1. TITLE PAGE

Full Title	Distal ventricular pacing and intraventricular gradient reduction for symptomatic relief in drug refractory hypertrophic cardiomyopathy patients with mid-cavity obstruction
Short Title/Acronym	Pacemaker therapy for drug-refractory symptoms in mid-cavity HCM
Sponsor	*Barts Health NHS Trust* *Contact person of the above sponsor organisations is:* Dr Sally Burtles Director of Research Services Queen Mary University of London 5 Walden Street, Whitechapel London E1 2EF sponsorsrep@bartshealth.nhs.uk +44 (0)20 7882 7260
REC Reference	17/LO/1725
Chief / Principal Investigator	*Saidi Mohiddin* Consultant Cardiologist and Honorary Senior Lecturer Barts Health NHS Trust 1 St Martins Le Grande St Martins Le Grande EC1A 4AS *A) Barts Health NHS Trust, Barts Heart Centre, St Bartholomew's Hospital* *B) Haematology Laboratories, Royal London Hospital*

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2. GLOSSARY of Terms and Abbreviations

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
DSMC	Data Safety Monitoring Committee
EC	European Commission
GAfREC	Governance Arrangements for NHS Research Ethics Committees
ICF	Informed Consent Form
JRMO	Joint Research Management Office
NHS REC	National Health Service Research Ethics Committee
NHS R&D	National Health Service Research & Development
Participant	An individual who takes part in a clinical trial
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
TMG	Trial Management Group
TSC	Trial Steering Committee

3. SIGNATURE PAGE

Chief Investigator Agreement

The clinical study as detailed within this research protocol **(Version 9, dated 9th November 2017)**, or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Chief Investigator Name: Saidi Mohiddin

Chief Investigator Site: Barts Heart Centre

Signature and Date:

4. SUMMARY/SYNOPSIS

Short Title	Pacemaker therapy for drug-refractory symptoms in mid-cavity HCM
Methodology	Randomised controlled double-blinded cross over trial
Research Sites	Barts Heart Centre, Barts Health NHS Trust
Objectives/Aims	**Primary** Phase IIb trial to test the efficacy of distal ventricular pacing for pressure gradient reduction across the site of mid-cavity obstruction. **Secondary** To test the feasibility of a double-blind cross-over study design in this cohort, collecting descriptive data on various symptom, imaging and performance markers, allowing establishment of baseline statistical data for the design of a larger outcomes-based clinical trial.
Number of Participants/Patients	25
Main Inclusion Criteria	a) Male or female, >18 years. b) Referred for PPM +/- ICD implantation for either primary prevention of sudden cardiac death or other indications such as heart block or obstructive physiology. c) HCM patients with a mid-cavity gradient of ≥30 mmHg demonstrated by echocardiography and gradient confirmed by cardiac catheterisation at rest or with isoprenaline provocation. HCM morphology confirmed by

	cardiac MRI. d) All patients should be taking maximum tolerated doses of beta blockers or verapamil with or without disopyramide. e) Symptoms refractory to optimum medical therapy as above, for example breathlessness, chest pain, dizziness, or syncope.
Exclusion Criteria	a) Patients with multi-level obstruction, i.e. across the mid-cavity and outflow tract. b) Patients with moderate or severe valvular stenosis or regurgitation due to primary valvular disease c) Patients with untreated symptomatic coronary disease. d) Patients in atrial fibrillation at the time of implantation. e) Pregnancy f) Renal failure with eGFR <20mL/min g) Any patient not suitable in the clinician's opinion h) Any patient who is for whatever reason is not expected for more than one year i) Patients unable to provide informed consent
Statistical Methodology and Analysis	All patients completing the initial invasive pacing study will be eligible for the primary analysis. The secondary aim is to collect descriptive data regarding the feasibility of a cross-over design trial and corresponding methods used to assess symptoms

	and physical performance in this cohort. A statistical analysis of the results will be undertaken at the completion of the study. Descriptive statistics will be collected in the form of mean ± standard deviations, and these outputs will form the statistical basis for a larger multi-centre RCT.
Proposed Start Date	December 2017
Proposed End Date	1st June 2021
Study Duration	Total duration: 41 months Recruitment duration: 28 months (ending March 2020)

5. INTRODUCTION

5.1 BACKGROUND AND RATIONALE

5.1.1 Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the commonest familial heart disease, with a prevalence of approximately 0.2% across multiple ethnicities.[1] It is characterised by left ventricular hypertrophy (LVH) in the absence of another disease process accounting for the magnitude of hypertrophy present.[2] Many patients are asymptomatic for decades, but may present with cardiac arrhythmias or with debilitating symptoms including chest pain, dyspnoea, dizziness and fatigue.[3] In severely symptomatic HCM, exertional intolerance may be similar to that of advanced heart failure.

