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Title

Mini-sternotomy versus conventional sternotomy for aortic valve replacement: a randomised controlled trial

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Abstract

Objective

To compare clinical and health economic outcomes after manubrium-limited mini-sternotomy (intervention) and conventional median sternotomy (usual care)

Design

A single blind, randomised controlled trial.

Setting

Single centre UK National Health Service tertiary hospital

Participants

Adult patients undergoing aortic valve replacement surgery

Interventions

Intervention was manubrium-limited mini-sternotomy performed using a 5-7cm midline incision. Usual care was median sternotomy performed using a midline incision from the sternal notch to the xiphisternum.

Primary and secondary outcome measures

The primary outcome was the proportion of patients who received a red cell transfusion post-operatively and within 7 days of index surgery. Secondary outcomes included proportion of patients receiving a non-red cell blood component transfusion and number of units transfused within 7 days and during index hospital stay, quality of life and cost effectiveness analyses.

Results

270 patients were randomised, received surgery and contributed to the intention to treat analysis. No difference between mini and conventional sternotomy in red-cell transfusion within 7 days was found; 23/135 patients in each arm received a transfusion, odds ratio 1·0 (95% CI: 0·5, 2·0) and risk

difference 0·0 (95% CI: -0·1, 0·1). Mini-sternotomy reduced chest drain losses (mean 181·6ml (SD 138·7) vs conventional, mean 306·9ml (SD 348·6)); this did not reduce red-cell transfusions. Mean valve size and post-operative valve function were comparable between mini-sternotomy and conventional groups; 23mm vs 24mm, and 6/134 moderate or severe aortic regurgitation vs 3/130, respectively. Mini-sternotomy resulted in longer bypass (82·7 minutes (SD 23·5) vs 59·6 minutes (SD 15·1)) and cross clamp times (64·1 minutes (SD 17·1) vs 46·3 minutes (SD 10·7)). Conventional sternotomy was more cost-effective with only a 5·8% probability of mini-sternotomy being cost-effective at a willingness to pay of £20,000/QALY.

Conclusions

AVR via mini-sternotomy did not reduce red blood cell transfusion within 7 days following surgery when compared to conventional sternotomy.

Clinical Trials Registry: ISRCTN29567910

Key word: minimally invasive, aortic valve

ARTICLE SUMMARY

1. Large proportion of eligible patients recruited, and all patient randomised contributed to the primary outcome
2. Clear protocols for transfusion of blood and blood products with high adherence throughout the trial
3. Patients were blinded to group allocation until two days following index surgery, reducing the likelihood of bias.
4. First randomised trial to perform detailed health economic evaluation of minimally invasive versus conventional sternotomy
5. The trial was undertaken by three experienced minimally invasive surgeons who were expert at both techniques.

Objectives

Aortic valve replacement (AVR) for severe symptomatic valvular disease is one of the most common cardiac surgical procedures performed worldwide. Outcomes are generally excellent with in-hospital observed mortality in the UK of 1·5% for first time elective procedures.[1]

These results are not observed in all patients; in high risk groups, conventional surgery risks perioperative organ injury and prolonged recovery, with death in up to 31% of patients within 1 year.[2] Minimally invasive surgery combines the durability of surgical repair with reductions in surgical trauma that should reduce perioperative morbidity. Observational analyses demonstrating reductions in morbidity and resource use[3,4] may be confounded by multiple sources of bias and are at odds with limited evidence from RCTs that have not shown improved outcomes.[5] This uncertainty is reflected by variations in uptake internationally[6,7].[8]

The move towards minimally invasive surgery is also driven by patient perceptions of pain reduction and rapid recovery. However, minimally invasive cardiac surgery is not without risks; limiting access to the heart can result in technically sub-optimal surgery, including concern about the size of the prosthesis that can be inserted, and paravalvular leak rates.

This trial evaluated Manubrium-limited Mini-sternotomy versus Conventional Sternotomy for Aortic Valve Replacement (MAVRIC). We hypothesised that mini-sternotomy would reduce red cell transfusion rates, a contemporary marker of surgical trauma and indicator of adverse outcomes;[9] this has been contested,[10] though the evidence is not conclusive.[11] An embedded cost effectiveness analysis evaluated whether the intervention was cost effective in a UK National Health Service (NHS) setting.

Patients and Methods

Trial Design

MAVRIC was a single centre, single-blind, RCT comparing AVR via manubrium-limited mini-sternotomy group (intervention) and AVR via conventional sternotomy group (usual care). A NHS

Research Ethics Committee approved the trial, which was conducted in accordance with the principles of the International Conference on Harmonisation of Good Clinical Practice.[12] South Tees Hospitals NHS Foundation Trust was the Sponsor and recruiting centre.

Patient Public Involvement

In designing the study, we asked patients their view on what factors may affect whether they took part in the study. This was done in an outpatient setting and via a postal questionnaire. They felt expertise was important. Most patients felt that although the cosmetic benefit of the minimally invasive approach was appealing, they expected some clinical benefit form minimally invasive surgery as well. Importantly most patients said they would accept being blind to the type of surgery they had received for 48 hours after the procedure.

Participants

Patients were eligible if they were aged 18 years or over; required first-time, non-emergency, isolated AVR surgery; and were willing to provide written informed consent. Full details of the eligibility criteria are in the **Supplementary Material**.

Randomisation

Eligible patients were randomised by members of the research team using a 24-hour, central, secure, web-based randomisation system with concealed allocation, managed by the Clinical Trials Unit; randomisation was in a 1:1 ratio between mini and conventional sternotomy and stratified by baseline logistic EuroSCORE and pre-operative Hemoglobin (Hb).

Interventions

Manubrium-limited mini-sternotomy was performed using a 5-7cm midline skin incision dividing the manubrium from the sternal notch to 1cm below the manubrium-sternal junction. Cardiopulmonary bypass was established with an ascending aortic cannula and percutaneous femoral venous cannulation. Conventional median sternotomy was performed using a midline incision from the

sternal notch to the xiphisternum. Key aspects of anaesthesia were standardised, and are detailed in the protocol.[13]

Blinding

All patients were blinded to type of sternotomy received until after their day 2 Quality of Life and pain assessments. All patients had trial-specific opaque dressings applied to their sternal wound, and groin before leaving theatre.

Transfusion Protocol

The post-operative period, and trial protocol in relation to red cell and non-red cell transfusion, began on admission to the Cardiothoracic Intensive Care Unit (CICU); it specified that patient's should receive a red cell transfusion if their Hb dropped below 80 g/L; or were bleeding by 400ml/h or more, or were bleeding 100ml/h or more for 4 or more hours with a Hb equal to or greater than 80g/L; or had blood loss with haemodynamic instability irrespective of thromboelastography (TEG) and/or clotting profile results. One unit of red cells was transfused and Hb level checked before transfusing another unit.

Participants received a non-red cell transfusion if both of the following criteria were met: bleeding defined by 400ml/h or more, or blood loss of 100ml/h or more for 4 hours or more; TEG or coagulation guided transfusion indicated.

Outcomes

All outomes were measured from index surgery.

Primary Outcome

The primary outcome was the proportion of patients who received a red cell transfusion post-operatively and within 7 days of index surgery.

Secondary Outcomes:

- proportion of patients receiving a red cell transfusion and number of units transfused within 7 days and during index hospital stay;

- proportion of patients receiving a non-red cell blood component transfusion and number of units transfused within 7 days and during index hospital stay;
- volume in chest drains at 6 and 12 hours, and drain removal;
- degree of aortic regurgitation using echocardiogram within 6 weeks;
- re-operation rates;
- conversion to conventional AVR during surgery;
- changes in lung function at 4 days and 6 weeks;
- Quality of life EuroQol (EQ-5D-3L, EQ-VAS) at 2 days, 6 and 12 weeks;
- time patients are deemed 'fit for discharge';
- health care utilisation to 12 weeks;
- cost and cost effectiveness analyses;
- adverse events to 12 weeks.

Statistical Analysis

Audit data had indicated 30% of patients undergoing AVR via conventional sternotomy (15 of 50 patients) received a red cell transfusion compared with 13% of patients (8 of 60 patients) undergoing AVR via mini-sternotomy. Using Fisher's Exact test, 90% power, 5% alpha, we estimated that 260 patients would be required to detect a 17% reduction in the proportion of patients requiring a red cell transfusion (13% compared with 30%), using a two-sided test. Allowing for loss to follow up, the sample size was increased to 270.

The primary analysis was based on intention-to-treat principles, in accordance with a pre-specified statistical analysis plan.

The primary efficacy analysis was based on a logistic regression model with only group (minimally invasive and conventional) and stratifying factors (baseline logistic EuroSCORE and Hb) as the

predictors. Odds ratios and their associated 95% confidence interval are reported in the primary analysis. Sensitivity analysis using alternating logistic regression was performed for the primary endpoint to sensitise for surgeon effects; the odds of receiving a red cell transfusion for two patients treated by the same surgeon was compared to two patients treated by different surgeons.

All analyses of secondary continuous efficacy endpoints at single time points were based on linear models where, if appropriate, a log normal model was fitted to sensitise the linearity assumption. Longitudinal analysis was performed for all endpoints with repeated data over time to investigate changes in trends over the trial period. The trial period was defined as baseline, up to 7 days (post-operative period), 6 week follow-up and 12 week follow-up. All analyses of binary endpoints at a single time point were based on logistic regression. Generalised estimating equation was used to analyse repeated binary data per patient to account for intra-patient correlation.

Further exploratory analysis was conducted to investigate the association between the treatment group and other clinical factors. All analyses were performed using R 3·3·3 (The R Foundation) and SAS 9·4 (SAS Institute Inc).

Economic Evaluation

A prospective economic evaluation applying a NHS perspective, following National Institute for Health and Care Excellence (NICE) reference case guidance,[14] was employed. Health care utilisation was captured up to three months following discharge from index surgery. Resource use was valued in 2016 pounds sterling using national sources,[15,16] and where necessary, local micro-costing (£1=$1·50). Resources included surgery, transfusions, length of hospital stay (by level of care), complications and further surgery, and community care following discharge.

