allocated in random order to six month treatment periods in each of the following two states (1) No His bundle pacing; (2) AV optimised His-bundle pacing. Endpoint measurements will be taken at baseline, 6 months and 12 months post randomisation. Treatment allocation will be blinded to the endpoint assessor.

3.2 Treatment regimens

Treatment regimens are summarised in the flow diagram in Appendix 1.

4 PARTICIPANT ENTRY

4.1 Study population

(i) Inclusion criteria

1. Aged 18 or above
2. *Ventricular Ejection Fraction (EF) ≤ 40%; BNP needs to be ≥250ng/L for patients with EF 36-40%,
3. New York Heart Association (NYHA) class II-IV
4. **PR interval ≥200ms
5. **Narrow QRS duration (≤140ms) or prolonged QRS duration with typical Right Bundle Branch Block (RBBB) morphology on 12 lead ECG and sinus rhythm

* Ejection Fraction should be based on patient's echocardiograph within the last 18 months; if that is not available a new echo will be performed. Patients with EF 36-40% must have at least one BNP result within the last 18 months having a value of ≥ 250ng/L, otherwise, a blood test will be done to assess BNP. Some centres use NT-pro BNP test instead of BNP. An NT-pro BNP result of ≥600ng/L is acceptable.

** ECG criteria should be based on patient's ECG within the last 18 months; if that is not available a new ECG will be performed.

(ii) Exclusion criteria

1 ***Permanent or persistent atrial fibrillation (AF)
2 Paroxysmal atrial fibrillation with history of sustained AF (more than 24 hours) in the 6 months prior to screening
3 Patients who are unable to perform cardiopulmonary exercise testing
4 Other serious medical condition with life expectancy of less than 1 year
5 Lack of capacity to consent

6 Pregnancy (female participants of reproductive age will be eligible for inclusion in the study, subject to a negative pregnancy test prior to randomisation)
7 Contraindication to use of the relevant study device or leads (as per current manuals from manufacturer)

***Patients who have persistent AF in their medical history but has then resolved can be included.

Eligible patients can be sub-divided into 2 groups: A) patients who do not have an indication for an implantable ICD (this group will receive His CRT-P); and B) patients who do have an indication for an implantable ICD (this cohort will receive His CRT-D)

Patients who meet the study inclusion criteria, but have completed other research studies or concurrently participating in a non-interventional study (e.g. observational studies) may be invited to take part in the trial at the Investigator's discretion.

5 PROCEDURES AND MEASUREMENTS

5.1 Screening and pre-randomisation evaluations

Written informed consent will be obtained before the subject undergoes any screening procedures.
Potential study participants will be identified following the review of medical notes of patients attending; general cardiology clinics, Heart Failure clinics, ICD clinics or during admission to hospital. 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.

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

1. ECG (can be taken at the visit or within the past 18 months; this ECG determines patient eligibility and will be reviewed centrally)
2. Echocardiography (new echo will be performed if no report is available within the past 18 months)
3. BNP or NTproBNP in some centres (sample is only taken for patients with EF 36-40% and have no available BNP result within the past 18 months).
4. Demographics
5. Medical History
6. Physical Examination
7. Pregnancy test will be performed for women of childbearing age

Eligible patients will be asked to complete a resource utilisation questionnaire at this visit.

5.2 Visit Schedule

A summary of study procedures/assessments by visit is presented in table 1.
Patients will be screened at participating hospitals and have implantation performed at the participating hospital or at the lead research site - Hammersmith Hospital, which is Imperial

College Healthcare NHS Trust. Two months after patients are implanted with their device, patients will attend 3 more study visits at Imperial College Healthcare NHS Trust. Patients coming from other hospitals will be registered with the Hammersmith Hospital for study visits.

5.3 Treatment

Patients entering the study will then attend for implantation of their device, this will be performed either at their local hospital or at Imperial College NHS Healthcare Trust, no later than 4 months of the patient's screening visit

Prior to implantation, blood tests will be performed to assess clotting function, full blood count and electrolytes. Additionally, blood will be taken for group and save if required as per local clinical practice. Antibiotic prophylaxis, analgesia and sedation can all be given as per the implanting institution's local policies and normal practice. As is standard clinical practice for pacemaker implantation, the following routine blood tests will be performed: creatinine level, haemoglobin level, prothrombin time (PT; clotting), and Group and Save (G+S). Tests performed up to a specified date prior to the implantation day can be accepted, please refer to Appendix 2 for details.