5.1.2 Obstructive HCM

The presence of obstruction to left ventricular (LV) emptying in systole is frequently detected in patients with symptomatic HCM. LV obstruction

contributes to symptoms and prognosis, and the presence and magnitude of obstruction dominates clinical decision making.[4] In the 'classical' variant of obstructive HCM, the systolic and closed mitral valve moves toward the hypertrophied interventricular septum. Mitral - septal contact (systolic anterior motion [SAM]) results in a dynamically developing LV outflow tract obstruction (LVOTO) and mitral regurgitation. In a less common HCM variant (up to 10%),[5, 6] a dynamic intracavity obstruction develops as a consequence of hypertrophy and apparent hypercontractility at the level of the papillary muscles causing LV mid-cavity obstruction (LVMCO).[7] LVMCO is not associated with mitral regurgitation or SAM and is often missed at echocardiography. This is due to the distal chamber being outside the sector of two-dimensional imaging as a result of foreshortening of the imaging plane, or unclear imaging due to echoes from lung tissue.[8]

5.1.3 Pathophysiology of LVMCO

In patients with LVMCO, circumferential mid-systolic muscular apposition in the LV cavity creates two distinct chambers, proximal and distal, separated by a zone of apposition.[9] During systolic ejection, the 'mid-cavity' zone of apposition impedes or completely obstructs the flow of blood from apex to base and a pressure gradient develops between the proximal 'sub-aortic' LV and the distal 'apical' LV.[10] The abnormally high intracavity pressure that develops in the apical chamber, and the increased LV wall stress, may be associated with reduced regional myocardial perfusion and ischaemia.[11] Over time, patients with LVMCO have been shown to be at higher risk of developing segmental or diffuse hypokinesia,[12] subsequent formation of an apical aneurysm,[11] and other clinically unfavourable consequences such as ventricular tachycardia (VT) have been reported.[13]

As a direct result of the risk of VT, many LVMCO patients receive device therapy with implantable defibrillators. It is in such patients that symptomatic benefits of ventricular pacing have been detected.

5.2 Therapeutic options for patients with LVMCO

Patients with LVMCO are reported to suffer from significant morbidity, with around 50% having severe symptoms,[6] and data suggest this sub-group have a poor prognosis.[13] β blocking agents and/or verapamil may improve congestive symptoms and functional limitation, although with little evidence that they are able to reduce intraventricular gradients with any consistency.[9] If β-blockers alone are ineffective, disopyramide (a class IA anti-arrhythmic drug), can reduce the degree of LV outflow obstruction and improve exercise tolerance.[14] However, approximately half of LVMCO patients have been reported to be refractory to medical therapy,[6] leaving few other treatment options. The invasive procedures of alcohol septal ablation (ASA) and surgical myectomy have limited evidence supporting their routine use in LVMCO and are technically challenging.[9]

Notably, the main prognostic intervention is device implantation with an implantable cardioverter defibrillator (ICD) for primary prevention of sudden cardiac death, having the option of dual chamber pacing (PPM +/- ICD).

5.3 Ventricular Pacing for LV Obstruction: Rationale

5.3.1 Right ventricular pacing as a therapeutic option in LVOTO

Patients with the more common LVOTO have several invasive treatment options to consider should optimum medical therapy fail to relieve their symptoms. The well-established septal reduction therapies of surgical myectomy and percutaneous alcohol septal ablation (ASA) have had similar success in reducing pressure gradients across the left ventricular outflow tract and reducing symptoms.[15] Previous studies have suggested a role for dual chamber permanent pacemaker (PPM) therapy from the right ventricular apex for LVOTO gradient reduction and symptomatic relief for HCM patients,[16] with long term maintenance of such benefits reported.[17] A recent Cochrane review found that the improvement in both physiological measure and symptoms has since been found to be variable and subject to a placebo effect,[18] yet the apparent placebo effect of the invasive procedure of PPM insertion is surely of similar level to the arguably more invasive ASA or myectomy procedures.[19]

5.3.2 Right ventricular pacing as a therapeutic option in LVMCO

In patients with MCO and drug-refractory symptoms, however, the therapeutic options are far more limited as ASA and surgical myectomy may be unable to target the affected area of the LV. Dual chamber pacemaker therapy from the right ventricular apex has, in small numbers of patients been shown to reduce the pressure gradient across the site of obstruction in the mid-cavity and provide symptomatic relief, with a trend towards increased exercise tolerance.[7]

5.3.3 Left ventricular pacing as a therapeutic option in LVMCO

Recently, several case studies have been published that demonstrate pacing from the left ventricular free wall, via the coronary veins, has yielded better reduction in LVOTO gradient compared to pacing from the right ventricular apex.[20] Furthermore, LV and biventricular pacing appeared to cause reverse LV remodelling with a reduction in LV mass.[21] Our own pilot data has demonstrated that pacing from the left ventricle via the distal middle cardiac vein may have clinical application in individuals with LVMCO also. In order to ascertain the optimal pacing site for acute gradient reduction, individuals are paced from the RV apex, then from the LV via the distal middle cardiac vein. It is our experience that acute gradient reduction is seen during distal RV ventricular pacing (by 59±36 mmHg), with a further reduction in gradient when pacing from the distal middle cardiac vein (by 66±26 mmHg).

5.4 Rationale and Risks/Benefits

The potential risk associated with pacemaker implantation is very small, however there are several small risks of infection (less than 1 in 100), air leak from a lung (1 in 100), and blood clot in the arm (1 in 50). These figures are from national databases, and our specialist Heart Centre has expert skill and a wealth of experience in implanting devices. Therefore, we estimate these risks to be even lower, having had no tension pneumothorax in the last year.