Mechanisms of missingness within the data were explored and multiple imputation methods were applied to impute missing data and minimise bias, using chained equations and predictive mean matching. Imputation sets were analysed within a bivariate analysis of costs and QALYS, to generate incremental within-trial cost per QALY estimates and credible intervals. Findings were presented on

the ICER plane and with Cost-Effectiveness Acceptability Curves, using the net monetary benefit approach.

Results

Trial Population

MAVRIC recruited to time and target; 313 patients were considered for the trial; 274 patients consented between 20th March 2014 and 25th July 2016. The analysis population was 270 eligible patients; 135 allocated to the AVR via mini-sternotomy group and 135 allocated to the AVR via conventional sternotomy group (**Figure 1**).

All 270 patients underwent surgery. Sixteen patients required cross-over from minimally-invasive to a conventional sternotomy due to anaesthetic emergency (n=2), difficulties due to vascular access (n=9), and intra-operative complications (n=5); further details and the number of operations performed by surgeon are in the Supplementary Material.

Baseline characteristics were similar between groups (**Table 1**).

Primary Outcome

There was no difference between groups in relation to the primary outcome (**Table 2**). The proportion of patients receiving red cell transfusion transfusions was 23 of 135 in both groups, Odds ratio 1·0 (95% CI 0·5, 2·0; p=0·9052) and risk difference of 0·0 (95% CI -0·1, 0·1; p=0·9999).

Secondary Outcomes

Red cell and non-red cell transfusion

There was no significant difference between groups with respect to any red cell transfusion at discharge (**Table 2**). There was no difference between groups in Hb from baseline to 4 days following index surgery (**Supplementary Material**). There was a statistically significant difference in the proportion of patients receiving any non-red cell transfusion within 7 days of surgery; mini 6/135 versus conventional 18/135, Odds ratio: 0·3 (95% CI 0·1, 0·8; p=0·0137) (**Table 3**).

Cross clamp time and cardiopulmonary bypass time

Mini-sternotomy resulted in longer Cardio Pulmonary Bypass times; mini group 82·7 minutes (SD 23·5), conventional 59·6 minutes (SD 15·1). Aortic cross clamp times were also longer; mini group 64·1 minutes (SD 17·1), conventional 46·3 minutes (SD 10·7) (**Table 4**).

Chest drain losses

Mini-sternotomy resulted in a 40·8% reduction in chest drain losses at 12 hours, the mini group mean was 181·6ml (SD 138·7), conventional group mean was 306·9ml (SD 348·6); the mean difference was -127·7ml (95% CI -191·7, -63·8, p=0.0001). At drain removal mean difference was -145·3ml (95% CI -218·1, -72·3; p=0.0001) (**Table 4**).

Ventilation time

Ventilation time between the groups was similar; 9·6 hours (SD 5·6) in the mini group and 9·8 hours (SD 6·9) in the conventional (**Table 4**).

Intensive care unit length of stay

There was no difference in intensive care unit length of stay between groups (**Supplementary Material**).

Post-operative pain

There was no difference in pain scores between groups (**Supplementary Material**).

Lung function

There was no difference between groups in lung function at baseline. At 4 days post-surgery, mean Forced Expiratory Volume 1 (FEV1) 1123mls (SD 433) and Forced Vital Capacity, FVC 1479mls (SD 583) were significantly reduced in the mini group, compared to the conventional; FEV1 1321 (SD 524), FVC 1698 (SD 707). Mean differences for FEV1 and FVC were statistically significant at 4 days post-surgery; -171mls (95% CI -265, -77; p=0·0004) and -130mls (95% CI -269, 0; p=0·0498)

respectively, after adjusting for baseline FEV1, FVC, and randomisation factors (**Supplementary Material**).

Hospital length of stay

The mean time to patients being fit for hospital discharge following index surgery was similar between groups. The mean post-operative hospital length of stay was 7·4 (SD 7·5, range 3-79) in the mini group, and 6·3 days (SD 3·2, range 3-31) in the conventional (**Supplementary Material**).

Post-operative valve function

The distribution of valve types and valve sizes were similar; mean valve size inserted was 23mm in the mini group and 24mm in the conventional (**Table 4**). Over 70% of patients in each group received a tissue valve, over 25% received a mechanical valve and 2-3% received a sutureless tissue valve. Post operative transthoracic echo showed a similar decrease in mean aortic valve gradient in both groups to 16mmHg; peak gradient decreased to 30mmHg in both groups (**Table 4**). 6/134 patients had moderate or severe aortic regurgitation in the mini group compared to 3/130 in the conventional (**Table 4**).

Adverse events

Adverse events in each group were broadly similar and within acceptable clinical limits. By 12 weeks, 4/135 patients in the mini-sternotomy group and 1/135 in the conventional group had suffered a stroke (defined as a persistent neurological deficit). Atrial arrhythmias were identified in 61/135 patients in the mini group and 51/135 in the conventional. By 12 weeks, 11/135 patients in the mini group and 3/135 patients in the conventional had a sternal wound infection (**Supplementary Material**).

Quality of Life, Costs and Cost-Effectiveness

Costs during the index admission were significantly greater for the mini group (mini-conventional: mean difference £1140; 95% CI 303, 1977), primarily reflecting the additional cost of theatre time (**Supplementary Material**). Overall costs were not significantly different (mini-conventional: mean

difference £746; 95% CI -245, 1737). There was no significant difference in quality of life between groups up to 12 weeks (mini-conventional: mean difference area under curve -0.009 QALYs; 95% CI 0.020, 0.002). Although differences in costs and quality-of-life were not individually significant, the bivariate cost-QALY distribution (combining these two) suggests conventional surgery might be more cost-effective (**Figure 2**). In the base-case model, mini was dominated by conventional surgery (due to greater cost and less benefit), with only a 5.8% probability of being cost-effective at a willingness to pay of £20,000/QALY (**Table 5**).

Sensitivity and Subgroup Analyses

There was no significant surgeon effect; the odds of receiving a red cell transfusion for two patients treated by the same surgeon compared to two patients treated by different surgeons was 1·2 (95% CI 0·9, 1·6; p=0·1379).

Protocol deviations in respect of cell tranfusions did not affect the results of the primary analysis; excluding these patients produced the same results as those from the intention-to-treat analysis.

Discussion

Main findings

Mini-sternotomy was not superior to conventional sternotomy with respect to red cell transfusion requirements within 7 days of surgery. Analysis of secondary endpoints showed a statistically significant difference in transfusion volumes of non-red cell blood components. Aortic valve size and post-operative function were comparable in the 2 groups. Mini-sternotomy resulted in a relative reduction in chest drain losses however, higher blood loss in the conventional group did not translate into red cell transfusions. Mini patients had substantially longer bypass and cross clamp times and worse lung function at 4 days post-surgery. Lung function at twelve weeks, and adverse event rates were otherwise not different between groups. Conventional sternotomy was found to be more cost-effective. MAVRIC findings contradict those from other trials.[17,18]

Strengths and limitations

This is the largest single trial to have compared minimally invasive sternotomy to conventional median sternotomy for AVR. A recent Cochrane review identified 511 patients from 7 previous RCTs.[5] In MAVRIC, the mini-sternotomy technique divided only the manubrium and is therefore less invasive than other minimally invasive techniques. The trial was undertaken by three experienced minimally invasive surgeons who were expert at both techniques. Patients were blinded to group allocation until two days following index surgery, reducing the likelihood of bias. The trial recruited a significant proportion of eligible patients; 274/313 (86%), with few requiring conversion to conventional sternotomy, increasing the likelihood that the trial findings are generalisable. A further strength was the detailed health economic evaluation; this has not been performed previously.

The trial had some limitations, including the single centre design. This will tend to have biased treatment effect estimates away from the null, which is at odds with our observed effect. There were no significant levels of protocol non-adherence, with no effect on the main trial finding. The event rate for the primary outcome, was much lower than expected at 17%; nationally red cell transfusion rates following valve surgery are 46·4%.[19] In our pre-trial audit, 30% of mini-sternotomy patients received a red cell transfusion. We attribute the observed transfusion rate in MAVRIC to the restrictive red cell transfusion threshold applied; this followed evidence at the time of trial design. The consultant (expert) led nature of the trial interventions is also likely to have reduced the need for transfusions post-operatively and to have biased trial results towards the null.

Clinical importance

MAVRIC contributes important evidence to the minimally invasive AVR evidence base, summarised in a Cochrane review.[5] MAVRIC demonstrated longer cross-clamp and bypass times with the manubrium-limited mini-sternotomy, attributed to known differences between the interventions. Minimally-invasive techniques in MAVRIC required a number of surgical steps to be performed with the aortic clamp in place (drain insertion and pacing wire insertion for example), meaning cross-clamp and bypass were longer. This is not an absolute requirement in other minimally invasive

approaches; for example, where the incision is extended into the body of the sternum, or where rapid deployment valves are used, there are no differences in cross clamp and bypass times.[5] The size of MAVRIC and event rate prevents formal comparison of adverse events between the groups, of note is the difference in stroke rate; this would benefit from exploration in a future trial.

The cost-effectiveness plane indicates that conventional surgery is less costly and more beneficial than minimally-invasive surgery; contact with healthcare professionals was greater in the mini group, although there was no clear pattern of use. Wide confidence intervals mean that differences are imprecise. MAVRIC does not support the use of funds to expand AVR via manubrium-limited mini-sternotomy practice.

MAVRIC, the world's largest RCT at low risk of bias, found no additional clinical benefit of minimally invasive AVR. Results are in agreement with the findings of a Cochrane review of trials that have evaluated mini-sternotomy AVR.[5] This information should be disseminated to patients, clinicians and commissioners to inform decisions about AVR surgery including commissioning.

Role of funding source

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The views and opinions expressed are those of the authors and do not necessarily reflect those of the National Institute for Health Research (NIHR) Research for Patient Benefit Programme, the National Health Service or the Department of Health and Social Care.

Declaration of Interests

Helen C Hancock (HCH): None

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Authors contributions

EFA, HCH, RHM, and JMM and GJM designed the trial, and sought funding. EFA, ATG and WAO recruited patients to the trial and performed surgery. ASK conducted the statistical analysis and JMM conducted the health economic analysis. All authors contributed to the final manuscript.