All patients will be implanted with a Pacemaker or Implantable cardioverter defibrillator (ICD). In all patients, a pacing lead will be positioned in the right atrium (typically the right atrial appendage). All patients will have a pacemaker lead positioned on the His bundle in order to obtain His-bundle capture. If it is not possible to successfully implant a His-bundle lead with selective His bundle capture or non-selective capture with < 40ms prolongation of the QRS duration, then a lead will be implanted in a lateral branch of the coronary sinus.

In patients who do not have an indication for an Implantable cardioverter defibrillator (ICD), a second ventricular lead will be implanted in a lateral branch of the coronary sinus. If His pacing has not been successfully achieved then a further lead will be positioned at the RV apex. In patients who do have an indication for an Implantable cardioverter defibrillator, the ICD lead will be positioned in the right ventricle (either RV apex or RV septum).

A chest X-Ray will be taken after the procedure to ensure the pacemaker leads are in position.

AV delay optimisation: will be performed using acute non-invasive blood pressure acquired using the Finometer device (Finapres Medical Systems, Netherlands). The BHF alternation protocol we have previously described will be used in order to minimise the effect of background noise [22].

The optimal AV delay will be determined during atrial sensing and atrial pacing. For atrial pacing the optimisation will be performed at 10-20 bpm above the resting heart rate provided AV conduction is 1:1 during AAI pacing at this heart rate. If Wenkebach conduction or heart block occurs at this rate then we will lower heart rate in order to achieve 1:1 conduction. If 1:1 conduction is not achievable at the lower heart rate, then the paced AV delay optimisation will be performed with a reference setting of His pacing with an AV delay of 120ms.

For atrial sensing, optimisation will be performed at resting heart rate.

After implantation of the device, there will be a 2 month run-in period prior to randomisation, the device will be programmed not to deliver His pacing therapy during this period.

5.4 Randomisation and Crossover

Two months after patients are implanted with their device, patients will be randomised to either receive active His pacing treatment or no His pacing treatment (e.g. pacemaker programmed to VVI or DDD/I 30 bpm). After a further 6 months, they will be crossed over to the alternative treatment arm. Treatment allocation will be obtained using an Interactive Web Response System (IWRS) programmed with a randomisation schedule provided by the trial statistician. Appropriate blocking will be used.

The patient will have study assessments listed in table 1 and described in the section 5.5.

The physiologists performing study tests will be blinded to the treatment arm. A separate investigator will be responsible for programming the device.

5.5 Study assessments

Physical examination

Patients will have a physical examination where vital signs will be taken.

Cardiopulmonary exercise testing:

Patients will exercise on a treadmill using a “smoothed modified Bruce” protocol [30]. A physiologist and another HOPE HF study team member (e.g. research nurse, research fellow or another physiologist) will be present for this test. For safety reasons, it is necessary to perform ECG monitoring during this test. It may be possible to see pacing spikes in the ECG. Therefore to ensure that the physiologist who is leading the exercise test is blinded, the screen displaying the ECG will only be visible to the second study personnel who will be responsible for monitoring ECG. They will only request that a test is stopped if there are ECG findings which make this necessary on clinical safety grounds. This way both the patient and the physiologist leading the exercise test will remain blinded to the treatment arm. Exercise capacity will be measured as peak exercise oxygen consumption in ml/kg/min.

BNP:

We will take 5mls of blood to measure B type Natriuretic Peptide (BNP) in an EDTA bottle. The samples will be analysed at the Hammersmith hospital and no sample will be stored.

Echocardiography:

Patients will have a standard HOPE HF echo protocol performed including left ventricular dimensions, volumes, ejection fraction and quantification of mitral regurgitation. No ECG will be recorded during the echocardiogram once the patient is randomised. The physiologist performing the test will be blinded to the treatment arm.

Daily Activity Measurement:

All implanted devices in the study can provide data on daily activity measured in minutes per day. The comparison will be made between the His pacing and no His pacing arms.

