Minimally invasive thoracoscopically-guided right minithoracotomy versus conventional sternotomy for mitral valve repair: a multicentre randomised controlled trial (UK Mini Mitral).

PROTOCOL

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Funder: National Institute of Health Research – Health Technology Assessment Programme (project reference 14/192/110)

Sponsor: South Tees Hospitals NHS Foundation Trust

Trial Identifiers: ISRCTN: ISRCTN13930454

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1. Protocol Synopsis

Trial Title:	Minimally invasive thoracoscopically-guided right minithoracotomy versus conventional sternotomy for mitral valve repair: a multicentre randomised controlled trial (UK Mini Mitral).
Internal Reference:	UK Mini Mitral.
Trial Design:	A multi-centre randomised controlled trial of minimally invasive thoracoscopically-guided right minithoracotomy versus conventional sternotomy for mitral valve repair (MVr). The trial includes an internal pilot, which will assess the likelihood of meeting the recruitment targets.
Trial Participants:	Adult patients due to receive isolated MVr for degenerative mitral valve disease.
Inclusion Criteria:	• Adult patients with degenerative mitral valve disease, requiring isolated MVr (patients requiring concomitant Atrial Fibrillation (AF) ablation and Patent Foramen Ovale (PFO) closure will be included). • Written informed consent. • Fit for cardiac surgery and cardiopulmonary bypass.
Exclusion Criteria:	• Concomitant cardiac surgery other than AF ablation and PFO closure. • Planned mitral valve replacement. • Acute infective endocarditis. • Emergency or salvage surgery. • Only conventional median sternotomy or only minimally-invasive surgery indicated. • Pregnant. • Four weeks or more as an inpatient prior to randomisation. • Currently participating in another interventional clinical trial. • Previous cardiac surgery.
Sample Size:	400 patients in total, including those recruited in the internal pilot phase. 200 patients per treatment arm.
Trial Centres:	Initially 4 tertiary cardiac surgical units, with additional units added if required following the internal pilot.
Trial Period:	Individual patients will be in the trial for one year following their index surgery. Patients will be consented to long-term follow up using routine data. The main trial, including the internal pilot is anticipated to take 5 years (60

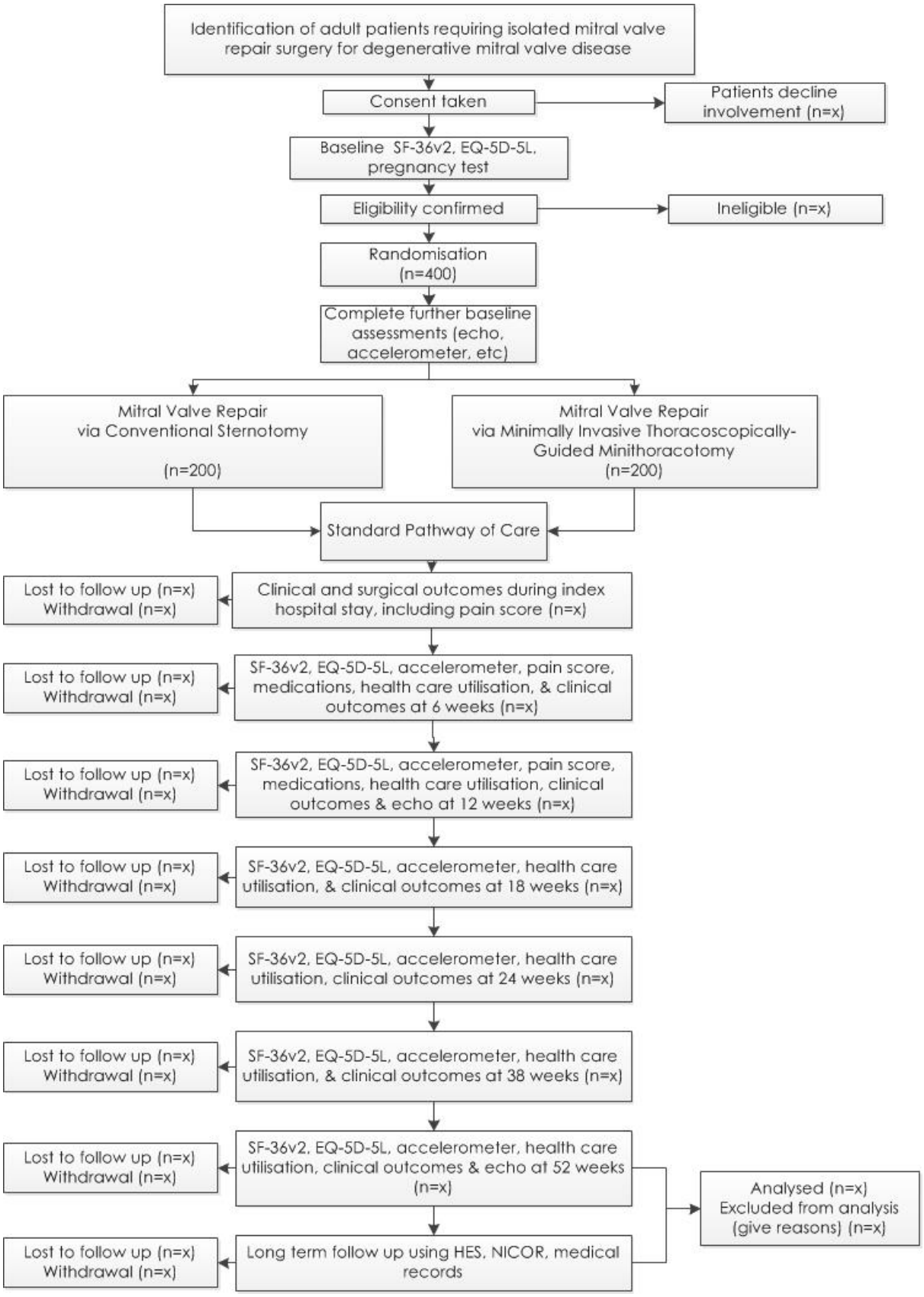
	months). For the purposes of notification, the end of the trial is defined as the last visit for the last patient. Serious Adverse Events will be reported from the day of index surgery until 52 weeks following index surgery.
Primary Objective:	To determine if physical functioning and associated return to usual activities improves in patients who undergo mitral valve repair via minimally invasive thoracoscopically-guided right minithoracotomy compared to conventional sternotomy at 12 weeks. Primary Economic Objective: To estimate if minimally invasive thoracoscopically guided right minithoracotomy compared to conventional sternotomy is more cost-effective at 52 weeks.
Primary Outcome:	Change in SF-36v2 physical functioning scale (1) at 12 weeks following surgery. Primary economic outcome: incremental cost per QALY gained at 52 weeks following surgery.
Secondary Objectives:	• To explore the feasibility of study recruitment by means of an internal pilot trial; these data will be included in the main data for analysis. • To assess cardiac function echocardiographically, with measurements of left ventricular volumes, dimensions and function, mitral regurgitation severity and estimates of both right heart function and pulmonary artery pressure early (3 days to 12 weeks) and late (52 weeks) after surgery, using blinded echocardiography. • To compare mitral valve and mitral valve surgery related events and survival (morbidity and mortality) at 52 weeks and at 4.5 years. • To compare physical functioning and overall quality of life over 52 weeks post MVr (using SF-36v2(1)). • To quantify the level and variability in physical activity and quality of sleep (using an accelerometer (GENEActiv(6-10)) over 52 weeks post MVr). • To quantify a range of surgical outcomes over the 52 weeks from index surgery. • To compare costs, including intervention-specific estimates, of the two operations in the first 52 weeks following the index operation. • To estimate QALYs from responses to the EQ-5D-5L (2-4) and SF-6D (derived from the SF-36v2). • To estimate costs to the NHS over 4.5 years. • To model costs and QALYs up to the end of the patients lifetime. • To model the incremental cost per QALY gained over the patient lifetime.

	• To determine if HES data adequately captures mitral valve related events.
Secondary Outcomes:	**Internal pilot trial outcomes** • Patient recruitment within the first 6 months of the trial across 4 NHS cardiac surgery centres. **12 week outcomes:** • Level of physical activity. • Quality of sleep. • Surgical outcomes (including duration of operation, cardiopulmonary bypass times, protocol adherence). • Costs, including intervention-specific estimates, of the two operations. • Mitral valve related events determined using HES, NICOR, and medical record data. • Left ventricular volumes and function, mitral regurgitation, right heart function, and pulmonary artery pressure. • Survival. • Physical functioning using SF-36v2. • Quality of life using SF-36v2 and EQ-5D-5L. • Adverse Events and Serious Adverse Events. • Health care utilisation. • Wound pain. • NYHA class. • Length of hospital stay. • Concomitant medication. • Re-operation. • Conversion (minimally-invasive arm only). • Red blood cell and blood product transfusions. • Time on CICU, HDU and ward. • Duration of ventilation. • Discharge destination. • Blood loss following surgery. **One year outcomes:** • Level and variability in physical activity. • Mitral valve related events determined using HES, NICOR, and medical record data. • Costs, including intervention-specific estimates, of the two operations.

	• Survival. • Physical functioning using SF-36v2. • Quality of life using SF-36v2 and EQ-5D-5L. • Quality of sleep. • Adverse Events and Serious Adverse Events. • Health care utilisation. • Medication usage. • Quality Adjusted Life Years (QALYs) derived from EQ-5D-5L and SF-36v2. • Left ventricular volumes and function, mitral regurgitation, right heart function, and pulmonary artery pressure. **Long term outcomes:** • Quality Adjusted Life Years (QALYs) to the end of the patients lifetime. • Incremental cost per QALY over the patient lifetime. • Mitral valve related events determined using HES, NICOR and medical records data to 4.5 years.
Process Outcomes:	• Protocol adherence (including protocol violations). • Fidelity of the operation (including surgeons' report and local variation). • Patient withdrawals. • Conversion from minimally invasive to conventional.
Interventions	**Intervention group:** Minimally invasive surgery is by thoracoscopically-guided right minithoracotomy. The patient is intubated with a single or double lumen endotracheal tube. Cardiopulmonary bypass is established by aortic or femoral artery cannulation and venous return is achieved from the venae cavae using a single bicaval cannula placed from the femoral vein or with an additional cannula in the superior venae cava. Transoesophageal echocardiography (TOE) confirms the optimum location of the venous and arterial cannulas. A 4-7 cm right antero-lateral mini-thoracotomy, is then used to enter the thorax through the third or fourth intercostal space. A soft tissue retractor with or without a small thoracic retractor is utilized to spread the ribs with minimal rib-spreading. The pericardium is opened 3-4 cm anterior and parallel to the phrenic nerve from the distal ascending aorta to the diaphragm. A video camera is inserted through a 5-10 mm port. Endoballoon occlusion or a transthoracic clamp achieves aortic occlusion. Cardiac arrest is achieved with single or repeated doses of cardioplegia. The mitral valve is approached through a paraseptal incision and a left atrial retractor

	is used to expose the mitral valve. Following the mitral valve procedure, the left atrium is closed, the heart de-aired and aortic occlusion removed. Cardiopulmonary bypass is then discontinued and the thoracotomy incision closed once haemostasis has been achieved. **Control group:** Conventional mitral valve surgery will be performed via a median sternotomy, in which the sternum is divided completely (from the collarbone to the bottom of the breastbone). The operation includes cardiopulmonary bypass established by siting cannulas in the right atrium and inferior venae cava and ascending aorta. The heart is stopped with cardioplegia and the mitral valve is approached via the left atrium. The valve is repaired and assessed intra-operatively by water testing. If the repair is deemed satisfactory, the atrium is closed, de-airing manoeuvres are performed, and the aortic cross clamp is removed to allow reperfusion of the heart. Cardiopulmonary bypass is then discontinued and once haemostasis is performed the sternum is closed.

2. Trial Flow Diagram



3. Abbreviations

AE	Adverse Event
AF	Atrial Fibrillation
CI	Chief Investigator
CICU	Cardiac Intensive Care Unit
CPB	Cardiopulmonary Bypass
DCTU	Durham Clinical Trials Unit
GCP	Good Clinical Practice
GP	General Practitioner
HDU	High Dependency Unit
HES	Hospital Episode Statistics
HSCIC	Health and Social Care Information Centre
HTA	Health Technology Assessment
ICF	Informed Consent Form
ICU	Intensive Care Unit
IDMEC	Independent Data Monitoring and Ethics Committee
IG	Information Governance
IP	Intellectual Property
MVr	Mitral Valve Repair
MVR	Mitral Valve Replacement
NHS	National Health Service
NICOR	National Institute for Cardiovascular Outcomes Research
NIHR	National Institute for Health Research
PFO	Patent Foramen Ovale
PI	Principal Investigator
PIS	Patient Information Sheet
QALYs	Quality Adjusted Life Years
R&D	NHS Trust Research and Development Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SUSAE	Suspected Unexpected Serious Adverse Event
TSC	Trial Steering Committee

4. Introduction

4.1. Background

Mitral valve repair (MVr) surgery for mitral valve regurgitation is frequently performed (61) and patient numbers have increased by a third between 2003 and 2012 (from 1,549 to 2118 (31-33)); this rise will continue in an ageing population alongside a recognition in the international guidance that asymptomatic patients may also benefit from early surgery (34,35). Isolated mitral valve repair surgery more than doubled over the same time (681 in 2003 to 1456 in 2012) (31-33).