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Data Sharing Statement

Anonymised data from this study may be available to the scientific community subject to appropriate ethical approval. Requests for data should be directed to the senior author.

Table 1 – Baseline Characteristics

	Mini-sternotomy group (n=135)	Conventional sternotomy group (n=135)
Baseline characteristics		
Age: (years)		
Mean ± SD	69·3 ± 9·3	68·7 ± 8·4
Range	43 - 85	39 - 88
Gender: n (%)		
Male	78 (57·8)	87 (64·4)
Female	57 (42·2)	48 (35·6)
Ethnicity: n (%)		
White British	135 (100)	135 (100)
Body Mass Index (kg.m^{-2})		
Mean ± SD	30·5 ± 5·6	30·4 ± 6·1
Range (Min – Max)	19·0 - 45·4	19·3 - 52·0
EuroSCORE: Mean ± SD (Min-Max)		
Logistic	5·2 ± 3·5 (1·5 - 29·5)	5·1 ± 3·5 (1·5 - 21·0)
II – Mean	1·5 ± 1·1 (0·5 - 10·2)	1·5 ± 1·2 (0·5 - 10·0)
Diagnosis echocardiogram: n (%)		
Regurgitation	3 (2·2)	8 (5·9)
Stenosis	132 (97·8)	127 (94·1)
NYHA class: n (%)		
I	24 (17·8)	18 (13·3)
II	68 (50·4)	66 (48·9)
III	40 (29·6)	46 (34·1)
IV	3 (2·2)	5 (3·7)
***Haemoglobin prior to randomisation: g/dl**		
Mean ± SD	137·9 ± 14·3	137·1 ± 16·1
Range (Min – Max)	97 -173	90 -175
Surgery type: n (%)		
Elective	111 (82·2)	112 (82·6)
In-house urgent	24 (17·8)	23 (17·4)

*One patient had a baseline hemoglobin (Hb) of 95 g/L at randomization, which had fallen to 83 immediately prior to surgery. This Hb drop was not identified until after surgery and the patient continued in the trial with their data included in the analyses based on the intention to treat principle.

Table 2 - Red Cell Transfusions*

	Mini-sternotomy group	Conventional sternotomy group	Odds Ratio (95% CI; p value)	Risk difference (95% CI; p value)
Red Cell transfusions				
Post-operatively to 7 days number of patients (%)	23/135 (17·0)	23/135 (17·0)	1·0 (0·5, 2·0; p=0·9052)	0·0 (-0·1, 0·1; p=0·9999)
Post-operatively to discharge number of patients (%)	34/135 (25·2)	29/135 (21·5)	1·4 (0·7, 2·7)	
Red Cell Units – post operatively to 7 days				
Number of patients	23/135	23/135		
Mean ± SD	1·6 ± 0·7	2·3 ± 1·7		
Range (Min – Max)	1 - 3	1 - 9		
Red Cell Units – post operatively to discharge				
Number of patients	34/135	29/135		
Mean ± SD	2·5 ± 2·5	2·6 ± 2·0		
Range (Min – Max)	1 - 13	1 - 11		

*Reprinted from Journal of the American College of Cardiology Vol 73 (19); Hancock HC, Maier RH, Kasim AS, Mason JM, Murphy GJ, Goodwin AT, Owens WA, Kirmani BH, Akowuah EF. Mini-Sternotomy Versus Conventional Sternotomy for Aortic Valve Replacement. pp. 2491-2492. 2019, with permission from Elsevier.

	Mini-sternotomy group	Conventional sternotomy group	Odds Ratio (95% CI; p value)
Non-Red Cell transfusions			
Post-operatively to 7 days number of patients (%)	6/135 (4·4)	18/135 (13·3)	0·3 (0·1, 0·8; p=0·0137)
Post-operatively to discharge number of patients (%)	13/135 (9·6)	21/135 (15·6)	0·6 (0·3, 1·2)
Non-Red Cell Component Units – Post operatively to 7 days			
Number of patients	6	18	
Mean ± SD	3·2 ± 0·9	4·6 ± 1·6	
Range (Min – Max)	2 - 5	1 - 7	
Non-red Blood Cell Units – post operatively to discharge			
Number of patients	13	21	
Mean ± SD	4·8 ± 2·3	4·9 ± 2·3	
Range (Min – Max)	1 - 8	1 - 12	
Non-red Cell Component Transfusions			
Post-operatively to 7 days number of patients (%)	6 (4·4)	18 (13·3)	0·3 (0·1, 0·8)
Post-operatively to discharge number of patients (%)	13 (9·6)	21 (15·6)	0·6 (0·3, 1·2)

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Table 4 - Secondary Outcomes

	Mini-sternotomy group (n=135)	Conventional sternotomy group (n=135)	Mean Difference (95% CI; p value)
Cardio Pulmonary Bypass time (minutes)			
Mean ± SD	82·7 ± 23·5	59·6 ± 15·1	
Range (Min – Max)	41·0 - 199	37·0 -170·0	
Aortic cross clamp time (minutes)			
Mean ± SD	64·1 ± 17·1	46·3 ± 10·7	
Range (Min – Max)	32·0 - 132·0	32·0 -97·0	
Drain losses at 12 hours			
Mean ± SD	181·6 ± 138·7	306·9 ± 348·6	-127·7 (-191·7,-63·8; p=0·0001)
Range (Min – Max)	25 - 925	25 - 3000	
Drain losses at drain removal			
Mean ± SD	251·7 ± 198·4	393·7 ± 378·7	-145·3 (-218·1,-72·3; p=0·0001)
Range (Min – Max)	25 - 1425	50 - 3000	
Valve Characteristics			
Valve size: mm			
Mean ± SD	23·1 ± 2·1	23·6 ± 2·5	
Range (Min – Max)	19·0 - 29·0	19·0 - 31·0	
Valve type: n (%)			
Biological and sutureless valve	4 (3·0)	3 (2·2)	
Biological prosthesis	96 (71·1)	98 (72·6)	
Mechanical prosthesis	35 (25·9)	34 (25·2)	
Valve function			
Mean Gradient			
Baseline			
n	111*	110*	
Mean ± SD	47·9± 15·7	47·7 ± 20·2	0·2 (-4·6,5·0)
Min - Max	10-93	8-110	
6 weeks			
n	120*	126*	
Mean ± SD	15·7 ± 5·5	15·7 ± 5·8	0·5** (-1·0,2·1)
Min - Max	6-33	4-34	
Peak Gradient			
Baseline			
n	125*	124*	
Mean ± SD	82·3 ± 25·9	77·1 ± 29·1	5·2 (-1·7,2·3)
Min - Max	16-152	8-173	
6 weeks			
n	130*	130*	
Mean ± SD	29·9 ± 10·5	29·7 ± 10·8	-0·3** (-2·9,2·3)
Min - Max	12-62	11-61	
Aortic Valve Regurgitation			
Nil/trivial			
n/n (%)	109/134* (81·3)	109/130* (83·8)	218/264 (82·6)
Mild			
n/n (%)	19/134* (14·2)	18/130* (13·9)	37/264 (14·0)
Moderate			
n/n (%)	5/134* (3·7)	2/130* (1·5)	7/264 (2·7)
Severe			

*** It was not possible to quantify valve function in all patients**

****After adjusting for randomisation factors and baseline data**

n/n (%)	1/134* (0·8)	1/130* (0·8)	2/264 (0·8)

***** It was not possible to record valve regurgitation in all patients

Table 5 - Cost-effectiveness, cost/QALY (£): mini-sternotomy vs· conventional surgery

	Model	Incremental cost (95%CI)	Incremental QALYs (95%CI)	ICER (95%CI)	p[1]	p[2]
1	Multiple imputation, covariate adjusted[4]	508 (-202 to 1217)	-0·007 (-0·016 to 0·002)	Dominated[3]	0·058	0·052
2	Multiple imputation, unadjusted	859 (-116 to 1833)	-0·008 (-0·018 to 0·003)	Dominated	0·023	0·021
3	Complete case, covariate adjusted[4]	630 (25 to 1224)	-0·007 (-0·016 to 0·002)	Dominated	0·013	0·011
4	Complete case, unadjusted	544 (-99 to 1142)	-0·009 (-0·02 to 0·002)	Dominated	0·027	0·022

1 probability cost-effective or net monetary benefit if willing to pay £20,000/QALY
2 probability cost-effective or net monetary benefit if willing to pay £30,000/QALY
3 dominance indicates average costs were less and average benefit greater for conventional surgery
4 regression estimates adjusted for trial stratifying covariates and baseline EQ-5D