Quality of Life (QOL) and Cost Effectiveness Evaluation questionnaires:
The economic evaluation will compare incremental costs and incremental outcomes of the direct His-bundle pacing against standard medical care. The economic evaluation will consist of two parts, a cost-effectiveness analysis (CEA) and a cost utility analysis (CUA). In the CEA the incremental cost-effectiveness ratio (ICER) will be expressed as the incremental costs per point improvement in exercise capacity in peak VO_2. The primary outcome measure in the CUA will be Qualitative Adjusted Life Years (QALYs), based on the EuroQoL EQ-5D scores.
In order to measure the costs of the resources patients use, a resource use measurement (RUM) questionnaire will be developed and validated for the HOPE-HF study. The RUM questionnaire consists of a standard RUM questionnaire with small adaptations specific to the subject of heart failure patients.

We will use the Minnesota Living with Heart Failure Questionnaire (MLHFQ) (http://www.mlhfq.org/) and EQ-5D to assess for changes in quality of life (QoL). The MLHFQ questionnaire is a validated condition-specific measure with good sensitivity and discrimination. It will be complemented with the EuroQoL EQ-5D both of these are well validated generic measures of QoL.

The trial staff administering these questionnaires will be blinded to the treatment arm.

5.6 Final study visit

At 12 months post randomisation, the patient will have a final study visit and the above tests performed. After this treatment allocation will be revealed and the patient will have the chance to decide whether they wish to continue receiving AV optimised His pacing. If they prefer not to decide the decision will be left to their direct medical care team.

The patient's GP and direct medical care team will be notified that the patient has completed the study and the patient will return to routine clinical care.

At the final study visit, participants will also be given the option of whether they would like to be contacted when the study results are available. They will be given the following options:

- Written communication of results
- Telephone call from research team
- Visit to discuss results with research team
- Meeting with direct medical care team to discuss results

Once patients have been informed of the study results they will be given the option of changing their choice of pacing treatment (1) Active treatment: His pacing with the AV delay programmed to the optimal sensed and paced delays identified during the optimisation process or 2) No His pacing treatment: device is programmed according to clinical indication). Should the patient want more time to consider this decision, further reviews or telephone communications could be scheduled.

5.7 Unblinding

Patients will be blinded to treatment arm. We anticipate that some patients may request a change in their treatment arm, particularly if there is a change in their symptom status. If this occurs we will try to encourage patients to continue with their designated treatment (either His pacing or no His pacing) until they cross over to the other treatment to complete

the study. However, if they are not willing to continue treatment then their request for a change in treatment will be met. Our analysis will be made on an intention to treat basis. The master randomisation list will be stored electronically within a specialised 'blinded' folder in the statistics section of the Trial Master File (TMF) to ensure that the trial statistician does not have access to the list. A copy will also be made available to dedicated personnel in the research unit who will support unblinding of individual patient's treatment allocation upon request. Requests for unblinding should be discussed with the Chief Investigator or delegate beforehand.

6 TREATMENTS

6.1 Medical Devices

Medtronic CRT-D or CRT-P devices which meet the following criteria:

1. contains an IS1 port for the His lead (required)
2. contains a DF4 slot for the defibrillator lead (preferred)
3. certified MRI conditional

The His-bundle will be paced with a Medtronic SelectSecure 3830 69cm steroid eluting, bipolar, implantable, non-retractable screw-in catheter delivered transvenous pacemaker lead. The lead will be positioned using the C315 His delivery catheter, the SelectSite C304-L69/C304-S59 or other His delivery sheaths as per the implanting operator's discretion.

6.2 Labelling and Packaging

Refer to current manuals for the relevant product from the manufacturer.

6.3 Storage and Administration

Refer to current manuals for the relevant product from the manufacturer.

6.4 Monitoring Device Performance

Device data will be reviewed in person when patients attend for review at Visit 3, 4 and 5 (2 months, 8 months and 14 months post device implantation respectively). This will provide details on pacing thresholds, R wave amplitude and lead impedance. Details of any arrhythmia will also be seen. This data will be included in reports to the DMC for monitoring of any adverse consequences.

Device follow-up after cessation of the trial will be at the patient's local cardiology centre.