Left untreated severe mitral regurgitation carries a poor prognosis. In asymptomatic patients the estimated 5-year rates of death from any cause, death from cardiac causes and adverse cardiac events (death, heart failure or new atrial fibrillation), are 22%, 14% and 33% respectively (36). The prognosis for symptomatic severe mitral regurgitation is substantially worse and is further adversely affected by increasing age, atrial fibrillation, pulmonary hypertension, left atrial dilatation, and worsening left ventricular systolic function (37-43).

Mitral regurgitation is most commonly caused by degenerative mitral valve disease, which leads to dilatation of the mitral valve annulus, leaflet prolapse or leaflet restriction. Mitral regurgitation can also be caused by rheumatic valve disease, or infective endocarditis.

In contemporary UK practice, rheumatic mitral valve disease is uncommon and generally found in immigrant populations. The valve is usually not amenable to repair and therefore mitral valve replacement is the most common form of surgical treatment. Similarly, infective endocarditis is relatively rare and generally results in the destruction of the valve tissue; in most cases, optimal surgical treatment requires valve replacement rather than repair.

It is widely accepted that mitral valve repair surgery is the optimal treatment for patients with severe mitral regurgitation caused by degenerative disease. When compared to mitral valve replacement, it carries a lower peri-operative mortality, improved survival, better preservation of left ventricular function and lower long-term morbidity (62-67)

4.2. Choice of Comparators

Mitral valve surgery is routinely performed via a sternotomy incision. Sternotomy involves dividing the sternum completely enabling easy access to the heart and cannulation of the great vessels centrally to establish cardiopulmonary bypass. It allows flexibility in myocardial protection strategies and potentially simplifies de-airing and haemostasis at the end of the procedure.

Disadvantages of a sternotomy incision include an increase in bleeding because of the size of the incision. The mitral valve is posterior to the incision and access to the valve can be difficult. Wound infections occur in 2-3% of patients and significant morbidity, and mortality, can result from this complication (68-72). Importantly, the sternotomy incision is usually closed using multiple stainless steel wires facilitating immobilization of the sternum whilst sternal union occurs. It can take up to 3 months for the sternum to heal completely (44). During this period, the activity

of patients is significantly limited to reduce the risk of sternal dehiscence. These limitations reduce the speed of recovery and limit patients' ability to return to usual activities including work and physical activities. Moreover, limited activity during this period can increase the risk of complications in the recovery period (45, 46).

Minimally invasive approaches are increasingly used in all surgical specialties. They are often popular with patients, promoted by industry, and are being adopted by surgeons (73-75). In cardiac surgery, minimally invasive approaches are also used for coronary revascularisation (76) aortic valve surgery (77) aortic root surgery (78), and surgery for assist devices (79).

The first minimally invasive mitral valve repair via a lateral thoracotomy was reported in 1996 (81). Initial reports of minimally invasive surgery raised concerns about safety, especially increased incidence of stroke, aortic dissection, peripheral vascular injury, bleeding and increased rates of re-operation due to failed valve repair (81-83).

In more recent reports the safety profile has improved significantly with no significant differences in safety outcomes when minimally invasive surgery is compared to conventional surgery (29, 59). This has predominantly been due to technical improvements, which have simplified the procedure. For example: the aortic endo balloon clamp has been significantly re-engineered to decrease the risk to peripheral vessels (84); improved aortic clamps negate the need to substantially manipulate the aorta (85); and the introduction of automatic knot applicators and pre-measured gortex loops have substantially decreased the time the procedure takes (48). Concurrently operative techniques, including the ability to directly cannulate the aorta, have evolved significantly and decreased complication rates (49, 85).

As a result, there have been several recent publications establishing the safety of minimally invasive mitral valve surgery. Outcomes in a cohort of 1000 patients undergoing minimally invasive mitral valve surgery demonstrated a mortality of 0.8%, and 15-year survival of 79% (25). Of those surviving, freedom from reoperation at 15 years was 90% (25). The approach may also significantly reduce morbidity and mortality in high-risk patients (26) including in the elderly (86). Other data from 1011 patients suggests no difference in mortality or major morbidity, but a reduction in blood transfusions and residual mitral regurgitation following surgery (20); similar findings have been shown in other cohort studies (30). There is also emerging evidence that the minimally invasive approach is less costly than conventional sternotomy; with cost savings driven by reduced intensive care stay and hospital stay as well as reduced need for blood transfusion (16, 22, 23, 27-30, 87).

Five meta-analyses comparing minimally invasive to conventional mitral valve repair have been published (15-19). These all identify only one randomised controlled trial (RCT) reporting short (12) and long term (13) outcomes and base their main conclusions on evidence from observational studies (20-30) which show no significant differences between the two surgical techniques in regard to clinical outcomes. These data show longer cardiopulmonary bypass and cross clamp times, but shorter duration of ICU and overall hospital stay, translating into reduced

costs in patients receiving the minimally invasive operation (15-30). Findings also indicate less bleeding and reduced need for blood transfusion, less pain and wound infection, and an increased risk of aortic dissections from minimally invasive surgery (17). The most consistent finding was that the existing literature is severely limited by the absence of data on comparative outcomes between the two techniques. (15-19) This finding was confirmed through our own review of the available literature. We searched the Cochrane database, and systematically searched PubMed using search terms reflecting those used by cardiac surgeons and reported in the literature: (thoraco OR minithoracotomy) AND (sternotomy) AND (mitral valve OR mitral). We limited the search to those published in English, between 1995 and May 2015. We excluded studies that included patients with non-degenerative mitral valve disease, and that reported more than one third of patients who underwent valve replacement, as well as studies reporting concomitant procedures other than AF or PFO in over one third of patients; this revealed 73 relevant papers. We scrutinized these papers in detail, finding only one small RCT (reporting short and long term follow-up (12,13), 5 meta-analyses (15-19) and 11 observational studies (20-30). There are no relevant studies registered in clinical trial databases, nor any ongoing studies funded by the NIHR.

The one small RCT comparing 140 patients undergoing minimally invasive versus conventional mitral valve surgery was restricted to patients with Barlow's disease and reported early (12) and 3 year outcomes (13). The trial reported no evidence of a differences in mortality or major morbidity but those receiving minimally invasive surgery had a shorter ventilation time, ICU stay, and lower pain scores. There were no differences in freedom from moderate mitral regurgitation and freedom from repeat surgery from valve failure between groups at one and three-year follow up. Despite this, significant differences were seen in SF-36 scores at 6 months, but this was no longer evident at one year. This trial is severely limited by the very selective diagnosis of the patients included, the small number of patients studied, and the limited detail provided on the primary outcome.

Over the last 5 years, the number of patients undergoing the procedure has increased as some patients and clinicians have realised there are potential benefits of minimally invasive surgery (25, 88-91). This expansion in minimally invasive mitral valve surgery has occurred particularly in Europe and the United States (90, 91), but has been more limited within the UK NHS.

4.3. Current Evidence Supporting the Rationale for the Trial

There is equipoise in the current literature concerning the safety of the two techniques. A RCT is urgently needed to determine whether minimally invasive mitral valve repair surgery should be more widely adopted in the NHS. The International Society of Minimally invasive Cardiac surgery (ISMICS) has recently published a consensus document on the role of minimally invasive mitral valve surgery in contemporary cardiac surgery practice (47). The document highlights the limitations of the evidence they had to consider in reaching a consensus, particularly the lack of adequately powered prospective RCTs to establish the comparative efficacy of the two

approaches. Its recommendation was for further prospective RCT, adequately powered to assess quality of life, complications (especially stroke rates), efficacy (repair rates) and clinically relevant outcomes, particularly long term survival, patient functionality and freedom from re-operation (47).

The UK is uniquely placed to perform a RCT of this nature for a number of reasons. At present in the UK, minimally invasive mitral surgery is not standard care, unlike in many centres in the USA and Europe, allowing patients to be recruited and randomised into such a trial. Moreover, there are now an adequate number of cardiothoracic units which have mature minimally invasive mitral valve programs within which such a trial can occur prior to wider adoption of the procedure by the wider community.

There are on-going attempts to concentrate mitral valve repair practice to surgeons and cardiac surgical units who perform a relatively large volume of the procedure (92, 93). There is a unique opportunity for UK mitral valve surgeons to have large volume practices, in dedicated units, in keeping with the current policy for streamlining cardiac services. This context would facilitate investment and uptake of minimally invasive surgery, provided there is evidence to support improved quality of life, cost effectiveness, efficacy, safety, durability of repair, when compared to the conventional sternotomy approach.

Less than 5% of patients having mitral valve surgery in the UK currently have a minimally invasive approach. There are multiple reasons for this; the most important factor is the lack of clear and definitive evidence, from RCT.

There is consensus in the cardiac surgical community that the optimum surgical approach to treat these patients needs to be urgently defined.

5. Trial Objectives

The trial will compare two surgical strategies to establish the optimal surgical management of patients requiring mitral valve repair surgery.

The trial will answer the question 'Are improvements in physical functioning and associated return to usual activities seen in patients who undergo minimally invasive mitral valve surgery compared to conventional surgery?'

5.1. Primary Objective

To compare the physical functioning and associated return to usual activities in patients who undergo mitral valve repair via minimally invasive thoracoscopically-guided right minithoracotomy versus conventional sternotomy at 12 weeks.

5.2. Primary Economic Objective

To estimate the cost-effectiveness of minimally invasive thoracoscopically guided right minithoracotomy versus conventional sternotomy, estimating the incremental cost per quality-adjusted life year (QALY) gained after 52 weeks.

5.3. Secondary Objectives

- To explore the feasibility of study recruitment by means of an internal pilot trial; these data will be included in the main data for analysis.
- To assess cardiac function echocardiographically, with measurements of left ventricular volumes, dimensions and function, mitral regurgitation severity and estimates of both right heart function and pulmonary artery pressure early (3 days to 12 weeks) and late (52 weeks) after surgery, using blinded echocardiography.
- To compare mitral valve and mitral valve surgery related events and survival (morbidity and mortality) at 52 weeks and at 4.5 years (234 weeks).
- To compare physical functioning and overall quality of life over 52 weeks post MVr (using SF-36v2 and EQ-5D-5L(1-4)).
- To quantify the level of physical activity and quality of sleep (using an accelerometer (GENEActiv(6-10)) over 52 weeks post MVr).
- To quantify a range of surgical outcomes over the 52 weeks from index surgery.
- To compare costs, including intervention-specific estimates, of the two operations in the first 52 weeks following the index operation.
- To estimate QALYs from responses to the EQ-5D-5L (2-4) and SF-6D (derived from the SF-36v2).
- To estimate costs to the NHS over 4.5 years (234 weeks).
- To model costs and QALYs up to the end of the patients lifetime.
- To model the incremental cost per QALY gained over the patient lifetime.
- To determine if HES data adequately captures mitral valve related events.

6. Trial Design

6.1. Summary

A multi-centre, randomised controlled trial of minimally invasive thoracoscopically-guided right minithoracotomy versus conventional sternotomy for mitral valve repair.

The trial includes an internal pilot phase.

The trial is anticipated to take 60 months to complete and will randomise 400 patients receiving mitral valve repair at participating hospitals in England.

6.2. Inclusion Criteria

- Adult (≥18 years old at consent) patients with degenerative mitral valve disease, requiring isolated MVr (patients requiring concomitant surgery for Atrial Fibrillation and/or Patent Foramen Ovale (PFO) closure will be included).
- Written informed consent.
- Fit for cardiac surgery and cardiopulmonary bypass.

6.3. Exclusion Criteria

- Concomitant cardiac surgery other than for AF and PFO closure.
- Requiring mitral valve replacement.
- Acute infective endocarditis.
- Emergency or salvage surgery.
- Only conventional median sternotomy or only minimally invasive surgery indicated.
- Pregnant*.
- Currently participating in another interventional clinical trial.
- Four weeks or more as an inpatient prior to randomisation.
- Previous cardiac surgery.