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MAVRIC Trial Figures

Figure 1 – CONSORT Diagram

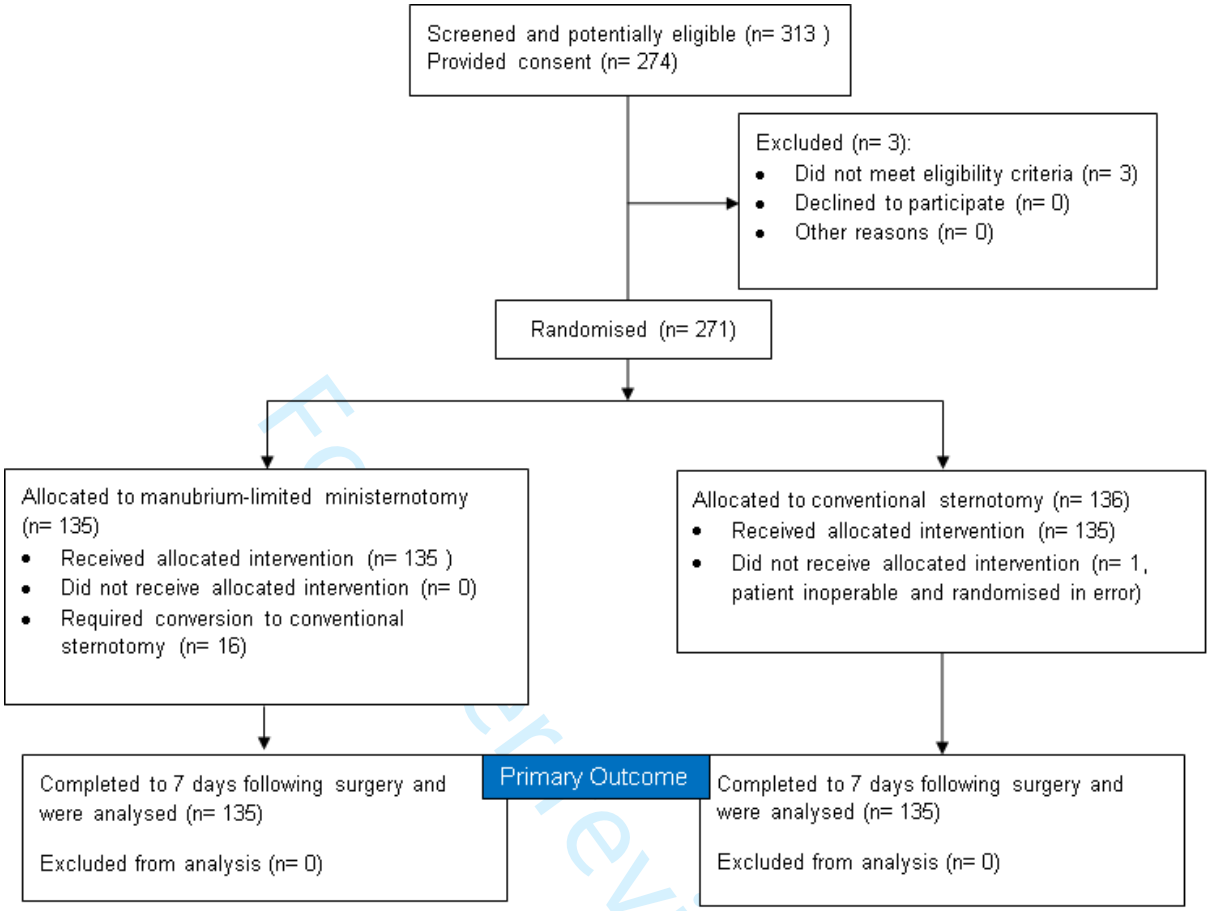
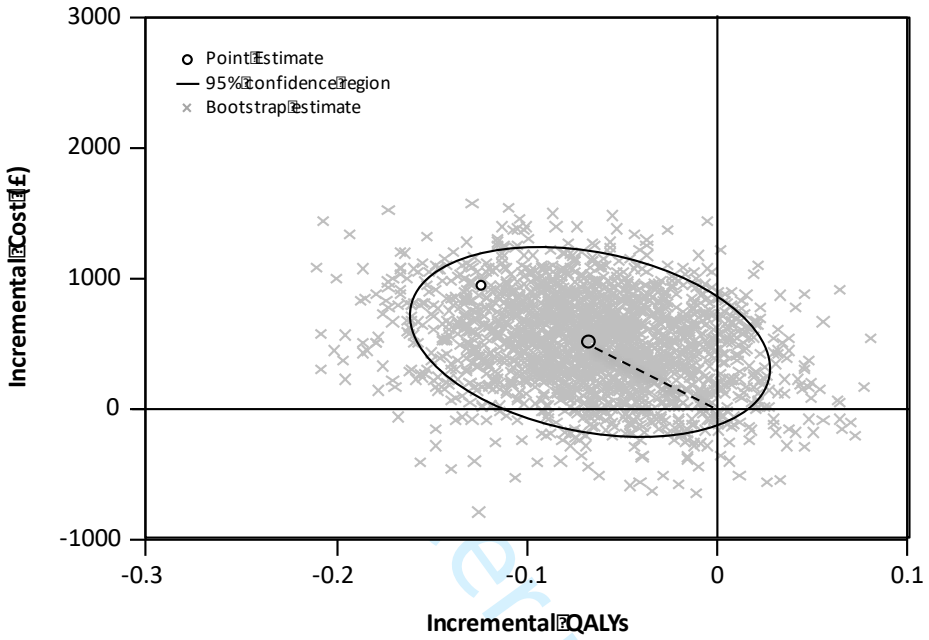


Figure 2 - Cost-effectiveness plane: mini-sternotomy vs. conventional surgery (cost/QALY)



Appendix

Study Investigators: trial site, trials unit, statistics, health economics, committees

Trial Site
The James Cook University Hospital, South Tees Hospitals NHS Foundation Trust, Middlesbrough, United Kingdom

Investigators
- Mr Enoch Akowuah (Chief Investigator)
- Mr Andrew Goodwin (co-Investigator)
- Professor W Andrew Owens (co-Investigator)

Research Team
- Heather Robinson
- Jonathan Broughton
- Dr Khalid Khan

Clinical Trials Unit
Durham Clinical Trials Unit, Durham University; now Newcastle Clinical Trials Unit, Newcastle University

Investigators
- Professor Helen Hancock (co-Investigator)
- Rebecca Maier (co-Investigator)

Research Team
- Andrew Thorpe
- Jennifer Wilkinson
- Dr Leanne Marsay

Statistics
Statistics Group, Wolfson Research Institute for Health and Wellbeing, Durham University

Investigator
- Dr Adetayo Kasim (co-Investigator)

Health Economics
Durham Clinical Trials Unit, Durham University; now University of Warwick

Investigator
- Professor James Mason (co-Investigator)

Committees
Data Monitoring Committee Membership
- Mr Graham Cooper (Chair)
- Mr Heyman Luckraz
- Professor Chris Rogers

Trial Steering Committee Membership
- Mr Sukumaran Nair (Chair until Sep 2014)
- Professor Gavin Murphy (Acting Chair Oct 2014 to June 2015)
- Mr Peter Braidley (Chair, from July 2015)
- Mr Paul Modi
- Mr Brendan Ellis

Table 1 - Eligibility criteria

Inclusion Criteria

- Aged 18 years or older at the time of consent
- Requiring first-time, non-emergency, isolated Aortic Valve Replacement surgery
- Able and willing to provide written informed consent

Exclusion Criteria

- requiring concomitant cardiac procedure(s) including redo surgery, emergency or salvage surgery,
- only conventional median sternotomy indicated,
- haemoglobin level < 90g/L,
- pregnant*,
- currently participating in another interventional clinical trial,
- previous cardiac surgery,
- are unable to stop currently prescribed treatment affecting clotting (e·g·, heparin, warfarin), **
- a history of thrombophilia, thrombocytopenia or other haematological conditions that would affect participation in the trial as determined by one of the three operating surgeons,
- infective endocarditis,
- prevented from having red blood cells and blood products according to a system of beliefs (e·g· -HKRƉK¶V:LWQHVVHV
- having any other medical, psychiatric and or social reason as determined by the consenting surgeon that precludes participation.

* in women of child bearing age (18 ± 50) a pregnancy test was be performed within 14 days of surgery prior to randomisation.

**for patients in both trial arms, pre-operative antiplatelet drugs (including clopidogrel and ticagrelor), and anti-coagulants (including warfarin and heparin) were discontinued 5 days prior to surgery. These drugs were re-started following surgery at the discretion of the clinical team· The exception to this was aspirin, which was stopped 5 days prior to surgery where possible, however continuation until the day of surgery did not exclude a patient from the trial.