The length of each treatment phase is longer than previous pacemaker studies at 24 weeks in order to account for any wash-out periods for symptoms (where the participant still feels the effects of the treatment / non-treatment into the next phase of the study). This has historically been a

criticism of pacemaker studies in cardiomyopathy with a cross-over trial design. The time necessary for wash-out effects to no longer be experienced is unknown, therefore we have used a conservative approach and doubled the treatment / non-treatment arms to the 24 week duration.

6. TRIAL OBJECTIVES

6.1 Primary and secondary objectives and endpoints

6.1.1 Primary objective:

To test the efficacy of distal ventricular pacing for pressure gradient reduction across the site of mid-cavity obstruction.

6.1.2 Secondary objective:

To test the feasibility of a double blind cross-over study design in this cohort, collecting descriptive data on various symptom, imaging and performance markers, allowing establishment of baseline statistical data for the design of a larger outcomes-based clinical trial.

6.1.3 Primary Endpoint

Change in invasive gradient measured by intracardiac catheter during distal ventricular pacing (mmHg).

6.1.4 Secondary Endpoint

Feasibility of patients completing two arms of a cross-over trial design, and the corresponding performance tests and symptomatic assessments

6.2 Null Hypothesis

There will be no significant difference in mid-cavity obstructive gradients during ventricular pacing and normal sinus activation of the ventricle by invasive catheter measurement during pacemaker implantation.

7. METHODOLOGY

7.1 Inclusion Criteria

a) Male or female, >18 years.

b) Referred for PPM +/- ICD implantation for either primary prevention of sudden cardiac death or other indications such as heart block or obstructive physiology.

c) HCM patients with a mid-cavity gradient of ≥30 mmHg demonstrated by echocardiography and gradient confirmed by cardiac catheterisation at rest or with isoprenaline provocation. HCM morphology confirmed by cardiac MRI.

d) All patients should be taking maximum tolerated doses of beta blockers or verapamil with or without disopyramide.

e) Symptoms refractory to optimum medical therapy as above, for example breathlessness, chest pain, dizziness, or syncope.

7.2 Exclusion Criteria

a) Patients with multi-level obstruction, i.e. across the mid-cavity and outflow tract.

b) Patients with moderate or severe valvular stenosis or regurgitation due to primary valvular disease.

c) Patients with untreated symptomatic coronary disease.

d) Patients in atrial fibrillation at the time of implantation.

e) Pregnancy.

f) Renal failure with eGFR <20mL/min.

g) Any patient not suitable in the clinician's opinion.

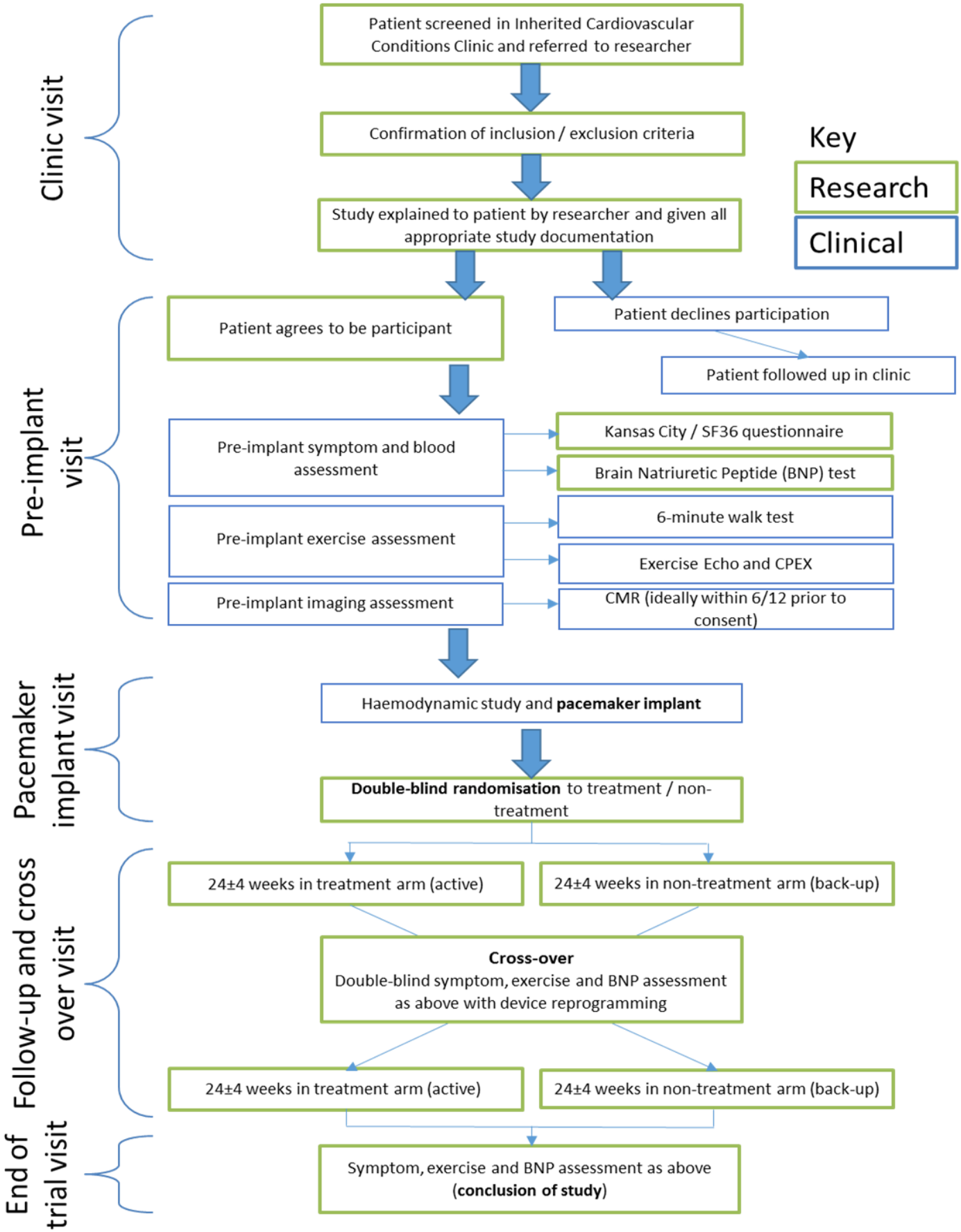
h) Any patient who is for whatever reason is not expected for more than one year.