*Female patients between the ages of 18 and 50 will receive a pregnancy test at baseline.

6.4. Setting

The trial will be conducted at UK NHS cardiac surgery units with established minimally invasive and conventional mitral valve services. All centres have the ability to accommodate the needs of this trial including established minimally invasive mitral valve repair services, adequate research nurse support, facilities to carry out the trial interventions and assessments and echocardiographers able to carry out scans (to be reviewed and reported at the lead centre in a blinded manner).

Only units that are in equipoise in the way they manage their patients requiring MVr are able to participate.

6.5. Expertise of Cardiac Surgeons

Each surgeon will perform only one of the operations; either MVr via thoracoscopically-guided right minithoracotomy or via median sternotomy within each centre. Before performing surgery within the trial, each surgeon will have independently completed 50 of these.

Each surgeon will, in advance of the trial starting at their centre, submit a record of the number of operations performed to the Trial Steering Committee.

6.6. Primary Outcome

- Change in SF-36v2 physical functioning scale at 12 weeks following surgery.

6.7. Primary Economic Outcome

- Incremental cost per QALY gained at 52 weeks following surgery.

6.8. Secondary Outcomes

Internal pilot trial outcomes:

- Patient recruitment within the first 6 months of the trial across 4 NHS cardiac surgery centres.

12 week outcomes:

- Level and variability in physical activity.
- Quality of sleep.
- Surgical outcomes (including duration of operation, cardiopulmonary bypass times, anaesthetic regime, protocol adherence).
- Costs, including intervention-specific estimates, of the two operations.
- Mitral valve related events determined using HES, NICOR, and medical record data.
- Left ventricular volumes and function, mitral regurgitation, right heart function, and pulmonary artery pressure.
- Survival.
- Physical functioning using SF-36v2.
- Quality of life using SF-36v2 and EQ-5D-5L.
- Adverse Events and Serious Adverse Events.
- Health care utilisation.
- Wound pain.
- NYHA class.
- Length of hospital stay.
- Medication usage.
- Re-operation.

- Conversion (minimally-invasive arm only).
- Red blood cell and blood product transfusions.
- Time on ICU, HDU and ward.
- Discharge destination.
- Duration of ventilation.
- Blood loss following surgery.

One year outcomes:

- Level and variability in physical activity.
- Quality of sleep.
- Mitral valve related events determined using HES, NICOR, and medical record data.
- Costs, including intervention-specific estimates, of the two operations.
- Survival.
- Physical functioning using SF-36v2.
- Quality of life.
- Adverse Events and Serious Adverse Events.
- Health care utilisation.
- Concomitant medications.
- Quality Adjusted Life Years (QALYs).
- Left ventricular volumes and function, mitral regurgitation, right heart function, and pulmonary artery pressure.

Long term outcomes:

- Quality Adjusted Life Years (QALYs) to the end of the patient's lifetime.
- Incremental cost per QALY over the patient lifetime.
- Mitral valve related events determined using HES, NICOR and medical records data to 4.5 years.

6.9. Process Outcomes

- Protocol adherence (including protocol violations).
- Fidelity of the operation (including care delivery, surgical and anaesthetic data, and surgeons' opinion).
- Patient withdrawals.
- Conversion from minimally invasive mini-thoracotomy to conventional sternotomy.

A process evaluation using qualitative and quantitative methods in both arms of the trial will assess the fidelity of both operations. Data from the wide range of surgical and anaesthetic parameters collected as part of the trial will be analysed to assess fidelity. Surgeons will record details of the operation using a pro-forma to detail their opinion of individual operations including their assessment of the fidelity of the operation to the protocol. To enable rigorous evaluation of

each surgical strategy, centres will be asked about the pathway of care for patients at the start of the trial, including anaesthetic regimens; these will be validated against the notes for a sample of 10% of patients from each centre.

7. Trial Procedures

7.1. Summary of Trial Assessments

	Baseline	Day of Surgery	Index Hospital stay	Follow up – time is calculated from the day of index surgery					
Study Procedure	-26 weeks to day of surgery	Day 0	Day 0 until discharge following index surgery	6 wks	12 wks	18 wks	24 wks	38 wks	52 wks
Consent[a]	X								
Medical History	X								
Physical Examination	X								
Demographics	X								
Concomitant Medications[b]	X			X	X				X
Pregnancy Test[c]	X								
NYHA Class	X			X	X				
ECHO (TTE)	X		X[d]	X[d]	X[d]				X
TOE[e]	X	X							
SF-36v2[f]	X			X	X	X	X	X	X
EQ-5D-5L[f]	X			X	X	X	X	X	X
euroSCORE	X								
Accelerometer	X			X	X	X	X	X	X
Eligibility Check	X								
Randomisation	X								
MVr surgery		X[g]							
Re-operation			X						
Post-operative details[h]			X						
VAS-Wound Pain score[i]			X[i]	X	X				
Ward usage and date of discharge			X						
Discharge destination			X						
RBC and other blood product transfusions[j]		X	X						
AEs and SAEs		X	X	X	X	X	X	X	X
Re-operation		X	X	X	X	X	X	X	X
Health Care Utilisation Questionnaire				X	X	X	X	X	X
HES Data				X	X	X	X	X	X
NICOR Data				X	X	X	X	X	X
Medical Record Review				X	X	X	X	X	X

a) Consent must be taken prior to baseline assessments and confirmation of eligibility.
b) A list of all medication currently being taken by the patient, including total daily dose, should be recorded.
c) Women between the ages of 18 and 50 must have a negative pregnancy test at baseline.
d) A Transthoracic Echo (TTE) must be performed at baseline if not available within 9 months of surgery. At the time of the TTE, blood pressure and heart rate should be measured, and recorded. One early post-surgical TTE is needed. This can be done from the 1st day post index surgery up to 12 weeks following surgery. A TTE will also be performed one year following index surgery. All TTEs must be transferred electronically to the Core laboratory for analysis as part of the trial.
e) The images from a pre-operative (baseline) TOE should be transferred to the Core laboratory for blinded echo review. The decision of whether or not to do a pre-operative TOE is at the discretion of the operating surgeon.
f) SF-36v2 and EQ-5D-5L should be performed by the blinded observer at The James Cook University Hospital at 6,12, 18, 24, 38 and 52 weeks following index surgery.
g) Details of the operation will be recorded on the trial surgical pro-forma including the lead surgeon's opinion on fidelity of the operation. Duration of operation, CPB times, need for conversion, and blood and blood product use will be recorded from the medical notes.
h) Total blood loss the time of drain removal following index surgery will be recorded, as well as time of drain removal and duration of ventilation
i) VAS-Wound pain should be used to record pain and analgesic use in the previous four hours on day 3 following index surgery, and at 6 and 12 weeks following index surgery.
j) The trigger for the RBC transfusion or blood product transfusion will be recorded (e.g. Drop in Hb, bleeding, clinical decision, etc).

7.2. Recruitment

Patients due to undergo isolated MVr surgery at participating centres will be identified at the point of referral (elective patients) and from the inpatient waiting list (urgent but non-emergency patients) by the clinical research team. Patient may be referred through the standard NHS referral pathways; in addition, cardiologists within each region will be made aware of the trial and will be able to refer patients to participating centres.

7.3. Informed Consent

Patients will be sent or given a covering letter and patient information sheet describing the study, and will be seen by one of the research team on the delegation log. The study will be discussed with the patient, and after opportunity for questions, a delegated and trained member of the research team will seek consent. The time between giving the information and taking consent may take a number of weeks. In-house urgent patients may have less time to consider participation however, all steps will be taken to ensure that they are afforded a reasonable time frame to do so and have had all their questions answered prior to consent.

Recruitment will continue until the target sample size is randomised. Patients who decline to participate in this trial will continue to receive care within the department as per usual care.

Written consent for the trial must be taken within 26 weeks (6 months) prior to surgery.

7.4. Eligibility check

Following consent, a consultant cardiac surgeon on the delegation log will confirm the patient's eligibility prior to randomisation, which should be performed as close to the date of surgery as practicable.

7.5. Screen Failures

Following consent, patients who do not meet trial eligibility criteria prior to surgery will be considered a 'screen failure' and withdrawn from the trial with no further data collected.

7.6. Randomisation

Eligible patients will be randomised by delegated and trained members of the research team at each centre using a 24-hour, central, secure, web-based randomisation system with concealed allocation. In the event that the randomisation system is not accessible, the team should contact DCTU.

Eligible patients will be randomised in a 1:1 ratio to undergo MVr using minimally invasive thoracoscopically-guided right minithoracotomy (intervention under study) or conventional median sternotomy (control arm/usual care).

Randomisation will be performed using a minimisation scheme to ensure patients randomised to MVr using minimally invasive thoracoscopically-guided right minithoracotomy (intervention under

study) and conventional median sternotomy (control arm/usual care) are comparable at baseline. The minimisation scheme will account for baseline SF-36v2 physical functioning score (0-≤33, >33-≥66, >66)*, and presence or absence of Atrial Fibrillation.

*Physical Functioning score is calculated as follows:

Following the completion of the full SF-36v2 the answers to questions 3a to 3j (10 questions in total) should be taken and scored as follows

- 0 to each answer “Yes, limited a lot”,
- 50 to each answer “Yes, limited a little”,
- 100 to each answer “No, not limited at all”.

The 10 scores should be added up to give a value of between 0 and 1000.

This value should then be divided by 10 to give a score between 0 and 100.

For the purpose of randomisation, the baseline SF-36v2 Physical Functioning scores will be grouped into three categories of low (0-≤33), moderate (>33-≤66) and high (>66).

This final value should then be used to select the correct SF-36v2 Physical Functioning category in the randomisation system, alongside the patient’s need for concomitant surgery.

7.7. Blinding

The trial will employ a prospective randomised blinded endpoint design; assessments of the SF-36v2 physical functioning scale and overall quality of life questionnaire as well as the EQ-5D-5L assessment will be completed by a blinded assessor at the lead centre.

All echocardiograms will be sent to an independent Core laboratory for assessment by a senior echocardiographer blind to the intervention.

All patients will be asked to consent to both operations and to conversion from minimally invasive thoracoscopically-guided right minithoracotomy to conventional sternotomy if randomised to this arm in the event that conversion becomes clinically indicated.

7.8. Informing General Practitioners of Patient Participation

General Practitioners will be informed of their patient’s decision to participate. A letter providing information about the study and inviting GPs to contact the investigators if they have questions must be sent following consent.

7.9. Withdrawal

Patients may withdraw from the study at any time if they wish to, without giving reason and without any adverse consequences for their future clinical management.

All patients will be made aware of their right to withdraw from the study, and this information will be included in the patient information sheet. Patients will be asked to consent for their continued participation in the event of loss of mental capacity during the trial.

Where possible, and with consent, data will be collected on patients that have withdrawn from the study to ensure completeness of data for the primary endpoint. Patients who choose to withdraw must be asked whether they are in agreement that this occurs. If a patient is not in agreement, only data collected to the point of withdrawal will be included in the analysis.

7.10. Baseline Assessments

In addition to usual care procedures, baseline assessments will take place prior to and within 6 months of surgery.

7.10.1. Cardiovascular and Significant Current and Past Medical History

A full medical history will be recorded for each patient at baseline and will include details of all clinically significant past cardiovascular medical conditions and all clinically significant on-going cardiovascular medical conditions. Review of other hospital notes (and GP notes) may be required to complete the medical history.

7.10.2. NYHA Class

NYHA Class assessment will be performed at baseline and repeated at 6 and 12 weeks following index surgery.

7.10.3. Physical Assessment

A physical assessment of height (measured in cm), and weight (measured in kg) will take place at baseline to determine Body Mass Index.

Body mass index will be calculated using the following formula:

Weight (kg) divided by height squared (m^2)

7.10.4. Current Medications

A list of the generic names of all medications currently taken by the patient, and their total daily dose, will be recorded at four time points during the trial:

- Baseline
- 6 weeks
- 12 weeks
- 52 weeks

7.10.5. Demographic Information

The following demographic data will be recorded as part of the trial:

- age on day of index surgery

- gender
- ethnic group

7.10.6. Pregnancy Test

A pregnancy test must be performed in all female patients between the ages of 18 and 50 prior to randomisation. The test must confirm that the patient is not pregnant.

7.10.7. Echocardiogram

Cardiac function will be assessed via transthoracic echocardiography (TTE) at baseline, post operatively (1 day to 12 weeks) and at 52 weeks. If an echo has not been done within 9 months of consent, this should be repeated at baseline. At the time of the echocardiogram, blood pressure and heart rate must be measured and recorded. Measurements of left ventricular volumes, dimensions and function, mitral regurgitation severity and estimates of both right heart function and pulmonary artery pressure will be recorded and reported by the Core laboratory.