Figure 1 - Recruitment

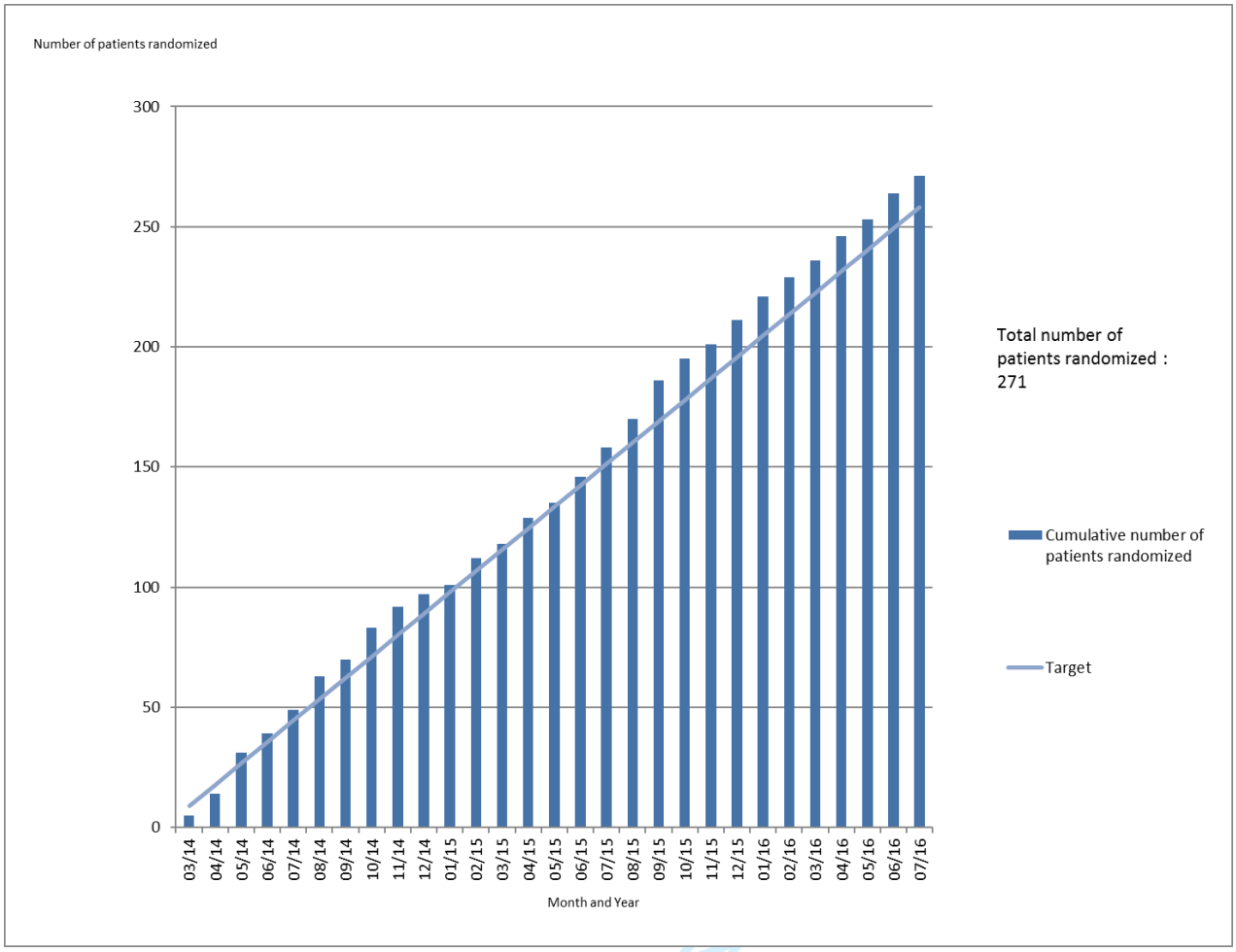


Table 2 - Conversion from mini-sternotomy to conventional sternotomy

Reason for conversion	Number of patients	Details
Anesthetic emergency	**2**	• Patient became unstable as they were transferred into theatre and BP dropped ± required conventional to re-stabilise • Anaphylactic reaction on induction needing CPR· Operation cancelled, patient taken to ITU· Widespread rash· Decision made the following morning to proceed to AVR (via full sternotomy)
Difficult vascular access (venous or arterial)	**9**	Venous • Femoral vessels unsuitable for cannulation • Poor venous drainage • Unable to pass venous dilators • Unable to insert pipe· Resistance felt, no back flow of blood· Femoral cannulation abandoned • Impossible to dilate femoral vein· Despite re-wiring, guide wire coiling within pelvic venous system Arterial • Difficulties cannulating femoral artery leading to haemodynamic instability • Poor access, unable to clamp aorta • Severe calcification of ascending aorta • Difficult access; aorta displaced to the left· Body habitus limited access
Intra-operative complications	**5**	• Bleeding from aortotomy site • Bleeding • Intra-operative decision to performed bypass graft to LAD • Post implant TOE showed small paravalvular leak and bleeding from aortotomy incision • Mild/moderate paravalvar leak on TOE· Required valve re-implant
TOTAL	**16**	

Table 3 - Number of operations by Surgeon

	Mini-sternotomy group n=patients (%)	Conventional sternotomy group n=patients (%)	Total n=patients (%)
Consultant Surgeon A	58 (43·0)	58 (43··0)	116 (43·0)
Consultant Surgeon B	43 (31·9)	35 (25·9)	78 (28·9)
Consultant Surgeon C	34 (25·1)	42 (31·1)	76 (28·1)

Figure 2 - Hemaglobin Profiles

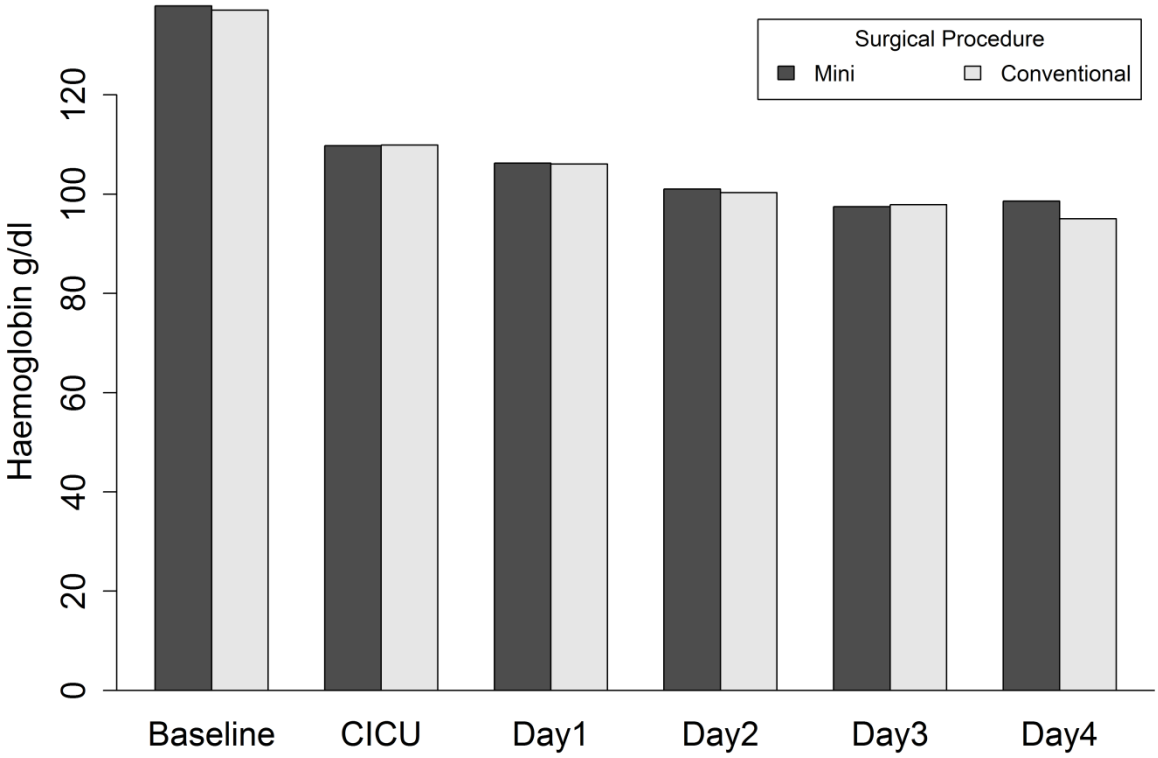


Table 4 - Analgesic use

Medication	Mini-sternotomy Group (135 patients) n = patients (%)	Conventional Sternotomy Group (135 patients) n = patients (%)	Total (270 patients) n = patients (%)
Analgesic use at baseline			
Buprenorphine patch	3 (2·2)	1 (0·7)	4 (1·5)
Codeine Phosphate	4 (3·0)	3 (0·7)	7 (2·6)
Dihydrocodeine Tartrate	0 (0·0)	1 (0·7)	1 (0·4)
Durogesic patch	0	1 (0·7)	1 (0·4)
Fentanyl	1 (0·7)	0 (0·0)	1 (0·4)
Gabapentin	1 (0·7)	0 (0·0)	1 (0·4)
Morphine Sulfate	0·0	1 (0·7)	1 (0·4)
Naxoproxen	1 (0·7)	0 (0·0)	1 (0·4)
Paracetamol	13 (9·6)	8 (5·9)	21 (7·8)
Tramadol Hydrochloride	0 (0·0)	2 (1·5)	2 (0·7)
At least one med at baseline	**16 (11·9)**	**12 (8·9)**	**28 (10·4)**
Analgesic use at day 2			
Buprenorphine patch	1 (0·7)	0 (0·0)	1 (0·4)
Codeine Phosphate	18 (13·3)	16 (11·9)	34 (12·6)
Dihydrocodeine Tartrate	4 (3·0)	6 (4·4)	10 (3·7)
Fentanyl	1 (0·7)	0 (0·0)	1 (0·4)
Gabapentin	1 (0·7)	0 (0·0)	1 (0·4)
Morphine Sulfate	13 (9·6)	13 (9·6)	26 (9·6)
Oramorph	1 (0·7)	1 (0·7)	2 (0·7)
Paracetamol	94 (69·6)	80 (59·3)	174 (64·4)
Pregabalin	1 (0·7)	0 (0·0)	1 (0·1)
Tramadol Hydrochloride	7 (5·2)	5 (3·7)	12 (4·4)
At least one med at day 2	**99 (73·3)**	**86 (63·7)**	**185 (68·5)**
Analgesic use at day 3			
Buprenorphine patch	1 (0·7)	0(0·0)	1 (0·4)
Codeine Phosphate	14 (10·4)	21 (15·6)	35 (13·0)
Dihydrocodeine Tartrate	4 (3·0)	7 (5·2)	11 (4·1)
Fentanyl	0 (0·0)	1 (0·7)	1 (0·4)
Gabapentin	1 (0·7)	1 (0·7)	2 (0·7)
Ibuprofen	0	1 (0·7)	1 (0·4)
Morphine Sulfate	6 (4·4)	1 (0·7)	7 (2·6)
Nefopam Hydrochloride	0	1 (0·7)	1 (0·4)
Oramorph	0	3 (2·2)	3 (1·1)
Paracetamol	89 (65·9)	99 (73·3)	188 (69·6)
Pregabalin	1 (0·7)	0 (0·0)	1 (0·4)
Tramadol Hydrochloride	8 (5·9)	3 (2·2)	11 (4·1)
At least one med at day 3	**90 (66·7)**	**101 (74·8)**	**191 (70·7)**
Analgesic use at Day 4			
Buprenorphine patch	1 (0·7)	0 (0·0)	1 (0·4)
Codeine Phosphate	15 (11·1)	15 (11·1)	30 (11·1)
Dihydrocodeine Tartrate	4 (3·0)	9 (6·7)	13 (4·8)
Fentanyl	1 (0·7)	1 (0·7)	2 (0·7)
Gabapentin	1 (0·7)	1 (0·7)	2 (0·7)
Ibuprofen	0 (0·0)	1 (0·7)	1 (0·4)
Paracetamol	86 (63·7)	75 (55·6)	161 (59·6)
Morphine Sulfate	1 (0·7)	2 (1·5)	3 (1·1)
Pregabalin	1 (0·7)	0 (0·0)	1 (0·4)
Tramadol Hydrochloride	3 (2·2)	3 (2·2)	6 (2·2)
At least one med at day 4	**88 (65·2)**	**81 (60·0)**	**169 (62·6)**
Analgesic use at Week 6			
Buprenorphine Patch	3(2·2)	0(0·0)	3(1·1)
Codeine Phosphate	7(5·1)	5(3·7)	12(4·5)
Dihydrocodeine Tartrate	1(0·7)	3(2·2)	4(1·5)
Fentanyl	1(0·7)	0(0·0)	1(0·4)
Gabapentin	2(1·5)	1(0·7)	3(1·1)
Ibuprofen	0(0·0)	1(0·7)	1(0·4)
Morphine Sulfate	0(0·0)	1(0·7)	1(0·4)
Paracetamol	35(25·9)	38(28·1)	73(27·0)
Pregabalin	1(0·7)	0(0·0)	1(0·4)
Tramadol Hydrochloride	2(1·5)	2(1·5)	4(1·5)
At least one med at week 6	**41(30·4)**	**41(30·4)**	**82(30·4)**
Analgesic use at Week 12			
Buprenorphine Patch	3(2·2)	0(0·0)	3(1·1)
Codeine Phosphate	7(5·2)	4(3·0)	11(4·1)