6.5 Device Precautions

Patients will be advised that prior to any future MRI scan or procedures that involve the use of diathermy, they should seek advice from their local pacing department so that their device settings can be adjusted to make the MRI/diathermy procedure safe and arrangements can be made to interrogate the device after the procedure.

6.6 Permanent Discontinuation of Study Treatment and Withdrawal from Study

(i) Permanent discontinuation of study treatment

Subjects may discontinue study treatment for the following reasons:

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

(ii) Withdrawal from Study

Withdrawal from the study refers to discontinuation of study treatment and study procedures and can occur for the following reasons:

- Subject decision
- Loss to follow-up

(iii) Procedures for Withdrawal from Study

If a patient wishes to withdraw from the study, they will be asked at what level they wish to withdraw i.e. if they would like to terminate pacing treatment but are willing to attend follow-up visits, or if they do not wish to be contacted about the study including results of the study. Reason for and level of withdrawal must be recorded in the eCRF and medical records. Patients will not be replaced and follow-up should continue if the patient agrees. In the event that a subject wishes to terminate treatment after implantation of the study device, the patient's GP or direct medical care team will be notified and the patient will return to routine clinical care.

7 ADVERSE EVENTS AND DEVICE VIGILANCE

7.1 Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the medical device.

7.2 Adverse Event recording

All adverse events will be recorded using the InForm System with the following exceptions.

Exemptions:

All planned elective non-cardiac admissions/procedures/surgeries do not need to be reported as adverse events.

(i) Severity of Adverse Events

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

(ii) Causality of Adverse Events

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 administration of the medical device). 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 (e.g. because the event occurs within a reasonable time after administration of the medical device). 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 are unlikely.
Definite: There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

7.3 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 subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
** "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

All SAEs will be reported to the Sponsor within 24 hours of an Investigator becoming aware of the event. Reporting procedures are detailed in the study's SAE reporting instructions. If the investigator becomes aware of safety information that appears to be related to the

medical device or study procedures, involving a subject who participated in the study, even after an individual subject has completed the study, this should be reported to the Sponsor.

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 (InForm).

7.4 Adverse Device Effects

Relatedness should be assessed in relation to both the medical device and to the procedures which are associated with the device function (e.g., insertion, removal).

Incidents related to the device will be reported to the Device Manufacturer (Medtronic) within 48 hours of the event happening to the designated Medtronic contact.

(i) Adverse Device Effects (ADE)

An ADE is defined as an AE related to the use of the medical device and includes any AEs resulting from insufficient or inadequate instructions for use, deployment, installation or operation, or any malfunction of the medical device (device deficiency). It also includes any AE resulting from user error or from intentional misuse of the medical device.

Anticipated Device adverse events are listed in the corresponding current device manual.

(ii) Serious Adverse Device Effect (SADE)

A SADE is an ADE that results in any of the consequences characteristic of an SAE.

(iii) Unanticipated Serious Adverse Device Effect (USADE)

Those SADEs which by nature, incidence, severity or outcome have not been identified in the current protocol or device brochure are considered an Unanticipated Serious Adverse Device Effect (USADE).

(iv) Anticipated Serious Adverse Device Effect (ASADE)

An ASADE is an effect which by nature, incidence, severity or outcome has been identified in the current device manual.

The Sponsor will be informed of all SADEs, either unanticipated or anticipated.

7.5 Reporting of Unexpected and Serious Adverse Events

Any SAE occurring to a study participant should be reported to the REC if in the opinion of the Chief Investigator the event was:

Related – that is, it resulted from administration of the medical device or any of the research procedures, and

Unexpected – that is, the type of event is not listed in the protocol/device manual as an expected occurrence and serious adverse events will be reported to the REC

Reporting of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event.

Safety reports will be included in the annual progress report submitted to the Sponsor and the Ethics Committee.