Valve function may also be assessed pre-operatively and will usually be assessed intra-operatively using a transoesophageal echocardiogram (TOE) as part of usual care in both arms of this trial and to ensure valve integrity prior to closure. Where a pre-operative TOE is performed, the images should be transferred to the Core laboratory. Decisions about TOEs rest with the lead operating surgeon for each case.

All echocardiograms will be assessed by a Core laboratory, led by Dr Mike Stewart, at The James Cook University Hospital. Images will be transferred from the study centre to the Core laboratory.

Dr Stewart and his team will be blinded to the arm of the study to which patients are allocated. Images will be quality checked in 'real time', with the exception of echocardiograms from JCUH at the start of the study, which will be delayed until other centres are providing images, to preserve blinding. If images haven't been taken according to the trial template, and quantification according to the protocol is unlikely to be possible, a repeat scan will be requested.

All transthoracic echocardiograms will be performed according to the standard British Society of Echocardiography template, and assessed according to the recommendations for the echocardiographic assessment of native valvular regurgitation from the European Association of Cardiovascular Imaging (95).

The UK Mini Mitral Echocardiogram Manual provides further guidance to all centres involved in the study, detailing the number, quality and types of images to be acquired. The Core laboratory will work with centres and their IT services to enable timely transfer of images.

7.10.8. Echocardiogram Measures

All images should be provided to the Core laboratory according to the UK Mini Mitral Echocardiogram Manual; the following measures will be reproduced in the Core laboratory and used for secondary endpoint analyses:

- Left ventricular end systolic and end diastolic dimensions by M Mode (2D calliper measurement from parasternal long axis view if peripendicular M-mode not available)
- Left ventricular end systolic and end diastolic volumes indexed for body size, estimated using Simpsons biplane method.
- Mitral regurgitation severity – a) vena contracta, b) regurgitant volume by PISA methodology and c) regurgitant fraction
- Left atrial volume by biplane method of discs
- Right ventricular function as assessed by tricuspid annular plane systolic excursion (TAPSE)
- Estimated pulmonary artery pressure from Doppler measurement of tricuspid regurgitation velocity (to estimate right ventricular systolic pressure) and inferior vena cava dimensions (to estimate right atrial pressure)
- All measurements will be the average of 3 sequential beats if in sinus rhythm and 5 sequential beats if in atrial fibrillation

Mitral regurgitation will be graded according to the European Association of cardiovascular imaging guidelines from 2013. Mitral regurgitation will be graded as mild, moderate or severe based on quantitative (regurgitant volume, regurgitant fraction and effective regurgitant orifice area) and qualitative (colour Doppler) criteria.

7.10.9. EuroSCORE

EuroSCORE II will be determined prior to surgery, with the score recorded and reported as part of the trial. The elements that determined the euroSCORE II pre-operatively will be recorded.

EuroSCORE II is accessible using the following weblink:

http://www.euroscore.org/calc.html

7.10.10. SF-36v2, EQ-5D-5L

A member of the research team should administer the SF-36v2 and EQ-5D-5L questionnaires to each patient at baseline. The baseline SF-36v2 and EQ-5D-5L questionnaire completion must be prior to randomisation; the SF-36v2 physical functioning scale is used as a stratifying variable. Questionnaire completion will be repeated, by a blinded assessor at the lead centre, at 6, 12, 18, 24, 38 and 52 weeks following the index operation.

The contact details (name, study ID and telephone number(s)) for individual patients need to be securely sent to the Blinded Observer at the Lead Centre by a member of the research team

using nhs.net email addresses. Contact details will be used by the Blinded Observer to contact patients at 6, 12, 18, 24, 38 and 52 weeks following surgery.

Members of the research team at participating centres will need to contact the Blinded Observer to confirm the date the patient has their index operation. The Blinded Observer will keep in close contact with participating centres and for all visits, check that it remains appropriate to carry out assessments (SF-36v2 and EQ-5D-5L) at each time-point. Where possible, research team members and the Blinded Observer should co-ordinate their phone calls to minimise disruption to patients who are participating in the trial.

7.10.11. Accelerometer

Participants will be asked to wear an accelerometer on their non-dominant wrist nonstop for 7 consecutive days at seven time-points during the trial (baseline, 6 weeks, 12 weeks, 18 weeks, 24 weeks, 38 weeks, 52 weeks following index surgery).

Patient handedness (right or left handed) must be recorded. Patients should be asked to wear the accelerometer on their other (non-dominant) wrist during the 7 days of measurements. The wrist on which they wear the accelerometer must be recorded.

Accelerometers should be either given to the patient, or sent by post using the specific packaging provided for the trial. Following baseline, patients do not need to attend hospital for the sole purpose of starting or ending a week of accelerometer measurements.

Following the seven days of measurements, accelerometers will be returned in person or by post to the research team at each centre who will download the data and enter details in the Case Report Form, storing the .csv data files, and PDF files as source data.

Where a patient is an in-house urgent patient, accelerometer measures will not be possible for 7 days prior to surgery and will therefore not be measured at any time point during the trial for that patient.

Further details about all processes required to enable the accelerometer measures are detailed in the Accelerometer Manual.

7.11. Surgical Interventions

The intervention group will receive mitral valve repair via minimally invasive thoracoscopically-guided right minithoracotomy. The control group will receive MVr via conventional sternotomy.

7.11.1. Conventional Surgery

Conventional mitral valve surgery will be performed via a median sternotomy, in which the sternum is divided completely (from the collarbone to the bottom of the breastbone). The operation includes cardiopulmonary bypass established by siting cannulas in the right atrium and inferior venae cava and ascending aorta. The heart is stopped with cardioplegia and the mitral valve is approached via the left atrium. The valve is repaired and assessed intra-operatively by

water testing. If the repair is deemed satisfactory, the atrium is closed, de-airing manoeuvres are performed, and the aortic cross clamp is removed to allow reperfusion of the heart. Cardiopulmonary bypass is then discontinued and once haemostasis is performed the sternum is closed.

7.11.2. Minimally Invasive Surgery

Minimally invasive surgery is by thoracoscopically-guided right minithoracotomy. The patient is intubated with a single or double lumen endotracheal tube. Cardiopulmonary bypass is established by aortic or femoral artery cannulation and venous return is achieved from the venae cavae using a single bicaval cannula placed from the femoral vein or with an additional cannula in the superior venae cava. Transoesophageal echocardiography (TOE) confirms the optimum location of the venous and arterial cannulas.

A 4-7 cm right lateral mini-thoracotomy, is then used to enter the thorax through the third or fourth intercostal space. A soft tissue retractor with or without a small thoracic retractor is utilized to spread the ribs. The pericardium is opened 3-4 cm anterior and parallel to the phrenic nerve from the distal ascending aorta to the diaphragm. A video camera is inserted through a 5 -10 mm port.

Endoballoon occlusion or a transthoracic clamp achieves aortic occlusion. Cardiac arrest is achieved with repeated doses of cardioplegia. The mitral valve is approached through a paraseptal incision and a left atrial retractor is used to expose the mitral valve.

Following the mitral valve procedure, the left atrium is closed, the heart de-aired and aortic occlusion removed. Cardiopulmonary bypass is then discontinued and the thoracotomy incision closed once haemostasis has been achieved.

7.11.3. Concomitant Procedures

Concomitant surgery for Atrial Fibrillation (AF) and closure of Patent Foramen Ovale (PFO) will be allowed within the trial. Patients will be stratified based on whether they have AF at randomisation.

7.11.4. Anaesthetic Protocol

All patients will receive a standard cardiac anaesthetic. The anaesthetic protocol for individual units will be described before the trial starts and will be verified in a 10% sample of patients at each centre at routine visits by the research team.

The anaesthetic protocol for individual patients does not need recording in the Case Report Form.

7.11.5. Intra-operative Assessments

Details of the operation will be recorded on the trial surgical pro-forma including the lead surgeon's opinion on fidelity of the operation.

Duration of operation (time of patient entry and exit from operating theatre), CPB times, need for conversion, and blood and blood product use (including number of units), will also be recorded.

7.12. Post-operative Assessments

The post-operative period will begin once the patient has been admitted to CICU. Date and time of admission and discharge from CICU will be recorded.

7.12.1. Post-operative Blood Loss

Total blood loss until drain removal, will be measured (in mls) and recorded as part of the trial.

Clinically significant blood loss requiring clinical or surgical intervention should be recorded as an adverse event as part of this trial.

7.12.2. Further Surgery

Any additional cardiac surgery (defined as surgery requiring a General Anaesthetic) following the index operation will be recorded and reported as part of this trial.

Re-operation will be defined as another operation involving the mitral valve.

Conversion will only be recorded in the minimally invasive arm of the trial.

The reason will also be indicated.

7.12.3. Wound Pain Score

Pain will be assessed post-operatively using VAS-Wound pain at 3 days following index surgery, and at 6 and 12 weeks following index surgery.

At each time-point, the analgesia taken by, or administered to, the patient within the previous 4 hours will be recorded and reported.

7.12.4. Length of Hospital Stay Following Index Surgery

Length of hospital stay following admission for the index operation including cardiac intensive care unit (CICU), and ward (including any HDU) stays should be recorded.

To enable accurate reporting, the date and time of admission and discharge from each ward should be recorded.

7.12.5. Transfusion of Blood and Blood Products

Blood and blood product transfusion in the peri-operative period prior to discharge will be recorded. Indications for transfusions will be in accordance with individual centre protocols. The trigger (e.g. Hb, coags, bleeding, clinical decision etc.,) for any transfusions should be recorded at the time of transfusion.

7.12.6. HES and NICOR Data

Following hospital discharge after the index event, and by agreement with the Health and Social Care Information Centre (HSCIC) we will capture hospital episode statistics (HES) to identify any hospital attendance for mitral valve related events along with HES-linked mortality data. We will also capture these data from the National Institute for Cardiac Outcomes Research database (NICOR). Hospital records will be reviewed by the clinical research teams at each centre to establish how the events identified by HES and NICOR have been classified. Triangulation and validation in this way is needed because the identification of relevant outcomes has not been previously validated.

The data will be adjudicated and validated by an independent expert panel who will meet yearly throughout the trial. Patients will be asked to consent to long term follow up of these data extending beyond the duration of this trial.

7.12.7. Healthcare Utilisation Questionnaire

A questionnaire will be used to capture primary and secondary care visits following hospital discharge to 52 weeks, and medications prescribed. Patients will be asked to record each visit and the reason for this. Patients will return this at the 6 week visit and receive a telephone call from the research team at 12, 18, 24, 38 and 52 weeks to gather the information.

Where an SAE is foreseeable and requires hospitalisation, the dates of hospitalisation and ward usage should be reported on the CRF for up to 52 weeks following index surgery.

7.13. Follow-up Assessments

At 6, 12, 18, 24, 38 and 52 weeks following index surgery a range of assessments require completion as follows by a member of the research team at each centre.

All assessments must be completed within one week, either side, of the scheduled assessment date. Dates of assessments might not coincide with clinic visits, and therefore phone calls to patients at the appropriate time-point will be needed. Unless dates coincide with a planned hospital visit, accelerometers will need to be sent to patients in advance to enable data collection and to avoid the need for unnecessary hospital visits. In the event that a patient does not respond to phone calls, their GP should be contacted to confirm that details for the patient are correct and that it is still appropriate to continue to contact them.

At 6 and 12 Weeks:

- Concomitant medications, including total daily dose
- NYHA Class
- Echo (TTE)*
- Accelerometer
- VAS-Wound pain
- Adverse Events and Serious Adverse Events
- Details of any further surgery since the previous assessment
- Health Care Utilisation Questionnaire

* One early post-surgical TTE is needed. This can be done from the 1st day post index surgery up to 12 weeks following surgery. All TTEs must be transferred electronically to the Core laboratory for analysis as part of the trial.

At 18, 24 and 38 Weeks:

- Accelerometer
- Adverse Events and Serious Adverse Events
- Details of any further surgery since the previous assessment
- Health Care Utilisation Questionnaire

At 52 Weeks:

- Concomitant medications, including total daily dose
- Echo (TTE)*
- Accelerometer
- Adverse Events and Serious Adverse Events
- Details of any further surgery since the previous assessment
- Health Care Utilisation Questionnaire

* A TTE will be performed one year following index surgery. All TTEs must be transferred electronically to the Core laboratory for analysis as part of the trial.