Dihyrocodeine Tartrate	0(0·0)	1(0·7)	1(0·4)
Gabapentin	2(1·5)	0(0·0)	2(0·7)
Ibuprofen	1(0·7)	0(0·0)	1(0·4)
Morphine Sulfate	1(0·7)	1(0·7)	2(0·7)
Naproxen	1(0·7)	0(0·0)	1(0·4)
Paracetamol	19(14·1)	20(14·8)	39(14·4)
Tramadol Hydrochloride	1(0·7)	1(0·7)	2(0·7)
At least one med at week 12	**23(17·0)**	**22(16·3)**	**45(16·7)**

Table 5 - Adverse Events

Adverse Event	Mini-sternotomy Group n = patients (%)	Conventional Sternotomy Group n = patients (%)	Total n = patients (%)
Death			
In hospital	0/135 (0·0)	0/135 (0·0)	0/270 (0·0)
12 weeks	2/135 (1·5)	2/135 (1·5)	4/270 (1·5)
Stroke			
In hospital	3/135 (3·0)	1/135 (0·7)	4/270 (1·5)
12 weeks	4/135 (3·0)	1/135 (0·7)	5/270 (1·9)
Transient Ischaemic Attack			
In hospital	0/135 (0·0)	1/135 (0·7)	1/270 (0·4)
12 weeks	3/135 (2·2)	1/135 (0·7)	4/270 (1·5)
Renal failure			
In hospital	4/135 (2·3)	0/135 (0·0)	4/270 (1·5)
12 weeks	4/135 (2·3)	1/135 (0·7)	5/270 (1·9)
Atrial Arrhythmias			
In hospital	51/135 (37·8)	42/135 (31·1)	93/270 (34·4)
12 weeks	61/135 (45·2)	51/135 (37·8)	112/270 (41·5)
Ventricular Arrhythmias			
In hospital	2/135 (1·5)	2/135 (1·5)	4/270 (1·5)
12 weeks	2/135 (1·5)	2/135 (1·5)	4/270 (1·5)
Pericardial Effusion			
In hospital	4/135 (2·3)	1/135 (0·7)	5/270 (1·9)
12 weeks	9/135 (6·7)	6/135 (4·4)	15/270 (5·6)
Pulmonary Embolism			
In hospital	0/135 (0·0)	0/135 (0·0)	0/270 (0·0)
12 weeks	0/135 (0·0)	2/135 (1·5)	2/270 (0·7)
Chest Infection			
In hospital	7/135 (5·2)	10/135 (7·4)	17/270 (6·3)
12 weeks	18/135 (13·3)	26/135 (19·3)	44/270 (16·3)
Sternal wound infection			
In hospital	3/135 (2·2)	1/135 (0·7)	4/270 (1·5)
12 weeks	11/135 (8·1)	3/135 (2·2)	14/270 (5·2)
Re-operation for bleeding	3/135 (2·2)	5/135 (3·7)	8/270 (3·0)

Table 6 - Health status, resource use and cost (complete cases)

	Conventional [C]			Mini-sternotomy [M]			[M]-[C][1]	
	mean	(SD)	N	mean	(SD)	N	mean	(95%CI)
Health status[2]								
EQ-5D Baseline	0·764	0·245	130	0·763	0·235	128	-0·001	(-0·060 to 0·057)
EQ-5D 2 days	0·349	0·349	133	0·353	0·291	128	0·004	(-0·074 to 0·082)
EQ-5D 6 weeks	0·798	0·194	118	0·751	0·221	112	-0·048	(-0·101 to 0·006)
EQ-5D 12 weeks	0·838	0·207	124	0·782	0·248	127	-0·056	(-0·112 to 0·001)
EQ-5D AUC (0-12 weeks)	0·162	0·041	105	0·153	0·040	98	-0·009	(-0·020 to 0·002)
Resource use								
Index Admission								
Length of stay (d)[3]	8·26	4·28	135	9·29	7·88	135	1·03	(-0·48 to 2·54)
CICU (d)	1·21	0·99	135	1·61	5·52	135	0·39	(-0·55 to 1·34)
HDU (d)	1·27	1·52	135	1·60	1·75	135	0·33	(-0·07 to 0·72)
Cardiac ward (d)	5·67	3·52	135	5·70	3·18	135	0·03	(-0·77 to 0·83)
Stroke ward (d)	0·03	0·34	135	0·11	1·00	135	0·08	(-0·10 to 0·26)
Time in first surgery (h)	2·24	0·51	135	2·98	0·69	135	0·74	(0·60 to 0·89)
Time in further surgery (h)[4]	0·08	0·34	135	0·03	0·17	135	-0·05	(-0·11 to 0·02)
Time in surgery (h)[4]	2·32	0·63	135	3·01	0·71	135	0·69	(0·53 to 0·85)
RBC (u)[4]	0·59	1·45	135	0·55	1·28	135	-0·04	(-0·37 to 0·28)
FFP (u)[4]	0·57	1·43	135	0·34	1·21	135	-0·23	(-0·55 to 0·09)
Platelets (u)[4]	0·22	0·64	135	0·12	0·46	135	-0·10	(-0·24 to 0·03)
Cryoprecipitate (u)[4]	0·01	0·09	135	0·00	0·00	135	-0·01	(-0·02 to 0·01)
Post discharge contacts								
GP surgery	1·47	1·52	129	1·40	1·32	131	-0·07	(-0·41 to 0·28)
GP home	0·09	0·32	129	0·19	0·56	131	0·10	(-0·01 to 0·21)
GP telephone	0·12	0·45	129	0·15	0·63	131	0·03	(-0·10 to 0·16)
Nurse surgery	1·38	2·56	129	2·07	3·54	131	0·69	(-0·06 to 1·44)
Nurse home	0·43	1·30	129	0·56	1·87	131	0·12	(-0·27 to 0·51)
Nurse telephone	0·05	0·25	129	0·04	0·26	131	-0·01	(-0·07 to 0·05)
Outpatient hospital	0·40	0·78	129	0·57	1·98	131	0·17	(-0·20 to 0·53)
Inpatient hospital	0·30	0·68	129	0·27	0·60	131	-0·03	(-0·18 to 0·13)
Inpatient hospital (d)	2·09	7·79	129	1·09	2·69	131	-1·00	(-2·42 to 0·42)
Total Contacts	4·29	3·53	129	5·47	4·90	131	1·18	(0·14 to 2·22)
Cost[5]								
Cost of index admission	7674	2055	135	8815	4517	135	1140	(303 to 1977)
Cost post discharge	824	2485	129	547	925	131	-277	(-734 to 180)
Cost	8527	3558	129	9274	4542	131	746	(-245 to 1737)

1 OLS regression-estimated means and 95% confidence intervals
2 EQ-5D-3L index score
3 Length stay by ward does not sum to length of stay due to theatre and transit time, and rounding
4 Item includes index and post-discharge usage
5 Resource items were costed using national reference costs except for the index procedures which were costed by South Tees Hospitals NHS Foundation Trust

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	3,5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	3,4,5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	4 (+appendix)
	4b	Settings and locations where the data were collected	4
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	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
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*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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Title

Mini-sternotomy versus conventional sternotomy for aortic valve replacement: a randomised controlled trial

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Abstract

Objective

To compare clinical and health economic outcomes after manubrium-limited mini-sternotomy (intervention) and conventional median sternotomy (usual care)

Design

A single blind, randomised controlled trial.

Setting

Single centre UK National Health Service tertiary hospital

Participants

Adult patients undergoing aortic valve replacement surgery

Interventions

Intervention was manubrium-limited mini-sternotomy performed using a 5-7cm midline incision. Usual care was median sternotomy performed using a midline incision from the sternal notch to the xiphisternum.

Primary and secondary outcome measures

The primary outcome was the proportion of patients who received a red cell transfusion post-operatively and within 7 days of index surgery. Secondary outcomes included proportion of patients receiving a non-red cell blood component transfusion and number of units transfused within 7 days and during index hospital stay, quality of life and cost effectiveness analyses.

Results

270 patients were randomised, received surgery and contributed to the intention to treat analysis. No difference between mini and conventional sternotomy in red-cell transfusion within 7 days was found; 23/135 patients in each arm received a transfusion, odds ratio 1·0 (95% CI: 0·5, 2·0) and risk difference 0·0 (95% CI: -0·1, 0·1). Mini-sternotomy reduced chest drain losses (mean 181·6ml (SD

138·7) vs conventional, mean 306·9ml (SD 348·6)); this did not reduce red-cell transfusions. Mean valve size and post-operative valve function were comparable between mini-sternotomy and conventional groups; 23mm vs 24mm, and 6/134 moderate or severe aortic regurgitation vs 3/130, respectively. Mini-sternotomy resulted in longer bypass (82·7 minutes (SD 23·5) vs 59·6 minutes (SD 15·1)) and cross clamp times (64·1 minutes (SD 17·1) vs 46·3 minutes (SD 10·7)). Conventional sternotomy was more cost-effective with only a 5·8% probability of mini-sternotomy being cost-effective at a willingness to pay of £20,000/QALY.

Conclusions

AVR via mini-sternotomy did not reduce red blood cell transfusion within 7 days following surgery when compared to conventional sternotomy.

Clinical Trials Registry: ISRCTN29567910

Key word: minimally invasive, aortic valve, clinical trial, cardiac surgery, replacement,

ARTICLE SUMMARY

1. Large proportion of eligible patients recruited, and all patient randomised contributed to the primary outcome
2. Clear protocols for transfusion of blood and blood products with high adherence throughout the trial
3. Patients were blinded to group allocation until two days following index surgery, reducing the likelihood of bias.
4. First randomised trial to perform detailed health economic evaluation of minimally invasive versus conventional sternotomy
5. The trial was undertaken by three experienced minimally invasive surgeons who were expert at both techniques.