i) Patients unable to provide informed consent.

7.3 Study Design / Plan – Study Visits

This is a single centre, prospective Phase IIb study, with primary outcome assessed during device implant. Secondary aims assess the feasibility of a randomised controlled double-blind crossover design with one year follow-up in this patient population. Potential participants will be identified by the patient's clinician team at consultant or registrar level. With the patient's permission, their details will be given to the research team who will make secondary contact with the patient to discuss the study in more detail and give appropriate study literature, and offer the patient the opportunity to take part in the study. There will be a minimum of 24 hours between the study explanation and the taking of informed consent. Possible participants will then attend for informed consent and baseline assessment by a researcher over one encounter. The patient will then attend for device implantation and invasive haemodynamic pacing study as part of their standard care. Patients will then have two additional study visits to hospital at 24±4 weeks (for symptom / exercise testing and cross-over) and 48±4 weeks (for symptom / exercise testing and conclusion of trial). The length of each treatment phase is longer than previous pacemaker studies at 24 weeks in order to account for any wash-out periods, which have historically been a criticism of cross-over trial designs.

7.4 Study Scheme Diagram



8. STUDY PROCEDURES

8.1 Recruitment setting

This study will take place in a tertiary care cardiology department in collaboration with Queen Mary University of London. All members of the study research team will hold substantive or honorary contracts with their hospital institution.

8.2 Screening and Recruitment

Patients considered for study inclusion will be invited to join during their clinic appointment, after an explanation of the study.

They will be provided with a complete description of the study protocol and the benefits and risks involved. The interested patient will undergo screening procedures listed below.

8.3 Informed Consent

Written and verbal versions of the Participant Information and Informed Consent will be presented to potential participants detailing: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal. The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. Potential participants will be given at least 24 hours to consider taking part in the study.

Eligibility of potential participants will be re-checked by pre-defined inclusion/exclusion criteria (see 7.1 and 7.2 for details) at the time of consent. Written informed consent will be obtained by an investigator who is familiar with the study protocol and procedures and listed on the study delegation log. The participant must personally sign and date the informed consent forms, which will be witnessed by the investigator who will also sign and date before any specific procedures are performed. A copy of the signed informed consents will be given to the participant, with one copy up-loaded electronically to the Care Records System and a paper copy to the patient's notes. The original signed forms will be retained securely at the study site in the trial master file. The participant will then be formally "registered" and given a study specific ID.

8.4 Randomisation, blinding and code-breaking

A trial randomisation service (such as https://www.sealedenvelope.com or www.randomize.net) will be used to assign participants to one of the cross over arms initially.

8.5 Baseline Assessments

8.5.1 Pre-pacing study assessment (several of these tests are standard pre-device implant care, denoted by SC. Research activity denoted by RES)

a) Symptomatic assessment with SF36 and Kansas City Cardiomyopathy questionnaires and determination of New York Heart Association (NYHA) functional class. **(RES)**

b) Venous blood sample taken **(SC),** BNP test **(RES)**

c) 6 minute walk test (6MWT) performed to assess baseline exercise tolerance. **(SC)**

d) Resting comprehensive transthoracic echocardiographic (TTE) study. **(SC)**

e) Cardiopulmonary exercise testing (CPET) with concomitant TTE. **(SC)**

f) Cardiac Magnetic Resonance Imaging (CMR). **(SC)**

8.5.2 Invasive pacing study (standard care denoted by SC, research activity denoted by RES)

a) Haemodynamic study performed for maximal pressure gradient across the mid-cavity with and without pacing from the RV apex, left middle cardiac vein, or both, sequentially. **(SC)**

b) For patients judged to be at significantly increased risk of sudden cardiac death, they will have a device with defibrillator functions as well as the pacemaker functions. Those thought not to be at significantly increased risk of sudden cardiac death may have a device with pacemaker functions only. PPM +/- ICD inserted at optimal settings of AV delay and lead polarity. **(SC)**

c) After one-day check as an inpatient to ensure proper PPM +/- ICD function, patient randomised in a double-blind, cross-over fashion. In one arm, the device will be set to the pacing mode “AAI”, which is a backup pacing mode at 30 beats per minute, so it will therefore not be activated (non-active pacing). In the other, the device will be set to the pacing mode “DDD”, with optimal atrio-ventricular delay as assessed during invasive haemodynamic study. This means it will pace almost all of the time (active pacing). Simultaneous Doppler echocardiography will be used to ensure the atrial component of LV filling is not truncated. **(RES)**