Patients should be given or sent information packs containing the VAS-wound pain score, Health care utilisation questionnaire, SF-36v2, EQ-5D-5L, accelerometer details, prior to discharge to facilitate completion of assessments.

Blinded Assessments:

The following assessments will be performed by the blinded assessor for the trial at 6, 12, 18, 24, 38 and 52 weeks, who will phone all patients to complete these:

- SF-36v2
- EQ-5D-5L

8. Safety Reporting

8.1. Adverse Events

Adverse events are defined as **any** new medical occurrence, or worsening of a pre-existing medical condition in a patient that has received surgery, or procedures associated with the surgery, as part of the trial, which does not necessarily have to have a causal relationship to the surgery, or to procedures associated with the surgery.

The adverse events of wound pain or an event leading to conversion during index surgery are outcomes and as such should not also be recorded as an AE unless they fulfil the criteria for a reportable SAE. The following are also not required to be reported during the trial:

- Haematological and biochemical parameters not deemed to be clinically significant or not requiring clinical intervention.
- Blood loss following surgery unless clinical intervention or further surgery is required.

8.2. Serious Adverse Events

Serious adverse events are defined as any untoward or unexpected medical occurrence that:

- Results in death,
- Is life-threatening,
- Requires hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability or incapacity,
- Is a congenital anomaly or birth defect,
- Any other important medical condition which, although not included in the above, may require medical or surgical intervention to prevent one of the outcomes listed.

8.3. Foreseeable Adverse Events

Foreseeable Serious Adverse Events are those which are foreseen in the patient population and as a result of the routine care of patients undergoing MVr surgery.

1. death (unless unforeseeable)
2. anaemia
3. anaphylaxis
4. atelectasis
5. atrial fibrillation
6. atrial flutter
7. bowel obstruction or perforation
8. cardiac arrest (where possible, the cause should be recorded as the AE)
9. cardiac pain
10. chest infection
11. collapse (where possible, the cause should be recorded as the AE)

12. deep vein thrombosis
13. dyspnoea (where possible, the cause should be recorded as the AE)
14. endocarditis (including infective endocarditis)
15. gastrointestinal disturbances including gastrointestinal bleeding
16. gut infarction
17. haematoma at surgical sites
18. haemodynamic instability
19. heart block
20. heparin induced thrombocytopenia or other haematological complications
21. hepatobiliary disturbances
22. hypotension
23. infection
24. intra or post-operative bleeding
25. lymphatic leak
26. lymphocele
27. mediastinitis
28. myocardial infarction
29. non-cardiac chest pain
30. oedema (e.g. pulmonary and peripheral)
31. pancreatitis
32. para valvular leak
33. pericardial effusion
34. permanent neurological deficit (stroke);
35. pleural effusion
36. pneumothorax
37. pulmonary embolus
38. renal failure or acute kidney injury
39. respiratory failure
40. sepsis
41. sternal dehiscence
42. sternal malunion
43. sudden ventricular arrhythmias
44. surgical injury (including peripheral vascular injury, lung herniation, diaphragmatic paralysis, and aortic injury)
45. temporary neurological deficit
46. urinary tract infection
47. ventricular fibrillation or tachycardia
48. wound infection
49. wound pain

8.4. Pregnancy

Where a patient becomes pregnant during their involvement in the trial, this must be reported to DCTU using the appropriate form. The pregnancy must be followed until the outcome is known, to determine if an SAE should be reported. Patients who become pregnant should be withdrawn from the trial; pregnancy is likely to have a significant impact on the primary and secondary endpoints within this trial.

8.5. Causality

The relationship of each adverse event to the surgery, and associated surgical procedures, must be determined by a medically qualified individual who is on the delegation log for the trial. The following definitions should be used to determine causality:

Unrelated	The event is not considered to be related to the surgery, or procedures associated with the surgery.
Unlikely to be related	The event is considered unlikely to be related to the surgery, or procedures associated with the surgery.
Possibly related	Although the relationship to the surgery, or procedures associated with the surgery, cannot be ruled out, the nature of the event, the underlying disease, concomitant medications or temporal relationship make other explanations plausible.
Probably related	The temporal relationship and an absence of a more likely explanation suggest that surgery, or procedures associated with the surgery, are the most likely cause.
Definitely related	The known effects of the surgery, or procedures associated with the surgery, indicate this to be the most likely cause.

8.6. Severity

The severity of each adverse event, must be determined by a medically qualified individual who is on the delegation log for the trial. The following definitions should be when determining severity:

Grade 1	Minor adverse event, not requiring medical intervention. May be asymptomatic and is likely to be a clinical or diagnostic observation only; or may be a symptomatic but minor, or transient event, with no necessity for medical intervention. This might include asymptomatic laboratory or radiographic findings. A minor adverse event is likely to have only marginal clinical relevance.
Grade 2	An adverse event which may require some medical intervention (local/non-invasive) and which is symptomatic to patient. May affect activities of daily living.
Grade 3	Significant symptoms reported, requiring medical intervention and possibly requiring hospitalisation. Medically significant and likely to be significantly affecting activities of daily living.
Grade 4	An adverse event that requires urgent intervention or may have life-threatening consequences.
Grade 5	Death related to the adverse event.

8.7. Adverse Event Reporting

Adverse Events (AEs) will be recorded in the patients' medical notes and on electronic case report forms. AEs will be recorded from the day of index surgery until 52 weeks following index surgery or until withdrawal, with the exception of adverse events considered related to MVr surgery, which will be followed until resolution, a stable outcome or death.

All AEs will be assessed for severity, causality, and seriousness by an Investigator. All events will be reviewed by the Independent Data Monitoring and Ethics Committee (IDMEC) as part of their ongoing assessment of safety.

8.8. Foreseeable Adverse Event Reporting

Foreseeable adverse events should be recorded as adverse events within the trial CRF, but do not require reporting as Serious Adverse Events for this trial.

8.9. Serious Adverse Event Reporting

Unforeseeable SAEs will be reported to Durham Clinical Trials Unit and to the Sponsor as soon as the research team become aware of the event, where it is both an SAE and does not appear on the list of foreseeable adverse events. Where required, these events will undergo expedited reporting to the Research Ethics Committee. Unforeseeable SAEs should be reported using the trial specific SAE form.

Where an SAE is foreseeable and requires hospitalisation, the dates of hospitalisation and ward usage should be reported on the CRF.

9. Statistics

9.1. Sample Size

The primary outcome measure is the change in physical functioning scale within SF-36v2 (1) from baseline at 12 weeks following index surgery. We believe that, on the basis of the literature and consulting with the cardiac and patient community, a minimally clinically important difference is 10 points on the scale. This trial is powered to investigate the superiority of thoracoscopically-guided right mini-thoracotomy over median sternotomy in terms of post-surgical physical functioning assessed using the SF-36v2 physical functioning scale.

One recent publication (13) reports a small variation (standard deviation (SD) of 8) in SF-36 physical function scores; this is not seen in other publications (11, 55) who report a SD of 30. We have therefore used the more conservative estimate to inform the power calculation for this trial.

Assuming alpha of 5% and 90% power, 382 patients (191 in each arm) are required to detect a minimally clinically important difference of 10 points in the SF-36v2(1) physical functioning scale at 12 weeks (assuming a SD of 30 (11)). Patients will be recruited from 4 centres to enable recruitment to target. Allowing for attrition, 400 patients will be randomised.

9.2. Statistical Analysis

Data cleaning and analysis will be provided by staff within DCTU. Primary analysis will follow intention to treat principles with patients analysed according to randomisation and irrespective of surgical intervention received; other analysis groups such as per-protocol may be considered subsequently. Every effort will be made to retain and include all patients who are part of the trial.

A full statistical analysis plan (SAP) will be developed for the outcome measures and agreed with the IDMEC and TSC prior to any analysis being undertaken.

Outcome data will be analysed at the end of the study, no interim analyses is planned.

Primary analysis of change in physical functioning as measured using SF-36v2 at 12 weeks using intention to treat principles will use a general linear model accounting for surgical intervention, baseline scores, valve pathology and concomitant surgery. Robust standard error will be incorporated to account for intra-patient correlation due to the repeated measures. A similar modelling approach will be used for the final analysis of change in physical functioning at week 52. Secondary outcomes: continuous outcomes will be analysed using a general linear model, binary outcomes will be analysed using a generalised estimating equation to account for repeated binary data over time, categorical outcomes (with more than two categories) will be analysed using baseline-category logit model, while log-rank test and frailty modelling will be used to analyse time-to-event outcomes. Analysis of all outcomes with repeated measures on the same patient will account for intra-patient correlation. Multiple imputation will be used if necessary to sensitise incomplete data. All outcomes will also be described using simple statistics to facilitate interpretations and communication of findings. Secondary analysis will also include hierarchical

modelling of patients, surgeons and centres, to provide an estimate of treatment effect at each of these levels.

Each question within the SF-36v2 physical functioning scale will be scored based on the RAND scoring system. The average of the per patient scale scores (assuming each question carries equal weight) will provide the primary outcome for physical functioning at 12 weeks.

10. Economic Analysis

The economic evaluation will include both a within trial; economic evaluation and a modelled based economic evaluation to estimate cumulative costs and QALYs and incremental cost per QALY gained over a patient lifetime. For the within trial economic evaluation patient estimates of costs and QALYs at 52 weeks will be used to estimate the incremental cost-effectiveness of the two surgical procedures, from an NHS perspective. Within the first year use of NHS services will be collected from medical records, HES and NICOR data and using a patient questionnaire to capture primary and secondary care visits. Use of secondary care health services between month 12 and 55 will be based on data extracted from Hospital Episode Statistics (HES) data, validated using medical records and the National Adult Cardiac Surgical Database which is administered by The National Institute for Cardiovascular Research (NICOR), adjudicated by an independent expert panel. The role of the independent expert panel will be to assess which use of health services is attributable or sequelae to the index surgery or underlying disease condition (e.g. surgical revision or complication, worsening mitral disease or infection) and/or which is unrelated.

The costs of all health services will be estimated using study specific estimates (the index surgery), and routine data sources e.g. NHS reference costs for other secondary care, PSSRU for primary care and the BNF for medications. For each trial participant we will estimate the total cost of care and then for each intervention group we will estimate incremental mean costs at 12 months and 4.5 years (see below). The costs over the longer follow-up period will also be reported separately both to illustrate how costs accrue over time and to provide an estimate of total costs up to 4.5 years.

For the within trial economic evaluation QALYs will be estimated from responses to the EQ-5D-5L (2-4) administered at baseline, 6, 12, 18, 24, 38 and 52 weeks post MVr. Response will be converted into health state valuations using the UK population tariffs. Currently, as a value set is not available for the EQ-5D-5L, responses will be cross walked from the EQ-5D-3L value set (3). These values will then be used to estimate QALYs for each participant using the area under the curve approach. In a sensitivity analysis, QALYs will also be estimated from responses to the SF-36v2 administered at the same time points. The responses to the SF-36v2 (1) will be converted into SF-6D tariffs and QALYs estimated using the same methodology as described above.

In the within trial economic evaluation the effect of surgery at 52 weeks will be estimated using bootstrapped, bivariate regression modelling of costs and QALYs adjusted for baseline scores and stratifying variables. Bootstrap replicates will be visualised on the incremental cost-effectiveness plane, with a cost-effectiveness acceptability curve and by net monetary benefit, highlighting NICE

reference case societal willingness to pay values. Given the timeframe of 52 weeks, discounting of future costs and benefits will not be applied. Multiple imputation will be used if necessary to manage incomplete data, exploring the missing at random assumption and using best practice for imputation. As noted above stochastic sensitivity analysis will be based on the bootstrapped estimates this will be combined with deterministic sensitivity analysis to explore other forms of uncertainty e.g. the use of alternative utility values based on the SF-6D, variation in costs.

We will construct a state transition model to extrapolate beyond the 52 week within trial analysis. The structure of the model will be developed according to best practice guidelines and will describe the patient pathway over their lifetime. Key data to populate the model will come from the within trial analysis. Longer term costs and events, which generate a cost and a HES record, will be extrapolated from the routine data sources used to estimate costs up to 4.5 years. Further data to populate the model will come from structured reviews of the literature e.g. review of the cost-effectiveness registry (https://research.tufts-nemc.org/cear4/Default.aspx) to identify health state utilities for events that occur in the long-term which are not captured within the trial data set. The results of the economic model will be presented as estimates of cost, QALY and incremental cost per QALY gained. As the time horizon is longer than 52 weeks both costs and QALYs will be discounted at the UK recommended rate (currently 3.5%). Probabilistic sensitivity analysis will be used to plot of costs and QALYs on the cost-effectiveness plane, with a cost-effectiveness acceptability curve showing the likelihood that each intervention is cost-effective at different threshold values for society's willingness to pay. The model will be calibrated with data collected for the trial but which is not directly used in the model (e.g. cumulative estimates of costs or of specific events at 4.5 years derived from the routine records). Both deterministic and probabilistic sensitivity analyses will be conducted to explore key uncertainties.