8 STATISTICAL ANALYSES

8.1 Sample Size and power considerations

We will use a smoothed modified Bruce protocol for patients with heart failure. This enables improved reproducibility of peak VO_2[30]. With this approach, reproducibility in heart failure patients between two separate visits to the hospital is 2.4 ml/kg/min, expressed as the standard deviation of the difference between two independent measurements[31]. Implantation of a cardiac resynchronisation therapy pacemaker in patients with broad QRS duration and heart failure results in a 0.5-2.5 (mean 1.5) ml/kg/min increase in peak $V0_2$[32-37]. Our published pilot data is that switching on classical cardiac resynchronisation therapy in patients with a broad QRS duration increments LV systolic blood pressure by ~10.3mmHg, and switching on direct His-bundle pacing in long-PR/narrow-QRS patients increment blood pressure by ~6.3mmHg, i.e. ~60% of that effect. Pro-rata we would therefore expect an estimated increment in peak VO2 of 60% of 1.5ml/kg/min, i.e. 0.9 ml/kg/min.

Adopting a conservative approach, a two-sided alpha of 0.05 is chosen. Using a paired t-test, in order to detect a difference of 0.7 with SD of 2.4, to achieve a power of 90% would require a total of 126 evaluable patients. Allowing for a combined mortality/dropout of 21%, the study would require a total sample size of 160 patients. Consequently, 160 patients will be randomised in a 1:1 manner to the treatment groups.

Detailed analysis methods will be documented in the study's Statistical Analysis Plan (SAP).

8.2 Data Analysis

Patient characteristics will be summarized. Summaries of 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.

The analysis will be performed according to the intention to treat principle.

(i) Endpoint Analysis

The primary outcome will be analysed using a two-level hierarchal model. We will include treatment, period and sequence effect within the model. Random subject effects will also be included in the regression model if appropriate. Differences in secondary outcomes will also be analysed using aforementioned two level hierarchal model. Normality will be checked and appropriate transformation or non-parametric methods will be used if it is not met.

All statistical tests will be two-tailed with a 5% significance level.

A separate statistical analysis plan will be prepared and finalised prior to database lock.

(ii) Safety Analysis

Safety analysis will consist of descriptive statistics of fluoroscopy time at the time of device insertion, pacing thresholds, R wave amplitude, lead impedance, the frequency of lead malfunction, hospitalisations and death. This will be reviewed by the Data Monitoring Committee.

(iii) Economic evaluation

The analysis will be based on an intention-to-treat (ITT) principle. The comparability of the groups, in both costs and outcomes, will be examined by a baseline analysis. When both groups are not comparable methods will be applied to control for these differences. Normal distribution of the costs and effects will be tested by Kolmogorov-Smirnov test. When the normal distribution is not present, non-parametric bootstrapping will be performed to analyse the differences between the intervention and control group. The bootstrap method will be used to calculate the 95% confidence intervals (CI). The incremental cost-effectiveness ratio (ICER) will be based on the incremental costs and incremental effects of the intervention group and the control group and will be calculated as followed: ICER = Δcosts/Δeffects. Δcosts and Δeffects are respectively the differences in costs and effects of the intervention and control group. Within the cost-effectiveness analysis the ICER will be expressed as costs per outcome rate and within the cost-utility analysis, the ICER will be expressed as the costs per QALY gain. A cost-effectiveness plane will be plotted with bootstrapped ICERs.

iv) Sub-group Analysis

1) Around 30% of patients (40 patients) recruited into the study are expected to have right bundle branch block. We will perform subgroup analysis to determine if the magnitude of haemodynamic response to AV optimised direct His bundle pacing is of a similar magnitude to that obtained in patients with narrow QRS duration.

2) We will perform analysis to determine whether a change in peak $V0_2$ and the haemodynamic response is related to baseline PR interval.

3) We will perform analysis to determine whether a change in peak VO2 and the haemodynamic response is related to E-A fusion as observed by baseline echocardiography.

4) We will perform analysis to determine the effect of AV delay optimised His Bundle pacing on daily activity level compared to control measured objectively in minutes per day by the CRT device.

5) If there are significant numbers of patients with non-selective His capture (where both the His and local ventricular myocardium are captured by the pacing stimulus) then we will perform subgroup analysis to determine whether there is a difference in the magnitude of either acute haemodynamic or change in peak $V0_2$.

6) If there are significant numbers of patients who are implanted with an LV lead due to the failure of His lead implantation we will perform subgroup analysis to determine whether there is a difference in their haemodynamic and peak VO2 response

compared to their control state and compared with the successful His implanted lead cohort.