8.5.3 Follow-up assessments (cross-over between study arms occurs at 24±4 weeks)

a) Patients device makes 3 monthly transmissions via telephone line to ensure device functioning appropriately. **(SC)**

b) Patients return for follow-up examination after 24±4 weeks **(Cross over testing)** and 48±4 weeks **(End of trial testing)** by a blinded research team member. Symptomatic assessment performed with SF36 and Kansas City Cardiomyopathy questionnaires and determination of New York Heart Association (NYHA) functional class. **(RES)**

Patients will be asked if their symptoms have become less severe, stayed the same, or worsened.

c) Cardiopulmonary exercise testing (CPET) with concomitant TTE at 24±4 weeks and 48±4 weeks follow-up. **(RES)**

d) 6 minute walk test for the assessment of exercise tolerance at 24±4 weeks and 48±4 weeks follow-up. **(RES)**

e) Venous blood sample taken at 24±4 weeks and 48±4 weeks. **(RES)**

8.6 Description of Assessments

8.6.1 History, physical examination and recording of prior test results

Patients will be asked to attend for initial assessment with physical examination and history taking.

8.6.2 12 lead ECG

A 12-lead ECG will be performed at baseline assessment and each clinical visit as standard care.

8.6.3 Transthoracic echocardiography

Comprehensive resting transthoracic echocardiography will be performed in accordance with European guidelines for the assessment of HCM[4] and the latest British Society recommendations.[22]

8.6.4 Cardiopulmonary exercise testing with concomitant TTE

Symptom limited cardiopulmonary exercise testing (CPET) will be performed in accordance with joint European and American guidelines.[23]

8.6.5 Blood sample collection

A small blood sample (<5mL) will be taken from the participant at each visit. Blood will be taken by needle from a vein in the participant's arm by a nurse or member of the research team trained to do so. The blood sample will be analysed at the local pathology lab for levels of N terminal pro B type natriuretic peptide (BNP).

8.6.6 6 minute walk test

A six minute walk test will be performed in accordance with the American Thoracic Society guidelines.[24]

8.6.7 Invasive haemodynamic pacing study in patient requiring PPM +/- ICD implant (SC)

a) Arterial access will be obtained by the Seldinger Technique from the right femoral artery (RFA) using a standard 7 French sheath. Venous access will be similarly obtained from the left subclavian or cephalic veins. The right atrial and right ventricular leads will be implanted as usual.

b) The coronary sinus will be intubated using a LV lead delivery guiding catheter. When necessary, coronary venous anatomy will be defined by balloon occlusion coronary sinus venography. The coronary veins will then be intubated with a deflectable quadripolar catheter or an angioplasty wire.

c) Intravenous heparin 5,000 units will be administered and the haemodynamic study performed. The LV apical pressures will be

measured with an end-hole pigtail catheter. The arterial pressure will be measured from the side arm of the RFA sheath. The pressure difference between LV and arterial pressures will be the mid-cavity gradient.

d) AV synchronous pacing will be performed from the right ventricular apex, right ventricular outflow tract, distal middle cardiac vein and posterior or lateral cardiac veins whilst measuring the respective LV gradients for 30 seconds before, during and after cessation of pacing.

e) If the best gradient reduction is achieved with LV pacing, a LV lead will be implanted with a biventricular device at the same sitting.

f) Following removal of the LV pigtail catheter, the activated clotting time will be checked. If it is more than 150 seconds, the heparin will be reversed with intravenous protamine sulphate.

g) The device will be programmed with the longest AV delay to allow continuous right or left ventricular pacing.

8.6.8 Invasive haemodynamic pacing study in patient with no other PPM +/- ICD indication or with an implanted dual chamber device (SC)

a) Arterial access will be obtained by the Seldinger Technique from the right femoral artery (RFA) using a standard 7 French sheath. Venous access will be similarly obtained from either the right femoral vein using two standard 7 French sheaths, or from the right femoral and right subclavian (assuming left sided device insitu) veins (depending upon the operator).

b) A quadripolar pacing catheter will be placed in the right atrial appendage. The coronary sinus will be intubated using a LV lead delivery guiding catheter. When necessary, coronary venous anatomy will be defined by balloon occlusion coronary sinus venography. The coronary veins will then be intubated with a deflectable quadripolar catheter or an angioplasty wire.

c) Intravenous heparin 5,000 units will be administered and the haemodynamic study performed. The LV apical pressures will be measured with an end-hole pigtail catheter. The arterial pressure will be measured from the side arm of the RFA sheath. The pressure difference between LV and arterial pressures will be the mid-cavity gradient.

d) AV synchronous pacing will be performed from the right ventricular apex, right ventricular outflow tract, distal middle cardiac vein and posterior or lateral cardiac veins whilst measuring the respective LV gradients for 30 seconds before, during and after cessation of pacing.

e) If the pacing study demonstrates significant mid-cavity gradient, the appropriate pacemaker will be implanted on the same or following day. If no mid-cavity gradient is demonstrable, the patient will not be suitable for the research study. A more conventional device will still be implanted if there are other indications. The more conventional device will almost always be one without the additional LV lead.