11. Structure and Duration of the Trial

The total duration of this trial is anticipated to be 60 months; this comprises a 6-month internal pilot and recruitment continuing for a further 37 months of the main trial. Patients will be followed for a minimum of 12 months following index surgery. The trial will randomise 400 patients from participating cardiac surgery centres in England. The final 5 months will comprise final data cleaning, analysis, report writing and dissemination of research findings.

The internal pilot phase, run over a 6 month period in four cardiac surgery centres will assess whether trial recruitment processes and assessments will enable recruitment targets to be achieved.

During the pilot the research team will monitor recruitment and retention at each centre and investigate their processes to identify good practice that can be shared, or, where lower than expected recruitment is seen, determine reasons for this and implement changes to boost recruitment. The research team will talk to clinical team members, current participants, and to patients

who have decided not to participate to fully understand the recruitment figures. Where helpful, we will set up meetings between centres to enable sharing of good practice across all participating centres.

The outcomes from the pilot trial will be reviewed by the Independent Data Monitoring and Ethics Committee, and the Trial Steering Committee prior to consideration by the HTA to confirm that the trial should continue.

The duration of trial participation will be from the day of consent until the 52-week follow-up assessments or withdrawal. Where a patient withdraws, but there is a study related adverse event, this will be followed until resolution, a state of persistence or permanence, or death. All participants will be asked to consent to longer-term follow up using routine data.

The trial will take 60 months to complete. The end of the trial for all participants will be defined as the collection of 52-week outcome data from the last participant.

11.1. End of Trial

The end of the trial will be defined as the last assessment at 52 weeks for the last patient in the trial.

11.2. Early Trial Cessation

If the Sponsor, Lead Investigator, DCTU, IDMEC, TSC, or TMG discover conditions arising during the trial that indicate the trial should be stopped, this action may be taken. The TSC carries the responsibility for deciding if the trial should be stopped early. Conditions likely to warrant study termination include, but are not limited to:

- Futility: the trial has no prospect of reaching its recruitment within the given time frame
- There is a substantial change in understanding/scientific advancement meaning that continuation of the trial is inappropriate
- Safety: overwhelming evidence for harm makes continuation non-viable

11.3. Remuneration

No financial or material incentives will be given to participants, however reasonable travel expenses will be given for participants who return to the hospital for the additional echo assessments.

12. Quality Control and Assurance

12.1. Risk Assessment

DCTU, in collaboration with the Sponsor, has assessed the risk of this trial and will review the risk level regularly throughout the trial.

12.2. Trial Registration

This trial has been registered with the International Standard Randomised Controlled Trial Number database.

12.3. Site Initiation and Training

Initiation visits at each participating cardiac centre will be performed by the Chief Investigator or his delegate and by representatives from DCTU once all appropriate approvals are in place.
Specific training will be given to centre staff on use of the randomisation system, eCRF system and accelerometers.

12.4. Centre Monitoring and Auditing

The trial will be monitored by Durham Clinical Trials Unit (DCTU) and representatives from DCTU will visit the centres periodically, and in accordance with a trial specific monitoring plan. DCTU representatives will review the quality of the data to confirm that the trial is being run in accordance with the protocol.

DCTU representatives will review the Case Report Forms of patients who sign consent forms for this study, and will compare these directly to the medical notes and source data (a process known as source data verification (SDV)). SDV of consent and full SDV of all data fields will occur for a proportion of patients who enter the trial, chosen at random.

At monitoring visits DCTU staff will also discuss the conduct of the trial with the local trial team and review the Investigator site file.

In addition, the study may be evaluated by an auditor or government inspector, who will also be allowed access to all case report forms, source documents, study files and study facilities.

12.5. Blinded Endpoint Review

This trial has blinded endpoint review of the primary outcome measure and of three secondary outcome measures.

A blinded assessor will conduct SF-36v2 and EQ-5D-5L questionnaire assessments over the telephone for all patients following surgery. Blinded assessments are performed at 6, 12, 18, 24, 38 and 52 weeks following index surgery.

All echocardiograms will be sent securely to the Core laboratory for review and reporting. The Core laboratory team will be blinded to surgical allocation.

12.6. Serious Breaches

A serious breach will be reported to the Sponsor and to the ethics committee as soon as it is identified. Serious breaches are defined as a breach of the protocol which is likely to affect to a significant degree the safety or physical or mental integrity of a trial patient or the scientific value of the trial

12.7. Ethics

12.7.1. Good Clinical Practice

The trial will be run according to the principles of ICH GCP, and in accordance with relevant UK legislation and the protocol.

12.7.2. Approvals

The trial will not start until a favourable opinion has been given by an NHS REC. In addition, governance approval must be confirmed by NHS Trust Research and Development (R&D) Offices for individual centres prior to starting recruitment.

12.8. Information Governance

The information collected as part of this trial will be stored securely both electronically and on paper and kept confidential. Data will be used according to the provision of the 1998 Data Protection Act, and applicable new regulations, and individuals will not be identifiable through any reports or publications that result from the trial.

Participating patients will be assigned a unique trial number at consent. All paper study files and documents, including personal data and each patient's consent form will be retained at the participating NHS Trust in a locked office prior to secure archiving at the end of the study. Electronic trial records will be kept on secure NHS servers with access restricted to the study team, these will be securely archived at the end of the trial. Research data will be transferred to Durham Clinical Trials Unit, and to Newcastle University for analysis by DCTU, and Newcastle University staff in collaboration with the clinical trial team.

Data will be entered onto an electronic case report form for each patient. Data will be stored on secure servers that are external to both the Sponsoring NHS Trusts and to Durham University.

Data extracted for review during the course of the trial, and for archiving at the end of the trial, will be stored securely in restricted access areas of the Durham University server system. This data will be accessible to the clinical research team and to Durham Clinical Trials Unit staff, as well as in summary form to members of the TSC, IDMEC, and TMG. Expert panel members may need unique study ID, age, gender and ethnicity when reviewing data; where possible data will be aggregated or fully anonymised. An auditor or regulatory inspector may access trial data as required. The personal identifiable data on these servers will be encrypted and all data will have access restricted to authorised personnel and be password protected.

The data stored electronically in the database will contain the date of birth, gender, and ethnicity, and assigned trial number for each patient, but no other personal identifiable data. NHS numbers will be recorded and kept by DCTU to enable data to be sent and linked from HES, ONS and NICOR.

Echocardiograms for each patient will be sent to the Echo Core Laboratory. These data will be included in the final research data set for analysis. Consent from individual patients will enable scan data, along with their other fully anonymised trial research data, to be used in future research following the end of UK Mini Mitral.

The Blinded Observer will be sent patient names, unique study ID, date of surgery and preferred contact details to enable follow up for questionnaire completion. These personal identifiable data will be kept securely on NHS servers during the trial, and destroyed at the end of the trial. Any paper copies of completed questionnaires will be securely archived for 15 years following the end of the trial.

Patients who withdraw from the trial will have all data collected up until the point of withdrawal included in the study, except where withdrawal is due to a trial related AE. In this event the patient will be followed until a stable outcome is achieved. Where a patient who has withdrawn agrees, data to answer the primary endpoint of the study can be collected; this will be recorded and used. Data will be submitted to DCTU and included in the trial analysis.

12.9. Retention of Personal Data

Personal data will be needed to enable follow up of patients, including access to HES, ONS and NICOR data, and to disseminate details of the trial and trial findings to patients.

Personal data will be held securely and confidentially, and will be kept beyond the end of this trial. Follow on funding may be sought to continue to follow patients using routinely collected data. As such, personal data will be kept for 15 years after the last data collection point for all patients, before being confidentially destroyed.

12.10. Funding

This trial has been funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme.

12.11. Insurance

NHS Indemnity is in place to cover all aspects of clinical treatment and care provided as part of this trial.

Durham University has insurance to cover Durham Clinical Trials Unit's contributions to the Trial.

13. Trial Governance

13.1. Centre Research and Development Approval

Recruitment at each centre will only begin following all applicable approvals.

13.2. Trial Sponsor

South Tees Hospitals NHS Foundation Trust is the trial Sponsor.

13.3. Co-ordinating Centre

The trial will be co-ordinated by Durham Clinical Trials Unit, Durham University, where the Trial Manager will be based.

DCTU will be responsible for the trial database, randomisation, trial management, data management, and statistical analyses. The Chief Investigator and the research teams at each centre will manage the day-to-day running of the trial including recruitment at centres, and in collaboration with DCTU, the training of staff. DCTU will service the trial related committees and the expert panel.

13.4. Trial Management Group (TMG)

The day-to-day supervision of the trial will be the responsibility of the Trial Management Group, who will report to the Trial Steering Committee. The TMG will meet regularly throughout the trial.

The TMG will consist of:

- The Chief Investigator
- The CTU co-Directors
- The Trial Manager

The Clinical Data Manager, lead Research Nurse, lead statistician, and other members of the co-applicant team may attend TMG meetings as required.

13.5. Trial Steering Committee (TSC)

DCTU, in collaboration with the Chief Investigator, will organise a trial steering committee (TSC) consisting of an independent chair and at least two other independent members. Independence will be defined as not employed by any organisation directly involved in trial conduct.

Patient representatives, the Chief Investigator, the DCTU co-Directors and other co-applicants will be joined by observers from DCTU. The HTA Programme Manager will be invited to attend all TSC meetings.

The TSC will meet at 6 monthly intervals. The TSC will report to the Sponsor and to the HTA.

The TSC will provide overall supervision of the trial, and will monitor progress, conduct and advise on the trial. The TSC will consider the recommendations of the IDMEC, and act where required.

The TSC carries the responsibility for deciding if the trial should be stopped early. Terms of reference for the TSC will be agreed at the first meeting.

13.6. Principal Investigators Meeting (PIM)

All Principal Investigators will be invited to an annual meeting to discuss trial progress and to share experiences of conducting the trial at their centre.

13.7. Independent Data Monitoring and Ethics Committee (IDMEC)

DCTU, in collaboration with the Chief Investigator will organise an independent data monitoring and ethics committee (IDMEC). The IDMEC will meet at 6 monthly intervals and will run in accordance with a trial specific DAMOCLES charter (53) which will be agreed at its first meeting.

The IDMEC will report to the TSC and will provide advice on the ongoing conduct and safety of the trial. The IDMEC will review trial outcomes, including adverse events and serious adverse events.

13.8. Expert Panel

DCTU, in collaboration with the Chief Investigator will organise an Expert Panel. The Panel will meet annually to review data from HES, NICOR and medical records, and will run in accordance with terms of reference which will be agreed at its first meeting.

The Expert Panel will comprise three independent clinical experts; they will report to the IDMEC.