7) A sub-group analysis will be performed to investigate patients recruited with a Ventricular Ejection Fraction of 35% and below against those recruited with an EF or greater than 35% for primary and secondary endpoints. Where possible, the analysis will be stratified by PR Interval in order to investigate whether PR is a predictor for treatment response.

8) It is anticipated that the vast majority of patients will have an indication for an implantable ICD. In the event where there is an even split between the two groups, an additional exploratory analysis may be carried out on the trial outcomes, using indication group as an additional stratification factor.

9) We will perform an analysis to assess the relationship between pacing device effect (in terms of change in peak VO2 and haemodynamic response) and BMI.

9 REGULATORY, ETHICAL AND LEGAL ISSUES

9.1 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.

9.2 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 guidelines).

9.3 Independent Ethics Committee Approval

(i) Initial Approval

Prior to the shipment of the medical device and accessories and the enrolment of subjects, the REC must provide written approval of the conduct of the study at named sites, the protocol and any amendments, the Subject Information Sheet and Consent Form, any other written information that will be provided to the subjects, any advertisements that will be used and details of any subject compensation. HRA approval is also needed before study start at each participating site.

(ii) Approval of Amendments

Proposed amendments to the protocol and aforementioned documents must be submitted to the REC for approval as instructed by the Sponsor. 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 subjects may be implemented prior to receiving Sponsor or REC approval. However, in this case, approval must be obtained as soon as possible after implementation.
HRA approval is also needed for implementation of amendments at respective participating sites.

(iii) Annual Progress Reports

The Sponsor and REC will be sent annual progress reports in accordance with national requirements.

(iv) End of Trial Notification

The Sponsor and REC will be informed about the end of the trial, within the required timelines.

9.4 Sponsorship, Insurance and Indemnity

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

9.5 Trial Registration

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

9.6 Informed Consent

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. Should a patient lose the capacity to consent during the trial follow-up period, the participant would be withdrawn from the study. Identifiable data or blood sample already collected with consent would be retained and used in the study. No further data or sample would be collected or any other research procedures carried out on or in relation to the participant.

9.7 Contact with General Practitioner

It is the investigator's responsibility to inform the subject's General Practitioner by letter that the subject is taking part in the study provided the subject agrees to this, and information to this effect is included in the Subject Information Sheet and Informed Consent. A master letter template will be kept in the Investigator Site File. A copy of the letter sent to each participant's GP should be filed in the patient's medical notes.

9.8 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained. On the CRF or other documents submitted to the Sponsor, subjects will be identified by a subject 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.

To facilitate follow-up visits of patients recruited at hospitals other than the Hammersmith Hospital, patients will be registered with the Hammersmith. Patient contact details and GP details will be made available to study's research team at Imperial College London. The research team will have access to data on InForm collected at earlier study visits. Patient medical records will be requested only if deemed necessary.

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

Principles of Data Protection Act 1998 will be adhered to.

9.9 End of Trial

The end of the trial will be after the last subject last visit and once the study database is locked.

9.10 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. Subject 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, a written agreement must be obtained from the Sponsor.

10 DATA MANAGEMENT

10.1 Source Data

Source documents will be specified for CRFs that required source data verification. Where data are directly entered into the eCRF it will also be documented.

10.2 Language

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

10.3 Database

The electronic data capture system InForm™ will be used in this study. The database will have built-in validation checks and generate auto-queries. The Trial Monitor will raise manual queries as required.

10.4 Data Collection

Details of procedures for eCRF completion will be provided in a study manual.

11 STUDY MANAGEMENT STRUCTURE

11.1 Trial Steering Committee

A Trial Steering Committee (TSC) will be convened including an independent Chair, independent clinician, the Chief Investigator and Trial Manager. The role of the TSC is to provide overall supervision of trial conduct and progress.

11.2 Trial Management Group

A Trial Management Group (TMG) will be convened including the Chief Investigator, co-investigators and key collaborators, trial statistician and trial manager. The TMG will be responsible for the day-to-day conduct of the trial and operational issues.

11.3 Data Monitoring Committee

A data monitoring committee composed of three independent professionals and including an independent statistician will be convened. The frequency of meeting and the data to be reviewed and whether the data will be blinded/unblinded will be documented in the DMC charter.