8.7 Discontinuation/Withdrawal of Participants from Study

Patients will be free to withdraw from the study at any point.

8.8 Procedure for Collecting Data Including Case Report Forms (CRFs) and storage

All source data will be collected by the investigator or a research nurse on paper CRFs, and data will be captured into the trial database (electronic data capture system) with electronic signatures and audit trail. All source data and CRFs will be kept securely in participant folders or the Trial Master File, which will be kept in a locked cupboard with restricted access in the Research Department.

8.9 Definition of End of Study

The end of the study is the last assessment of the last patient after 1 year of cross-over treatment and non-treatment arms (6 months of each).

8.10 Schedule of Assessment

	Visit 1	Visit 2	Visit 3		Visit 4
Procedure	**Pre-implant assessment**	**Implant**	**24±4 weeks post implant**	**Cross-over**	**48±4 weeks post implant**
NYHA classification	x		x		x
SF36 & KCCM Questionnaire	x		x		x
CMR with stress perfusion	x				
6MW test	x		x		x
CPET with concomitant TTE	x		x		x
Randomisation		x			
Device interrogation and programming at pacing clinic		x	x		x
Blood sample for BNP analysis	x		x		x

9. STATISTICAL CONSIDERATIONS

9.1 Sample size calculation

Effect size was calculated using our pilot work, where a reduction in mid-cavity gradient with distal ventricular pacing of around 60 mmHg was seen acutely, with a standard deviation of 26 mmHg. A clinically significant gradient reduction is 30 mmHg. Using a conservative approach, we aim to be able to detect a reduction of 25 mmHg. The magnitude of patient's resting gradients will be taken into consideration and accounted for during analysis. With two sided alpha level set at 0.05 a priori, and a power of 90%, the calculated sample size using a paired sample t-test was 15 to detect a 25mmHg acute reduction in gradient. In order to account for potential withdrawals from the study, the sample size has been increased to 25.

9.2 Statistical analysis

All patients completing the initial invasive pacing study will be eligible for the primary analysis. The secondary aim is to collect descriptive data regarding the feasibility of a cross-over design trial and corresponding methods used to assess symptoms and physical performance in this cohort. A statistical analysis of the results will be undertaken at the completion of the study by a senior statistician of the Cardiovascular Clinical Trials Unit. Descriptive statistics will be collected in the form of mean ± standard deviations, and these outputs will form the statistical basis for a larger multi-centre RCT.

Table 3: Sensitivity analysis table.

Delta	SD	Sig.	Power	Type	Alternative	Sample size
30	26	0.05	0.8	Paired	Two-sided	9
25	26	0.05	0.8	Paired	Two-sided	10
20	26	0.05	0.8	Paired	Two-sided	16
25	26	0.05	0.9	Paired	Two-sided	15
20	26	0.05	0.9	Paired	Two-sided	20

10. ETHICS

Whilst we do not believe the study raises significant ethical issues, we have considered several ethical practicalities.

The treatments for patients with hypertrophic cardiomyopathy and mid-cavity obstruction to blood flow are very limited, but include medicines and cardiac transplant. The use of a pacemaker is an experimental treatment which has not yet been explored in a formal clinical trial.

We do not know which treatment method is generally better, which is why we are conducting the study. Participants will experience both a treatment period (pacing all the time) and a non-treatment period (very little pacing), before comparison of patient experience in both settings. The order in which the participant experiences each setting is not decided by their doctor or the research team, but by randomly assigning you to one or other first, like tossing a coin. Setting the pacemaker to pace all the time or pace very little will not affect the defibrillator function of the participant's device if it has one.

We have designed a clear and concise patient information sheet to explain this to prospective study participants, allowing them to make an informed choice as to whether to take part.

Another potential issue that the study raises is common to all cross-over design studies. If a participant has been randomised to be in the treatment arm first, and feels better (as we expect), and then switches to the non-treatment arm and feels symptomatically worse, they may not wish to continue the non-treatment arm. Because we don't know whether patients feel better due to the pacemaker setting, or simply just because they have undergone a procedure (placebo effect), it is necessary for the research participants to "cross-over" from one setting (treatment) to the other (non-treatment). Whilst this could be interpreted as withholding treatment from a patient, it should be stressed that it is not known whether one setting provides a benefit to the patient over another (when the patient is unaware of their treatment to mitigate against placebo effect).

Cross-over design studies are often considered the 'gold-standard' of medical research; however they are at risk of statistical impracticalities due to their

design. For example, if all patients randomised to the treatment arm first, decided they were not willing to stay on the non-treatment arm after switching (they will be shielded to pacemaker settings), then we will be unable to make the comparison between the two pacemaker settings in those patients. This outcome still provides useful information about the feasibility of cross-over design, and will infer that patients really do feel better when the pacemaker is set to work almost all the time.