Objectives

Aortic valve replacement (AVR) for severe symptomatic valvular disease is one of the most common cardiac surgical procedures performed worldwide. The current joint guidelines of the American College of Cardiology and American Heart Association (ACC/AHA) and the current European Society of Cardiology guidelines for the management of aortic valve disease, state that surgical AVR is recommended for symptomatic patients with severe aortic stenosis and asymptomatic patients with severe aortic stenosis who meet an indication for AVR when surgical risk is low or intermediate.[1]

In the UK, the National adult cardiac cardiac surgery audit published by NICOR (National Institute for Cardiac Outcome Reporting) reported 13,027 procedures for aotic valve disease in the UK from April 2018 to March 2019.[2] Outcomes are generally excellent with in-hospital observed mortality in the UK of 1·5% for first time elective procedures.[3] In low risk patients with a Euroscore 2 of less than 4, a mortality of less than 0.7% was observed in over 15,000 patients undergoing AVR surgery in the UK between 2016 and 2019.[2]

These results are not observed in all patients; in high risk groups, conventional surgery risks perioperative organ injury and prolonged recovery, with death in up to 31% of patients within 1 year.[4] Minimally invasive surgery combines the durability of surgical repair with reductions in surgical trauma that should reduce perioperative morbidity. Observational analyses demonstrating reductions in morbidity and resource use[5,6] may be confounded by multiple sources of bias and are at odds with limited evidence from RCTs that have not shown improved outcomes.[7] This uncertainty is reflected by variations in uptake internationally.[8,9,10]

The move towards minimally invasive surgery is also driven by patient perceptions of pain reduction and rapid recovery. However, minimally invasive cardiac surgery is not without risks; limiting access to the heart can result in technically sub-optimal surgery, including concern about the size of the prosthesis that can be inserted, and paravalvular leak rates.

This trial evaluated Manubrium-limited Mini-sternotomy versus Conventional Sternotomy for Aortic Valve Replacement (MAVRIC). We hypothesised that mini-sternotomy would reduce red cell

transfusion rates, a contemporary marker of surgical trauma and indicator of adverse outcomes;[11] this has been contested,[12] though the evidence is not conclusive.[13] An embedded cost effectiveness analysis evaluated whether the intervention was cost effective in a UK National Health Service (NHS) setting.

Patients and Methods

Trial Design

MAVRIC was a single centre, single-blind, RCT comparing AVR via manubrium-limited mini-sternotomy group (intervention) and AVR via conventional sternotomy group (usual care). A NHS Research Ethics Committee approved the trial, which was conducted in accordance with the principles of the International Conference on Harmonisation of Good Clinical Practice.[14] South Tees Hospitals NHS Foundation Trust was the Sponsor and recruiting centre.

Patient Public Involvement

In designing the study, we asked patients their view on what factors may affect whether they took part in the study. This was done in an outpatient setting and via a postal questionnaire. They felt expertise was important. Most patients felt that although the cosmetic benefit of the minimally invasive approach was appealing, they expected some clinical benefit form minimally invasive surgery as well. Importantly most patients said they would accept being blind to the type of surgery they had received for 48 hours after the procedure.

Participants

Patients were eligible if they were aged 18 years or over; required first-time, non-emergency, isolated AVR surgery; and were willing to provide written informed consent. Full details of the eligibility criteria are in the **Supplementary Material**.

Randomisation

Eligible patients were randomised by members of the research team using a 24-hour, central, secure, web-based randomisation system with concealed allocation, managed by the Clinical Trials

Unit; randomisation was in a 1:1 ratio between mini and conventional sternotomy and stratified by baseline logistic EuroSCORE and pre-operative Hemoglobin (Hb).

Interventions

Manubrium-limited mini-sternotomy was performed using a 5-7cm midline skin incision dividing the manubrium from the sternal notch to 1cm below the manubrium-sternal junction. Cardiopulmonary bypass was established with an ascending aortic cannula and percutaneous femoral venous cannulation. Conventional median sternotomy was performed using a midline incision from the sternal notch to the xiphisternum. Key aspects of anaesthesia were standardised, and are detailed in the protocol.[15]

Blinding

All patients were blinded to type of sternotomy received until after their day 2 Quality of Life and pain assessments. All patients had trial-specific opaque dressings applied to their sternal wound, and groin before leaving theatre.

Transfusion Protocol

The post-operative period, and trial protocol in relation to red cell and non-red cell transfusion, began on admission to the Cardiothoracic Intensive Care Unit (CICU); it specified that patient's should receive a red cell transfusion if their Hb dropped below 80 g/L; or were bleeding by 400ml/h or more, or were bleeding 100ml/h or more for 4 or more hours with a Hb equal to or greater than 80g/L; or had blood loss with haemodynamic instability irrespective of thromboelastography (TEG) and/or clotting profile results. One unit of red cells was transfused and Hb level checked before transfusing another unit.

Participants received a non-red cell transfusion if both of the following criteria were met: bleeding defined by 400ml/h or more, or blood loss of 100ml/h or more for 4 hours or more; TEG or coagulation guided transfusion indicated.

Outcomes

All outomes were measured from index surgery.

Primary Outcome

The primary outcome was the proportion of patients who received a red cell transfusion post-operatively and within 7 days of index surgery.

Secondary Outcomes:

- proportion of patients receiving a red cell transfusion and number of units transfused within 7 days and during index hospital stay;
- proportion of patients receiving a non-red cell blood component transfusion and number of units transfused within 7 days and during index hospital stay;
- volume in chest drains at 6 and 12 hours, and drain removal;
- degree of aortic regurgitation using echocardiogram within 6 weeks;
- re-operation rates;
- conversion to conventional AVR during surgery;
- changes in lung function at 4 days and 6 weeks;
- Quality of life EuroQol (EQ-5D-3L, EQ-VAS) at 2 days, 6 and 12 weeks;
- time patients are deemed 'fit for discharge';
- health care utilisation to 12 weeks;
- cost and cost effectiveness analyses;
- adverse events to 12 weeks.

Statistical Analysis

Audit data had indicated 30% of patients undergoing AVR via conventional sternotomy (15 of 50 patients) received a red cell transfusion compared with 13% of patients (8 of 60 patients)

undergoing AVR via mini-sternotomy. Using Fisher's Exact test, 90% power, 5% alpha, we estimated that 260 patients would be required to detect a 17% reduction in the proportion of patients requiring a red cell transfusion (13% compared with 30%), using a two-sided test. Allowing for loss to follow up, the sample size was increased to 270.

The primary analysis was based on intention-to-treat principles, in accordance with a pre-specified statistical analysis plan.

The primary efficacy analysis was based on a logistic regression model with only group (minimally invasive and conventional) and stratifying factors (baseline logistic EuroSCORE and Hb) as the predictors. Odds ratios and their associated 95% confidence interval are reported in the primary analysis. Sensitivity analysis using alternating logistic regression was performed for the primary endpoint to sensitise for surgeon effects; the odds of receiving a red cell transfusion for two patients treated by the same surgeon was compared to two patients treated by different surgeons.

All analyses of secondary continuous efficacy endpoints at single time points were based on linear models where, if appropriate, a log normal model was fitted to sensitise the linearity assumption. Longitudinal analysis was performed for all endpoints with repeated data over time to investigate changes in trends over the trial period. The trial period was defined as baseline, up to 7 days (post-operative period), 6 week follow-up and 12 week follow-up. All analyses of binary endpoints at a single time point were based on logistic regression. Generalised estimating equation was used to analyse repeated binary data per patient to account for intra-patient correlation.

Further exploratory analysis was conducted to investigate the association between the treatment group and other clinical factors. All analyses were performed using R 3·3·3 (The R Foundation) and SAS 9·4 (SAS Institute Inc).

Economic Evaluation

A prospective economic evaluation applying a NHS perspective, following National Institute for Health and Care Excellence (NICE) reference case guidance,[16] was employed. Health care utilisation

was captured up to three months following discharge from index surgery. Resource use was valued in 2016 pounds sterling using national sources,[17,18] and where necessary, local micro-costing (£1=$1·50). Resources included surgery, transfusions, length of hospital stay (by level of care), complications and further surgery, and community care following discharge.

Mechanisms of missingness within the data were explored and multiple imputation methods were applied to impute missing data and minimise bias, using chained equations and predictive mean matching. Imputation sets were analysed within a bivariate analysis of costs and QALYS, to generate incremental within-trial cost per QALY estimates and credible intervals. Findings were presented on the ICER plane and with Cost-Effectiveness Acceptability Curves, using the net monetary benefit approach.

Imputation was conducted according to good practice guidance.[19,20] Multiple imputation provides unbiased estimates of treatment effect if data are missing at random (MAR) and the missingness process is adequately characterised : this assumption was explored in the data, for example by using logistic regression for missingness of costs and QALYs against baseline variables.[21] A regression model was used to generate multiple imputed datasets (or 'draws') for individual treatment groups, where missing values were predicted drawing on predictive covariates. Outcome measures and costs (at each time point) contributed as predictors and imputed variables. Each draw provided a complete dataset, reflecting the distributions and correlations between variables. Predictive mean matching drawn from the five nearest neighbours (knn=5) was used to enhance the plausibility and robustness of imputed values; normality was not assumed. The imputation model used fully conditional (MCMC) methods. Draws were analysed using bivariate regression (see below) within the Stata MI framework, capturing within and between variances for imputed samples.[22] After examining the fraction of missing information (FMI) from finite imputation sampling, 20 draws was taken in the final imputation model.

Results

Trial Population

MAVRIC recruited to time and target; 313 patients were considered for the trial; 274 patients consented between 20th March 2014 and 25th July 2016. The analysis population was 270 eligible patients; 135 allocated to the AVR via mini-sternotomy group and 135 allocated to the AVR via conventional sternotomy group (**Figure 1.**).

All 270 patients underwent surgery. Sixteen patients required cross-over from minimally-invasive to a conventional sternotomy due to anaesthetic emergency (n=2), difficulties due to vascular access (n=9), and intra-operative complications (n=5); further details and the number of operations performed by surgeon are in the Supplementary Material.

Baseline characteristics were similar between groups (**Table 1**).