14. Protocol Signature

14.1. Principal Investigator Signature

By signing this protocol page, I agree to:

- Conduct the trial in accordance with the protocol
- Personally conduct and supervise the trial and ensure that all colleagues assisting with the trial are appropriately delegated and are informed about their obligations
- Ensure that the requirements with regard to obtaining informed consent are adhered to without exception
- Report all AEs and SAEs that occur during the course of the trial, in accordance with the protocol
- Maintain accurate and complete records to enable confirmation of adherence to the protocol

Principal Investigator's Signature	Date

15. References

1. Ware JE, Jr, Kosinski M, Bjorner JB, Turner-Bowker, DM, Gandek, B and Maruish, ME (2007) User's Manual for the SF-36v2TM Health Survey (2nd Ed). Lincoln, RI, Quality Metric Incorporated
2. Van Hout B, Janssen MF, et al. Interim scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L value sets. Value in Health 2012 Jul-Aug;15(5):708-15
3. Van Reenen M, Janssen B. EQ-5D-5L user guide: basic information on how to use the EQ-5D-5L instrument. Version 2.1. EuroQoL group, 2015
4. Herdman M, Gudex C, Lloyd A, Janssen MF, Kind P, Parkin D, Bonsel G, Badia X. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of Life Research. 2011 Dec; 20(10): 1727–1736
5. The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed Little, Brown & Co; Boston, Mass: 1994. pp. 253–256
6. Esliger DW, Rowlands AV, Hurst TL, Catt M, Murray P, and Eston RG. Validation of the GENEActiv Accelerometer Med Sci Sport Exerc. 2011; Jun;43(6):1085-93
7. Pavey T, Gomersall S, Clark B, Waryouni F, Brown W. The validity of the GENEActiv wrist-worn accelerometer for measuring sedentary behaviour in free living . J Sci and Med in Sport Dec 2014 18 supp1 e34
8. Sirichana W, Moore-Gillon CE, Patel MH, Taylor M, Storer TW, Cooper CB. Daily Physical Activity in COPD: Quantification by Tri_Axial Accelerometry. Am J Respir Crit Care Med 187:2013:A1361
9. Troiano RP, McClain JJ, Brychta RJ, Chen KY. Evolution of accelerometer methods for physical activity research. Br J Sports Med 2014;48:1019–23.
10. Hildebrand M, Van Hees V, Hansen BH, Ekelund U. Age-group comparability of raw accelerometer output from wrist- and hip-worn monitors. Med Sci Sports Exerc 2014;46:1816–24
11. Ira RA Goldsmith, Gregory YH Lip, Ramesh L Patel. A prospective study of changes in the quality of life of patients following mitral valve repair and replacement. Eur J Cardiothorac Surg. 2001 Nov;20(5):949-55
12. Speziale G; Nasso G; Esposito G; Conte M; Greco E; Fattouch K; Fiore F; Del Giglio M; Coppola R; Tavazzi L. Results of mitral valve repair for Barlow disease (bileaflet prolapse) via right minithoracotomy versus conventional median sternotomy: a randomized trial. Journal of Thoracic & Cardiovascular Surgery. 142(1):77-83, 2011 Jul.
13. Nasso G; Bonifazi R; Romano V; Bartolomucci F; Rosano G; Massari F; Fattouch K; Del Prete G; Riccioni G; Del Giglio M; Speziale G. Three-year results of repaired Barlow mitral

valves via right minithoracotomy versus median sternotomy in a randomized trial. Cardiology. 128(2):97-105, 2014.

14. Colleen Gorman Koch, Farah Khandwala, Eugene H. Blackstone. Health-Related Quality of Life After Cardiac Surgery. Seminars in Cardiothoracic and Vascular Anaesthesia Vol 12, No. 3, September 2008 203-217
15. Sundermann SH; Sromicki J; Rodriguez Cetina Biefer H; Seifert B; Holubec T; Falk V; Jacobs S. Mitral valve surgery: right lateral minithoracotomy or sternotomy? A systematic review and meta-analysis. Journal of Thoracic & Cardiovascular Surgery. 148(5):1989-1995.e4, 2014 Nov.
16. Ding C; Jiang DM; Tao KY; Duan QJ; Li J; Kong MJ; Shen ZH; Dong AQ. Anterolateral minithoracotomy versus median sternotomy for mitral valve disease: a meta-analysis. [Review] Journal of Zhejiang University SCIENCE B. 15(6):522-32, 2014 Jun.
17. Cao C, Gupta S, Chandrakumar D, Nienaber TA, Indraratna P, Ang SC, Phan K, Yan TD A meta-analysis of minimally invasive versus conventional mitral valve repair for patients with degenerative mitral disease. Ann Cardiothorac Surg. 2013 Nov;2(6):693-703.
18. Modi P, Hassan A, Chitwood WR Jr. Minimally invasive mitral valve surgery: a systematic review and meta-analysis. Eur J Cardiothorac Surg. 2008 Nov;34(5):943-52.
19. Cheng DC, Martin J, Lal A, et al. Minimally invasive versus conventional open mitral valve surgery: a meta-analysis and systematic review. Innovations (Phila) 2011;6:84-103
20. Goldstone AB; Atluri P; Szeto WY; Trubelja A; Howard JL; MacArthur JW Jr; Newcomb C; Donnelly JP; Kobrin DM; Sheridan MA; Powers C; Gorman RC; Gorman JH 3rd; Pochettino A; Bavaria JE; Acker MA; Hargrove WC 3rd; Woo YJ. Minimally invasive approach provides at least equivalent results for surgical correction of mitral regurgitation: a propensity-matched comparison. Journal of Thoracic & Cardiovascular Surgery. 145(3):748-56, 2013 Mar.
21. Lamelas J; Sarria A; Santana O; Pineda AM; Lamas GA. Outcomes of minimally invasive valve surgery versus median sternotomy in patients age 75 years or greater. Annals of Thoracic Surgery. 91(1):79-84, 2011 Jan.
22. Mazine A, Vistarini N, Ghoneim A, Lebon JS, Demers P, Jeanmart H, Pellerin M, Bouchard D. Very High Repair Rate Using Minimally Invasive Surgery for the Treatment of Degenerative Mitral Insufficiency. Can J Cardiol. 2015 Jan 7.
23. Grossi EA, Goldman S, Wolfe JA, Mehall J, Smith JM, Ailawadi G, Salemi A, Moore M, Ward A(9), Gunnarsson C; Economic Workgroup on Valvular Surgery. J Thorac Cardiovasc Surg. 2014 Dec;148(6):2818-22.e1-3. doi: 10.1016/j.jtcvs.2014.08.029. Minithoracotomy for mitral valve repair improves inpatient and postdischarge economic savings.
24. Holzhey DM, Shi W, Borger MA, Seeburger J, Garbade J, Pfannmüller B, Mohr FW. Minimally invasive versus sternotomy approach for mitral valve surgery in patients greater than 70 years

old: a propensity-matched comparison. Ann Thorac Surg. 2011 Feb;91(2):401-5. doi: 10.1016/j.athoracsur.2010.08.006.

25. McClure RS, Athanasopoulos LV, McGurk S, et al. One thousand minimally invasive mitral valve operations: early outcomes, late outcomes, and echocardiographic follow-up. J Thorac Cardiovasc Surg 2013;145:1199-206.
26. Petracek MR, Leacche M, Solenkova N, Umakanthan R, Ahmad RM, Ball SK, Hoff SJ, Absi TS, Balaguer JM, Byrne JG. Minimally invasive mitral valve surgery expands the surgical options for high-risks patients. Ann Surg. 2011 Oct;254(4):606-11.
27. Cohn LH, Adams DH, Couper GS, Bichell DP, Rosborough DM, Sears SP, Aranki SF. Minimally invasive cardiac valve surgery improves patient satisfaction while reducing costs of cardiac valve replacement and repair. Ann Surg. 1997 Oct;226(4):421-6
28. Iribarne A, Easterwood R, Russo MJ, Wang YC, Yang J, Hong KN, Smith CR, Argenziano M. A minimally invasive approach is more cost-effective than a traditional sternotomy approach for mitral valve surgery. J Thorac Cardiovasc Surg. 2011 Dec;142(6):1507-14.
29. Seeburger J, Borger MA, Falk V, Kuntze T, Czesla M, Walther T, Doll N, Mohr FW. Minimal invasive mitral valve repair for mitral regurgitation: results of 1339 consecutive patients. Eur J Cardiothorac Surg. 2008 Oct;34(4):760-5
30. Yoo JS, Kim JB, Jung SH, Choo SJ, Chung CH, Lee JW. Echocardiographic assessment of mitral durability in the late period following mitral valve repair: minithoracotomy versus conventional sternotomy. J Thorac Cardiovasc Surg. 2014 May;147(5):1547-52.
31. Keogh B, Kinsman R Fifth National Adult Cardiac Surgical Database Report Improving outcomes for patients. The Society of Cardiothoracic Surgeons of Great Britain and Ireland 2003
32. Bridgewater B, Keogh B Kinsman R, Walton P Sixth National Adult Cardiac Surgical Database Report Improving outcomes for patients. The Society of Cardiothoracic Surgeons of Great Britain and Ireland 2008
33. SCTS Blue Book Online - Cardiac Surgery Audit Data bluebook.scts.org The Society for Cardiothoracic Surgery (SCTS) Blue Book
34. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Iung B, Lancellotti P, Pierard L, Price S, Schäfers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M. Guidelines on the management of valvular heart disease (version 2012). Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC); European Association for Cardio-Thoracic Surgery (EACTS), Eur Heart J. 2012 Oct;33(19):2451-96.
35. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM 3rd, Thomas JD, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Creager MA, Curtis LH, DeMets D, Guyton RA, Hochman JS,

Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Stevenson WG, Yancy CW; 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on PracticeGuidelines. American College of Cardiology; American College of Cardiology/American Heart Association; American Heart Association. J Thorac Cardiovasc Surg. 2014 Jul;148(1)

36. Enriquez-Sarano M, Akins CW, Vahanian A. Mitral regurgitation. Lancet 2009; 373:1382 – 1394. 119
37. Haan CK, Cabral CI, Conetta DA, Coombs LP, Edwards FH. Selecting patients with mitral regurgitation and left ventricular dysfunction for isolated mitral valve surgery. Ann Thorac Surg 2004;78:820 –825.
38. Enriquez-Sarano M, Tajik AJ, Schaff HV, Orszulak TA, McGoon MD, Bailey KR, Frye RL. Echocardiographic prediction of left ventricular function after correction of mitral regurgitation: results and clinical implications. J Am Coll Cardiol 1994;24:1536 –1543.
39. Enriquez-Sarano M, Avierinos JF, Messika-Zeitoun D, Detaint D, Capps M, Nkomo V, Scott C, Schaff HV, Tajik AJ. Quantitative determinants of the outcome of asymptomatic mitral regurgitation. N Engl J Med 2005;352:875 – 883.
40. Barbieri A, Bursi F, Grigioni F, Tribouilloy C, Avierinos JF, Michelina HI, Rusinaru D, Szymansky C, Russo A, Suri R, Bacchi-Regiani ML, Branzi A, Modena MG, Enriquez-Sarano M; Mitral Regurgitation International DAtabase (MIDA) Investigators. Prognostic and therapeutic implications of pulmonary hypertension complicating degenerative mitral regurgitation due to flail leaflet: a multicenter long-term international study. Eur Heart J 2011;32:751–759.
41. Tribouilloy C, Grigioni F, Avierinos JF, Barbieri A, Rusinaru D, Szymanski C, Ferlito M, Tafanelli L, Bursi F, Trojette F, Branzi A, Habib G, Modena MG, Enriquez-Sarano M; MIDA Investigators. Survival implication of left ventricular end-systolic diameter in mitral regurgitation due to flail leaflets: a long-term follow-up multicenter study. J Am Coll Cardiol 2009;54:1961 –1968.
42. Le Tourneau T, Messika-Zeitoun D, Russo A, Detaint D, Topilsky Y, Mahoney DW, Suri R, Enriquez-Sarano M. Impact of left atrial volume on clinical outcome in organic mitral regurgitation. J Am Coll Cardiol 2010;56:570 –578.
43. Grigioni F, Tribouilloy C, Avierinos JF, Barbieri A, Ferlito M, Trojette F, Tafanelli L, Branzi A, Szymanski C, Habib G, Modena MG, Enriquez-Sarano M. Outcomes in mitral regurgitation to flail leaflets: a multicenter European study. JACC: Cardiovascular Imaging 2008;1:133 – 141. 134.
44. Alhalawani AM, Towler MR. A review of sternal closure techniques. J Biomater Appl. 2013 Nov;28(4):483-97