However, it makes it difficult to make the comparison using the patient as their own control, as a comparison can only be made to the test scores before the device was implanted, and therefore cannot account for the placebo effect of device implantation alone regardless of settings.

It is important to note that the primary outcome is not affected by the ability of the patient to complete both arms of the cross-over, as this data is collected before randomisation occurs.

11. SAFETY CONSIDERATIONS:

A trial Data Safety Monitoring Committee (DSMC) will be formed to review the safety of the trial every 4 patients that are recruited and undergo invasive haemodynamic pacing study and device implant. The safety committee shall consist of an independent chairman, a cardiac device specialist, a cardiomyopathy doctor, and a clinical trialist. The CI (Dr Mohiddin), PhD student (J Malcolmson) will also be in attendance.

Participants do not receive exposure to higher doses of ionising radiation as part of this study.

The extra tests performed as part of the research, such as exercise stress echocardiography and 6-minute walk test are safe with very low risk to the participants.

12. DATA HANDLING AND RECORD KEEPING:

12.1 Confidentiality

All patient information held is bound by the Confidentiality Code of Practice. Access will be on a strict need-to-know basis, with patient information only being shared with those involved in that patient's care. All patients' identifiable details will be anonymised from all study documentation (apart from their original case file) and they will be kept in participant study files in a locked cupboard in a pass protected room within the Research Department. Information related to participants will be kept confidential and managed in accordance with the Data Protection Act, NHS Caldecott Principles, The Research Governance Framework for Health and Social Care, and the conditions of Research Ethics Committee Approval. All research team members have undergone Good Clinical Practice Training.

12.2 Study Documents

All study documents will be kept in a trial master file in a locked cupboard in a pass protected room with both paper and electronic backup of all documents. Access to electronic data will require password entry.

12.3 Case Report Form (CRF)

A case report form for each patient participating in the study will be kept in a trial master file in a locked cupboard in a pass protected room. All CRFs will be entered into the study database after collection of data, and access to this will require a password.

12.4 Record Retention and Archiving

Records will be archived according to Trust policy, and kept for the required 20 years after the research is completed. The approved repository for long-term storage of local records is the Trust Modern Records Centre.

12.5 Quality Control and Quality Assurance

All data collected will be consistent in adherence to the study protocol.

All CRF's will be completed by authorised persons only.

All data collected will be checked for accuracy and validity, through data checks and study monitoring.

13. LABORATORIES

Blood samples will be sent in accordance with Trust protocols and the Human Tissues Act to the Royal London Hospital laboratory for immediate analysis of Brain Natriuretic Peptide (BNP). Samples will be disposed of immediately after analysis in accordance with Trust protocols.

14. PRODUCTS, DEVICES, TECHNIQUES AND TOOLS

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14.1 Devices

The cardiac devices implanted during the duration of the study are selected at the discretion of the operator during the pacemaker procedure. This is as per local hospital policy. The research study is does not assess the implant technique, but captures haemodynamic data generated during the pacemaker implant as part of standard care.

14.2 Techniques and interventions

The techniques used to implant the pacemakers are not experimental and a full description is detailed in section 8.6, details of assessments.

14.3 Tools

14.3.1 – SF36 questionnaire – is a set of generic, coherent, and easily administered quality-of-life measures. These measures rely upon patient self-

reporting and are now widely utilized by managed care organizations and by Medicare for routine monitoring and assessment of care outcomes in adult patients.

14.3.2 – Kansas City Cardiomyopathy questionnaire - is a 23-item, self-administered instrument that quantifies physical function, symptoms (frequency, severity and recent change), social function, self-efficacy and knowledge, and quality of life.

In the KCCQ, an overall summary score can be derived from the physical function, symptom (frequency and severity), social function and quality of life domains. For each domain, the validity, reproducibility, responsiveness and interpretability have been independently established. Scores are transformed to a range of 0-100, in which higher scores reflect better health status.

15. SAFETY REPORTING

Adverse Events (AE)

An AE is any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with study activities.

Notification and reporting Adverse Events or Reactions

If the AE is not defined as SERIOUS, the AE is recorded in the study file and the participant is followed up by the research team. The AE is documented in the participants' medical notes (where appropriate) and the CRF.

Serious Adverse Event (SAE)

Notification and Reporting of Serious Adverse Events

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 paper SAE CRFs or the trial database to the trial Sponsor. SAEs will be followed up until resolution or stabilisation, and any follow-up information for an SAE will be reported within the same timelines as the original SAE (within 24 hours of notification)

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Urgent Safety Measures

The CI may take urgent safety measures to ensure the safety and protection of the clinical trial subjects from any immediate hazard to their health and safety. The measures should be taken immediately. In this instance, the approval of the REC prior to implementing these safety

measures is not required. However, it is the responsibility of the CI to inform the sponsor and Main Research Ethics Committee (via telephone) of this event immediately.

The CI will inform both the Main REC in writing within 3 days, in the form of a substantial amendment. The sponsor (Joint Research Management Office [JRMO]) must be sent a copy of the correspondence with regards to this matter.

Annual Safety Reporting

The CI will send the Annual Progress Report to the main REC using the NRES template (the anniversary date is the date on the MREC "favourable opinion" letter from the MREC) and to the sponsor.