11.4 Early Discontinuation of the Study

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

11.5 Risk Assessment

A study-specific risk assessment will be performed prior to the start of the study to assign a risk category. The 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.

11.6 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 guidelines and other national requirements and to review the completeness, accuracy and consistency of the data.

11.7 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.

11.8 Disclosure of Data and Publication

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 and related studies in the future.

All information obtained as a result of the study will be regarded as CONFIDENTIAL, at least until appropriate analysis and review by the investigator(s) are completed.

Anonymised study data will be shared with the other research institutions as well as private sector companies within and outside of the European Union, where data protection laws may not be the same. These data will be used for non-commercial research purposes. All reasonable steps will be taken to protect your privacy.

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SIGNATURE PAGE 1 (Chief Investigator)

The signature below constitutes approval of this protocol by the signatory 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:

AV optimisation delivered with direct His bundle pacing, in patients with heart failure, long PR without left bundle branch block: randomised multi-centre clinical outcome study. The His Optimised Pacing Evaluated for Heart Failure Trial (HOPE-HF)

Sponsor's reference : 15HH2828

Signed: _____

Dr Zachary Whinnett
Senior Lecturer in Electrophysiology and
Honorary Cardiologist and Electrophysiologist
Imperial College London
Hammersmith Hospital

Date: _____

SIGNATURE PAGE 2 (SPONSOR)

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

Study Title:

AV optimisation delivered with direct His bundle pacing, in patients with heart failure, long PR without left bundle branch block: randomised multi-centre clinical outcome study. The His Optimised Pacing Evaluated for Heart Failure Trial (HOPE-HF)

Sponsor's reference : 15HH2828

Signed: _____

Ms Becky Ward
Research Governance Manager
Joint Research Compliance Office
Imperial College London and Imperial College Healthcare NHS Trust

Date: _____

SIGNATURE PAGE 3 (STATISTICIAN)

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

Study Title:

AV optimisation delivered with direct His bundle pacing, in patients with heart failure, long PR without left bundle branch block: randomised multi-centre clinical outcome study. The His Optimised Pacing Evaluated for Heart Failure Trial (HOPE-HF)

Sponsor's reference : 15HH2828

Signed: _____

Ms Emanuela Falaschetti
Senior Clinical Trial Statistician
Imperial Clinical Trials Unit
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:

AV optimisation delivered with direct His bundle pacing, in patients with heart failure, long PR without left bundle branch block: randomised multi-centre clinical outcome study. The His Optimised Pacing Evaluated for Heart Failure Trial (HOPE-HF)