45. Brocki BC, Thorup CB, Andreasen JJ. Precautions related to midline sternotomy in cardiac surgery: a review of mechanical stress factors leading to sternal complications. Eur J Cardiovasc Nurs. 2010 Jun;9(2):77-84.
46. Cahalin LP, Lapier TK, Shaw DK. Sternal Precautions: Is It Time for Change? Precautions versus Restrictions - A Review of Literature and Recommendations for Revision. Cardiopulm Phys Ther J. 2011 Mar;22(1):5-15
47. Minimally Invasive Versus Open Mitral Valve Surgery: A Consensus Statement of the International Society of Minimally Invasive Coronary Surgery (ISMICS) 2010 Innovations: Technology & Techniques in Cardiothoracic & Vascular Surgery: March/April 2011 - Volume 6 - Issue 2 - pp 66-76 doi: 10.1097/IMI.0b013e318216be5c
48. von Oppell UO, Mohr FW. Chordal replacement for both minimally invasive and conventional mitral valve surgery using premeasured Gore-Tex loops. Ann Thorac Surg. 2000;70(6):2166-8.
49. Chan EY, Lumbao DM, Iribarne A, Easterwood R, Yang JY, Cheema FH, Smith CR, Argenziano M. Evolution of cannulation techniques for minimally invasive cardiac surgery: a 10-year journey. Innovations (Phila). 2012;7(1):9-14.
50. Jeffrey S Barkun, Jeffrey K Aronson, Liane S Feldman, Guy J Maddern, Steven M Strasberg, for the Balliol Collaboration. Surgical Innovation and Evaluation 1 Evaluation and stages of surgical innovations. Lancet 2009; 374: 1089–96
51. Patrick L Ergina, Jonathan A Cook, Jane M Blazeby, Isabelle Boutron, Pierre-Alain Clavien, Barnaby C Reeves, Christoph M Seiler, for the Balliol Collaboration. Surgical Innovation and Evaluation 2 Challenges in evaluating surgical innovation. Lancet 2009; 374: 1097–104
52. Peter McCulloch, Douglas G Altman, W Bruce Campbell, David R Flum, Paul Glasziou, John C Marshall, Jon Nicholl, for the Balliol Collaboration Surgical Innovation and Evaluation 3 No surgical innovation without evaluation: the IDEAL recommendations. Lancet 2009; 374: 1105–12
53. DAMOCLES Study Group. A proposed charter for clinical trial data monitoring committees: helping them to do their job well. Lancet 2005; 365: 711–22
54. The Data Protection Act. https://www.gov.uk/data-protection/the-data-protection-act
55. Marcus-André Deutsch, Markus Krane, Lisa Schneider, Michael Wottke, Matthias Kornek, Yacine Elhmidi, Catalin Constantin Badiu, Sabine Bleiziffer, Bernhard Voss, Rüdiger Lange. Health-Related Quality of Life and Functional Outcome in Cardiac Surgical Patients Aged 80 Years and Older: A Prospective Single Center Study. Journal of Cardiac Surgery. Volume 29, Issue 1, pages 14–21, January 2014
56. J Juenger, D Schellberg, S Kraemer, A Haunstetter, C Zugck, W Herzog, and M Haass. Health related quality of life in patients with congestive heart failure: comparison with other chronic diseases and relation to functional variables. Heart. 2002 Mar; 87(3): 235–241

57. Brinkman WT, Hoffman W, Dewey TM, et al. Aortic valve replacement surgery: comparison of outcomes in matched sternotomy and PORT ACCESS groups. Ann Thorac Surg 2010;90:131–5.

58. Dion Morton and Colin D Bicknell. Should surgical training include involvement in a clinical trial? BMJ 2015;350:h2045

59. Holzhey DM, Seeburger J, Misfeld M, Borger MA, Mohr FW. Learning minimally invasive mitral valve surgery: a cumulative sum sequential probability analysis of 3895 operations from a single high-volume center. Circulation. 2013 Jul 30;128(5):483-91

60. Misfeld M, Borger M, Byrne JG, Chitwood WR, Cohn L, Galloway A, Garbade J, Glauber M, Greco E, Hargrove CW, Holzhey DM, Krakor R, Loulmet D, Mishra Y, Modi P, Murphy D, Nifong LW, Okamoto K, Seeburger J, Tian DH, Vollroth M, Yan TD. Cross-sectional survey on minimally invasive mitral valve surgery. Ann Cardiothorac Surg. 2013 Nov;2(6):733-8.

61. Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Ba¨rwolf C, Levang OW, Tornos P, Vanoverschelde JL, Vermeer F, Boersma E, Ravaud P, Vahanian A. A prospective survey of patients with valvular heart disease in Europe: the Euro Heart Survey on Valvular Heart Disease. Eur Heart J 2003;24:1231 –1243

62. McNeely CA, Vassileva CM Long-term outcomes of mitral valve repair versus replacement for degenerative disease: a systematic review. Curr Cardiol Rev. 2015;11(2):157-62.

63. Gaur P, Kaneko T, McGurk S, Rawn JD, Maloney A, Cohn LH. Mitral valve repair versus replacement in the elderly: short-term and long-term outcomes. J Thorac Cardiovasc Surg. 2014 Oct;148(4):1400-6.

64. Coutinho GF, Correia PM, Antunes MJ Concomitant aortic and mitral surgery: to replace or repair the mitral valve? J Thorac Cardiovasc Surg. 2014 Oct;148(4):1386-1392

65. Candan O, Ozdemir N, Aung SM, Bakal RB, Gecmen C, Akpinar SH, Cem D, Onur O, Kaymaz C. Effect of mitral valve repair versus replacement on left ventricular rotational deformation: a study with speckle tracking echocardiography. J Heart Valve Dis. 2013 Sep;22(5):651-9

66. Markar SR, Sadat U, Edmonds L, Nair SK. Mitral valve repair versus replacement in the elderly population. J Heart Valve Dis. 2011 May;20(3):265-71. Review

67. Chikwe J, Goldstone AB, Passage J, Anyanwu AC, Seeburger J, Castillo JG, Filsoufi F, Mohr FW, Adams DH. A propensity score-adjusted retrospective comparison of early and mid-term results of mitral valverepair versus replacement in octogenarians. Eur Heart J. 2011 Mar;32(5):618-26.

68. Cheng W, Cameron DE, Warden KE, Fouger JD, Gott VL. Biomechanical study of sternal closure techniques. Ann Thorac Surg 1993;55:737–740.

69. Del Campo C, Heimbecker RO. Repair of refractory sternal dehiscence: a new technique. J Thorac Cardiovasc Surg 1982;83:937–938.

70. Culliford AT, Cunningham JN, Zeff RH, Isom OW, Teiko P, Spencer FC. Sternal and costochondral infections following open heart surgery: a review of 2,594 cases. J Thorac Cardiovasc Surg 1976;72:714–726.
71. Zacharias A, Habib RH. Factors predisposing to median sternotomy complications: deep vs superficial infections. Chest 1996;110:1173–1180.
72. The Parisian Mediastinitis Study Group. Risk factors for deep sterna wound infection after sternotomy: a prospective, multicenter study. J Thorac Cardiovasc Surg 1996;111:1200–1207.
73. Trastulli S, Cirocchi R, Desiderio J, Guarino S, Santoro A, Parisi A, Noya G, Boselli C. Systematic review and meta-analysis of randomized clinical trials comparing single-incision versusconventional laparoscopic cholecystectomy. Br J Surg. 2013 Jan;100(2):191-208.
74. Di B, Li Y, Wei K, Xiao X, Shi J, Zhang Y, Yang X, Gao P, Zhang K, Yuan Y, Zhang D, Wei X, Liu S, Wang J, Wang X, Zhang Y, Cai H Laparoscopic versus open surgery for colon cancer: a meta-analysis of 5-year follow-up outcomes.. Surg Oncol. 2013 Sep;22(3):e39-43
75. Nerland US, Jakola AS, Solheim O, Weber C, Rao V, Lønne G, Solberg TK, Salvesen Ø, Carlsen SM, Nygaard ØP, Gulati S. Minimally invasive decompression versus open laminectomy for central stenosis of the lumbar spine: pragmatic comparative effectiveness study. BMJ. 2015 Apr 1;350:h1603.
76. Rabindranauth P, Burns JG, Vessey TT, Mathiason MA, Kallies KJ, Paramesh V. Minimally invasive coronary artery bypass grafting is associated with improved clinical outcomes. Innovations (Phila). 2014 Nov-Dec;9(6):421-6
77. Burdett CL, Lage IB, Goodwin AT, White RW, Khan KJ, Owens WA, Kendall SW, Ferguson JI, Dunning J, Akowuah EF Manubrium-limited sternotomy decreases blood loss after aortic valve replacement surgery. Interact Cardiovasc Thorac Surg. 2014 Oct;19(4):605-10.
78. Shrestha M, Krueger H, Umminger J, Koigeldiyev N, Beckmann E, Haverich A, Martens A. Minimally invasive valve sparing aortic root replacement (David procedure) is safe. Ann Cardiothorac Surg. 2015 Mar;4(2):148-53
79. Rojas SV, Avsar M, Hanke JS, Khalpey Z, Maltais S, Haverich A, Schmitto JD. Minimally Invasive Ventricular Assist Device Surgery. Artif Organs. 2015 Mar 4
80. Carpentier A, Loulmet D, Carpentier A, et al. Open heart operation under videosurgery and minithoracotomy. First case (mitral valvuloplasty) operated with success. C R Acad Sci III 1996;319:219-23
81. Mohr FW, Falk V, Diegeler A, Walther T, Van Son JA, Autschbach R.Minimally invasive port-access mitral valve surgery. J Thorac Cardiovasc Surg. 1998 Mar;115(3):567-74;

82. Falk V, Walther T, Diegeler A, Wendler R, Autschbach R, Van Son JA, Siegel LC, Pompilli MF, Mohr FW. Echocardiographic monitoring of minimally invasive mitral valve surgery using an endoaortic clamp. J Heart Valve Dis. 1996 Nov;5(6):630-7

83. Chitwood WR Jr, Wixon CL, Elbeery JR, Moran JF, Chapman WH, Lust RM. Video-assisted minimally invasive mitral valve surgery. J Thorac Cardiovasc Surg. 1997 Nov;114(5):773-80; discussion 780-2

84. Krapf C, Wohlrab P, Häußinger S, Schachner T, Hangler H, Grimm M, Müller L, Bonatti J, Bonaros N.Remote access perfusion for minimally invasive cardiac surgery: to clamp or to inflate? Eur J Cardiothorac Surg. 2013 Nov;44(5):898-90

85. Mazine A, Pellerin M, Lebon JS, Dionne PO, Jeanmart H, Bouchard D. Minimally invasive mitral valve surgery: influence of aortic clamping technique on early outcomes. Ann Thorac Surg. 2013 Dec;96(6):2116-22.

86. Holzhey DM, Shi W, Borger MA, Seeburger J, Garbade J, Pfannmüller B, Mohr FW. Minimally invasive versus sternotomy approach for mitral valve surgery in patients greater than 70 years old: a propensity-matched comparison. Ann Thorac Surg. 2011 Feb;91(2):401-5.

87. Modi P, Rodriguez E, Hargrove WC 3rd, Hassan A, Szeto WY, Chitwood Minimally invasive video-assisted mitral valve surgery: a 12-year, 2-center experience in 1178 patients. WR Jr. J Thorac Cardiovasc Surg. 2009 Jun;137(6):1481-7

88. Benedetto U, Raja SG, Soliman RF, Albanese A, Jothidasan A, Ilsley CD, Amrani M; Harefield Cardiac Outcomes Research Group. Minimally invasive direct coronary artery bypass improves late survival compared with drug-eluting stents in isolated proximal left anterior descending artery disease: A 10-year follow-up, single-center, propensity score analysis. J Thorac Cardiovasc Surg. 2014 Jan 15. pii: S0022-5223(14)00039-7.

89. Merk DR, Lehmann S, Holzhey DM, Dohmen P, Candolfi P, Misfeld M, Mohr FW, Borger MA. Minimal invasive aortic valve replacement surgery is associated with improved survival: a propensity-matched comparison. Eur J Cardiothorac Surg. 2014 Mar 5. [Epub ahead of print

90. Gummert JF, Funkat AK, Beckmann A, Ernst M, Hekmat K, Beyersdorf F, Schiller W Cardiac surgery in Germany during 2010: A report on behalf of the German society for thoracic and cardiovascular surgery. Thoracic Cardiovascular Surg. 2011;59:259-267

91. Gammie JS, Zhao Y, Peterson ED, O'Brien SM, Rankin JS, Griffith BP. J. Maxwell Chamberlain Memorial Paper for adult cardiac surgery. Less-invasive mitral valve operations: trends and outcomes from the Society of Thoracic Surgeons Adult Cardiac Surgery Database. Ann Thoracic Surgery 2010 90(5): 1401-8

92. Ray S, Chambers J, Gohlke-Baerwolf C, Bridgewater B Mitral valve repair for severe mitral regurgitation: the way forward?. Eur Heart J. 2006 Dec;27(24):2925-8

93. Anyanwu AC, Bridgewater B, Adams DH. The lottery of mitral valve repair surgery. Heart. 2010 Dec;96(24):1964-7

94. EuroSCORE II. http://www.euroscore.org/

95. Patrizio Lancellotti, Christophe Tribouilloy, Andreas Hagendorff, Bogdan A. Popescu, Thor Edvardsen, Luc A. Pierard, Luigi Badano, and Jose L. Zamorano, On behalf of the Scientific Document Committee of the European Association of Cardiovascular Imaging: Thor Edvardsen, Oliver Bruder, Bernard Cosyns, Erwan Donal, Raluca Dulgheru, Maurizio Galderisi, Patrizio Lancellotti, Denisa Muraru, Koen Nieman, Rosa Sicari, Document reviewers: Erwan Donal, Kristina Haugaa, Giovanni La Canna, Julien Magne, Edyta Plonska. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. European Heart Journal – Cardiovascular Imaging (2013) 14, 611–644 doi:10.1093/ehjci/jet105

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UK Mini Mitral is funded by the National Institute for Health Research HTA Programme (project reference 14/192/110)