Overview of the Safety Reporting responsibilities

The CI/PI has the overall pharmacovigilance oversight responsibility. The CI/PI has a duty to ensure that safety monitoring and reporting is conducted in accordance with the sponsor's requirements.

16. MONITORING &AUDITING

The PhD student (James Malcolmson) will be responsible for day-to-day project management under close supervision from supervisors, Professor Petersen and Dr Mohiddin. A Gantt chart has been developed to ensure all study team members are aware of the timings of the research. The Trial Manager at the CTU will also provide oversight to the project.

In addition, the research management structure includes a number of mechanisms to ensure milestones are achieved:

a) We will seek the assistance of our CRN and the NIHR's Coordinated System for gaining NHS Permission

b) (HRA) for research management and governance advice & support.

c) QMUL's PhD programme includes formal assessments of progression at set intervals over the 4 year period.

d) Fortnightly meetings (1 hour) with the supervisors will review progression, plan scheduled meetings and review dissemination strategies.

e) Our plan for research management includes establishing a trial steering committee that includes two patient volunteers. This committee will meet at 6-monthly intervals to review recruitment and safety data. The committee will also have a role in formal closure of the trial, along with plans for dissemination of findings.

f) Financial Management: Professor Petersen and the finance officer at the Joint Research Management Office at Barts will manage the project's finances.

g) Cardiovascular Clinical Trials Unit: will provide data management, overall study management including augmenting recruitment, and quality management.

17. TRIAL COMMITTEES

17.1 Trial Steering Committee

A trial steering committee (TSC) has been set up for this trial, including a data manager, senior statistician, PhD student and supervisors (including chief investigator). A quality assurance manager has also been accounted for in the

finances. The committee includes 2 patient representatives and will meet at six monthly intervals throughout the study duration. The group's role is to oversee the project, ensuring protocol adherence and provide advice where necessary. The patient members of the group are able to provide expert input based upon their direct experience of the pacemaker treatment being investigated. Travel and communication costs have been accounted for in the study budget, and we have the facilities for teleconferencing to allow flexible communication and group meetings.

We have included specific roles for patient engagement in the following areas:

Design of research

As described above, a patients' perspective of this research has been used in study design. The group will play a central role in the design of the future research projects that this work plans to enable.

Management of the research (e.g. steering committee)

One of the group's roles is to elicit formal patient input at all stages of the project. For example, acting as patient advocates to those involved in the study, addressing recruitment difficulties, and producing research updates that are patient friendly. GCP training will be provided through QMUL to the patient members of the steering group, and this has been costed for in the finance section of this application.

Developing participant information resources

All patient literature, such as information sheets, consent forms, and signposting to further sources of information, will be produced in conjunction with the steering group and PPAG to ensure appropriate tone, language, and content.

Contributing to the study report

Preliminary findings of the study will be presented to the patient steering group at a formal meeting following which the study report will be produced.

Dissemination of research findings

On completion of the study, we will feedback to all patients and collaborative parties at an open meeting. Patients involved will be asked if they wish to receive a written research summary as well as notification of publications. Our collaboration with Cardiomyopathy UK and patient support groups (Let's talk hearts) will allow the target community (patients with cardiomyopathy) to be reached. We will also disseminate locally (intranet) at Barts Heart Centre.

18. FINANCE AND FUNDING

The study is fully funded via an NIHR Clinical Doctoral Research Fellowship. Costing was performed by Juan-Carlos Rodriguez-Prados (Barts/QMUL). The total funding secured for the 4 year fellowship is £294,615.

19. INDEMNITY

The trial sponsor is Barts Health NHS Trust, contact:

Dr Sally Burtles,
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Queen Mary University of London
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20. DISSEMINATION OF RESEARCH FINDINGS:

20.1 Study participants:

Study progress will be presented to the trial steering committee at quarterly meetings. The patient representatives of this group will be instrumental in the development of a dissemination strategy, and acknowledged for their contribution. On study completion, all participants will be informed about the outcome with a letter of thanks unless previously opted out of further contact.

20.2 Public and target community:

The results of the study will be shared via the internet through patient information forums with the target community (patients with cardiomyopathy), facilitated through collaborative work with Cardiomyopathy UK and the British Heart Foundation.

20.3 Research community:

Project results will be submitted for publication in peer-reviewed journals (e.g. European Heart Journal, Journal of the American College of Cardiology), irrespective of outcome, within 12 months of completion. The research will be synthesised in a research thesis to be submitted to Queen Mary University London.

20.4 Clinical community:

The target clinical community are the cardiologists, nurse specialists, and healthcare scientists responsible for the management of patients with cardiomyopathy. Abstracts for presentation at local (Barts Heart Centre), national (British Cardiovascular Society) and European (European Society of Cardiology) meetings will be submitted to help to engage this audience with the trial results and potential effects on management of patients.

20.5 Outputs:

This patient group is encumbered with a paucity of treatment options should optimum medical therapy fail. This research will provide the statistical input for a larger multi-centre trial. We have the aim of contributing to the clinical recommendations for management of HCM patients. We hope to provide further validation of cardiopulmonary exercise testing (CPEX) as an objective assessment of changing clinical state in this HCM sub-population.

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