Sponsor's reference : 15HH2828

Address of Institution: _____

_____

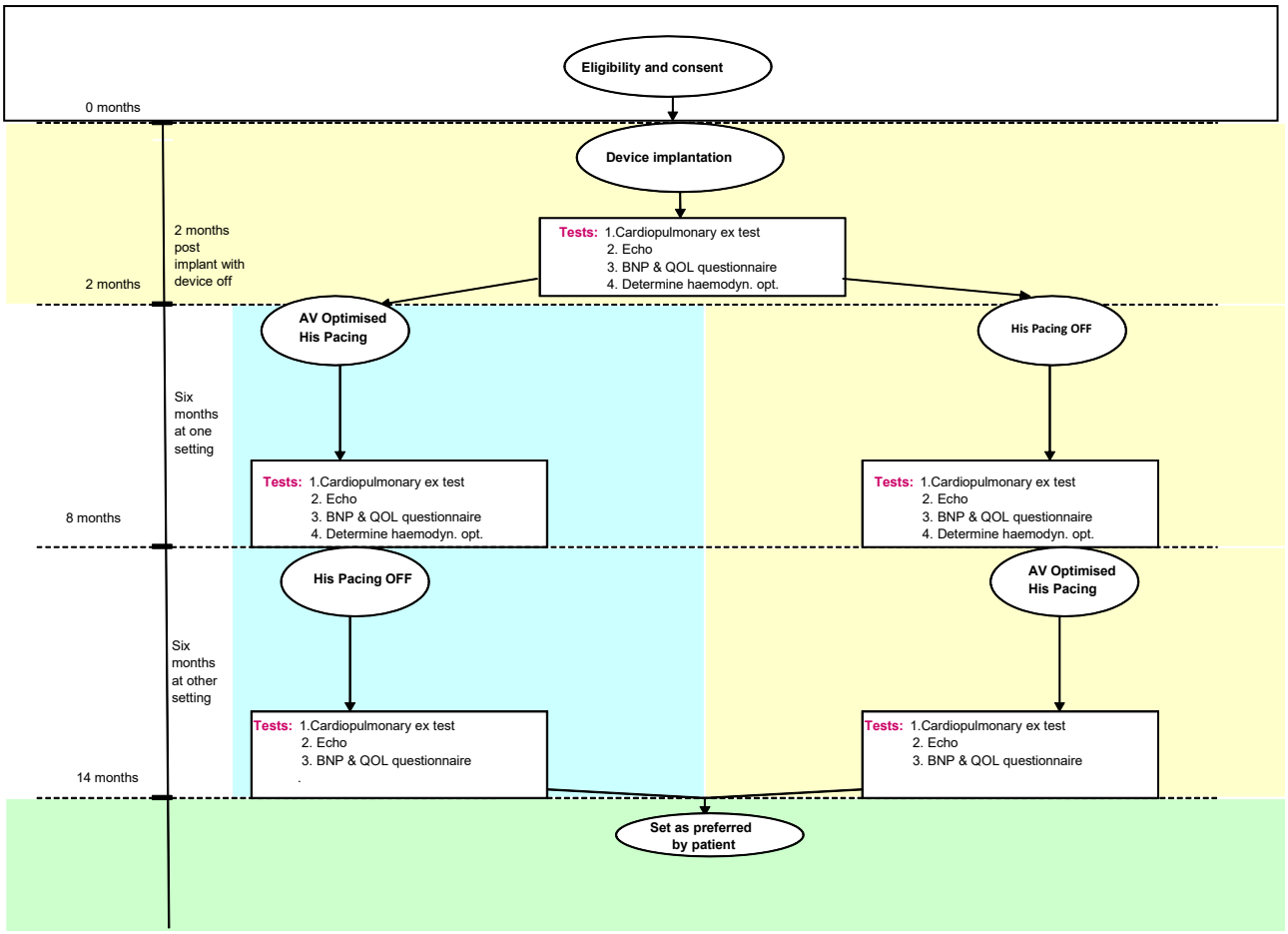
_____

Signed: _____

Print Name and Title: _____

Date: _____

Appendix 1. Treatment Regimens



Appendix 2. Summary of study procedures/assessments by visit

‡ Visit at local hospital where patient was identified
^ Performed at Imperial College Healthcare NHS Trust
& Taken at screening visit or within the past 18 months
* RUM questionnaire only at visit 1, all questionnaires for visits 3-5
# Either at local hospital or at Imperial College Healthcare NHS Trust
£ Taken on the day or within the last 12 months
$ Taken on the day of implantation or within the past 30 days
+ Taken at screening visit or within the past 18 months for patients with EF 36-40%

	Screening‡	**Implantation#**	**Randomisation^**	**Cross-over^**	**End of Study^**
Visit	**1**	**2**	**3**	**4**	**5**
Month/Week/Day	- 2 to 6 months	-2 months (± 14 days)	0	6 months (± 14 days)	12 months (± 14 days)
Informed consent	X				
Inclusion & exclusion criteria	X				
Demography	X				
Medical history	X				
Vital signs	X	X	X	X	X
Concomitant medication	X				
Pregnancy test for women of child bearing age	X				
Safety blood tests (Creatinine, Haemoglobin, PT, G+S)		X£			
ECG	X&	X$			
Device Implantation		X			
Post implantation chest radiograph		X			
Pacing check			X	X	X
Device programmed on/off			X	X	X
CPET			X	X	X
Echocardiography	X&		X	X	X
BNP	X+		X	X	X
QOL and Cost Effectiveness questionnaires (EQ5D-5L/MLHFQ and the HOPE-HF RUM)	X*		X	X	X
Haemodynamic optimisation			X	X	
Revelation of treatment sequence to patient					X
His pacing on/off according to patient's choice (Patient can make decision later)					X