Primary Outcome

There was no difference between groups in relation to the primary outcome (**Table 2**). The proportion of patients receiving a red cell transfusion was 23 of 135 in both groups, Odds ratio 1·0 (95% CI 0·5, 2·0; p=0·9052) and risk difference of 0·0 (95% CI -0·1, 0·1; p=0·9999).

Secondary Outcomes

Red cell and non-red cell transfusion

There was no significant difference between groups with respect to any red cell transfusion at discharge (**Table 2**). There was no difference between groups in Hb from baseline to 4 days following index surgery (**Supplementary Material**). There was a statistically significant difference in the proportion of patients receiving any non-red cell transfusion within 7 days of surgery; mini 6/135 versus conventional 18/135, Odds ratio: 0·3 (95% CI 0·1, 0·8; p=0·0137) (**Table 3**).

Cross clamp time and cardiopulmonary bypass time

Mini-sternotomy resulted in longer Cardio Pulmonary Bypass times; mini group 82·7 minutes (SD 23·5), conventional 59·6 minutes (SD 15·1). Aortic cross clamp times were also longer; mini group 64·1 minutes (SD 17·1), conventional 46·3 minutes (SD 10·7) (**Table 4**).

Chest drain losses

Mini-sternotomy resulted in a 40·8% reduction in chest drain losses at 12 hours, the mini group mean was 181·6ml (SD 138·7), conventional group mean was 306·9ml (SD 348·6); the mean difference was -127·7ml (95% CI -191·7, -63·8, p=0.0001). At drain removal mean difference was -145·3ml (95% CI -218·1, -72·3; p=0.0001) (**Table 4**).

Ventilation time

Ventilation time between the groups was similar; 9·6 hours (SD 5·6) in the mini group and 9·8 hours (SD 6·9) in the conventional (**Table 4**).

Intensive care unit length of stay

There was no difference in intensive care unit length of stay between groups (**Supplementary Material**).

Post-operative pain

There was no difference in pain scores between groups; analgesic use is also included to assist interpretation (**Supplementary Material**).

Lung function

There was no difference between groups in lung function at baseline. At 4 days post-surgery, mean Forced Expiratory Volume 1 (FEV1) 1123mls (SD 433) and Forced Vital Capacity, FVC 1479mls (SD 583) were significantly reduced in the mini group, compared to the conventional; FEV1 1321 (SD 524), FVC 1698 (SD 707). Mean differences for FEV1 and FVC were statistically significant at 4 days post-surgery; -171mls (95% CI -265, -77; p=0·0004) and -130mls (95% CI -269, 0; p=0·0498)

respectively, after adjusting for baseline FEV1, FVC, and randomisation factors (**Supplementary Material**).

Hospital length of stay

The mean time to patients being fit for hospital discharge following index surgery was similar between groups. The mean post-operative hospital length of stay was 7·4 (SD 7·5, range 3-79) in the mini group, and 6·3 days (SD 3·2, range 3-31) in the conventional (**Supplementary Material**).

Post-operative valve function

The distribution of valve types and valve sizes were similar; mean valve size inserted was 23mm in the mini group and 24mm in the conventional (**Table 4**). Over 70% of patients in each group received a tissue valve, over 25% received a mechanical valve and 2-3% received a sutureless tissue valve. Post operative transthoracic echo showed a similar decrease in mean aortic valve gradient in both groups to 16mmHg; peak gradient decreased to 30mmHg in both groups (**Table 4**). 6/134 patients had moderate or severe aortic regurgitation in the mini group compared to 3/130 in the conventional (**Table 4**).

Adverse events

There were no in-hospital deaths in either group. At 12 weeks follow up, there were 4 deaths; 2 in each arm of the study. Adverse events in each group were broadly similar and within acceptable clinical limits. By 12 weeks, 4/135 patients in the mini-sternotomy group and 1/135 in the conventional group had suffered a stroke (defined as a persistent neurological deficit). Atrial arrhythmias were identified in 61/135 patients in the mini group and 51/135 in the conventional. By 12 weeks, 11/135 patients in the mini group and 3/135 patients in the conventional had a sternal wound infection (**Supplementary Material**).

Quality of Life, Costs and Cost-Effectiveness

Costs during the index admission were significantly greater for the mini group (mini-conventional: mean difference £1140; 95% CI 303, 1977), primarily reflecting the additional cost of theatre time

(**Supplementary Material**). Overall costs were not significantly different (mini-conventional: mean difference £746; 95% CI -245, 1737). There was no significant difference in quality of life between groups up to 12 weeks (mini-conventional: mean difference area under curve -0.009 QALYs; 95% CI 0.020, 0.002). Although differences in costs and quality-of-life were not individually significant, the bivariate cost-QALY distribution (combining these two) suggests conventional surgery might be more cost-effective (**Figure 2.**). In the base-case model, mini was dominated by conventional surgery (due to greater cost and less benefit), with only a 5.8% probability of being cost-effective at a willingness to pay of £20,000/QALY (**Table 5**).

Sensitivity and Subgroup Analyses

There was no significant surgeon effect; the odds of receiving a red cell transfusion for two patients treated by the same surgeon compared to two patients treated by different surgeons was 1·2 (95% CI 0·9, 1·6; p=0·1379).

Protocol deviations in respect of cell tranfusions did not affect the results of the primary analysis; excluding these patients produced the same results as those from the intention-to-treat analysis.

Discussion

Main findings

Mini-sternotomy was not superior to conventional sternotomy with respect to red cell transfusion requirements within 7 days of surgery. Analysis of secondary endpoints showed a statistically significant difference in transfusion volumes of non-red cell blood components. Aortic valve size and post-operative function were comparable in the 2 groups. Mini-sternotomy resulted in a relative reduction in chest drain losses however, higher blood loss in the conventional group did not translate into red cell transfusions. Mini patients had substantially longer bypass and cross clamp times and worse lung function at 4 days post-surgery. Lung function at twelve weeks, and adverse event rates were otherwise not different between groups. Conventional sternotomy was found to be more cost-effective. MAVRIC findings contradict those from other trials that pre-date it.[23,24] Two 100 patient RCTs published since MAVRIC and the systematic review, do not alter the discussion.[25,26]

Both found no difference in major clinical outcomes, and findings relating to shorter hospital stay in mini-sternotomy; a reduction in bleeding through chest drains, and mean difference in EQ-5D scores at baseline and at 6 weeks[25] are consistent with MAVRIC findings.

Strengths and limitations

This is the largest single trial to have compared minimally invasive sternotomy to conventional median sternotomy for AVR. A recent Cochrane review identified 511 patients from 7 previous RCTs.[7] In MAVRIC, the mini-sternotomy technique divided only the manubrium and is therefore less invasive than other minimally invasive techniques. The trial was undertaken by three experienced minimally invasive surgeons who were expert at both techniques. Patients were blinded to group allocation until two days following index surgery, reducing the likelihood of bias. The trial recruited a significant proportion of eligible patients; 274/313 (86%), with few requiring conversion to conventional sternotomy, increasing the likelihood that the trial findings are generalisable. A further strength was the detailed health economic evaluation; this has not been performed previously.

The trial had some limitations, including the single centre design. This will tend to have biased treatment effect estimates away from the null, which is at odds with our observed effect. There were no significant levels of protocol non-adherence, with no effect on the main trial finding. The event rate for the primary outcome, was much lower than expected at 17%; nationally red cell transfusion rates following valve surgery are 46·4%.[27] In our pre-trial audit conducted over 5 years , ending 2009, 30% of mini-sternotomy patients received a red cell transfusion. We attribute the observed transfusion rate in MAVRIC to the restrictive red cell transfusion threshold applied; this followed evidence at the time of trial design. The consultant (expert) led nature of the trial interventions is also likely to have reduced the need for transfusions post-operatively and to have biased trial results towards the null.

Clinical importance

MAVRIC contributes important evidence to the minimally invasive AVR evidence base, summarised in a Cochrane review.[7] MAVRIC demonstrated longer cross-clamp and bypass times with the manubrium-limited mini-sternotomy, attributed to known differences between the interventions. Minimally-invasive techniques in MAVRIC required a number of surgical steps to be performed with the aortic clamp in place (drain insertion and pacing wire insertion for example), meaning cross-clamp and bypass were longer. This is not an absolute requirement in other minimally invasive approaches; for example, where the incision is extended into the body of the sternum, or where rapid deployment valves are used, there are no differences in cross clamp and bypass times.[7]

The size of MAVRIC and event rate prevents formal comparison of adverse events between the groups, of note is the difference in stroke rate; this would benefit from exploration in a future trial.

The cost-effectiveness plane indicates that conventional surgery is less costly and more beneficial than minimally-invasive surgery; contact with healthcare professionals was greater in the mini group, although there was no clear pattern of use. Wide confidence intervals mean that differences are imprecise. MAVRIC does not support the use of funds to expand AVR via manubrium-limited mini-sternotomy practice.

MAVRIC, the world's largest RCT at low risk of bias, found no additional clinical benefit, in terms of red blood cell transfusion rates of minimally invasive AVR. Results are in agreement with the findings of a Cochrane review of trials that have evaluated mini-sternotomy AVR.[7] This information should be disseminated to patients, clinicians and commissioners to inform decisions about AVR surgery including commissioning.

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The views and opinions expressed are those of the authors and do not necessarily reflect those of the National Institute for Health Research (NIHR) Research for Patient Benefit Programme, the National Health Service or the Department of Health and Social Care.

Declaration of Interests

Helen C Hancock (HCH): None

Rebecca H Maier (RHM): None

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Enoch F Akowuah (EFA): None

Authors contributions

EFA, HCH, RHM, and JMM and GJM designed the trial, and sought funding. EFA, ATG and WAO recruited patients to the trial and performed surgery. ASK conducted the statistical analysis and JMM conducted the health economic analysis. All authors contributed to the final manuscript.

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Data Sharing Statement

Anonymised data from this study may be available to the scientific community subject to appropriate ethical approval. Requests for data should be directed to the senior author.

Table 1. Baseline characteristics of participants by group

	Mini-sternotomy group (n=135)	Conventional sternotomy group (n=135)
Baseline characteristics		
Age: (years)		
Mean ± SD	69·3 ± 9·3	68·7 ± 8·4
Range	43 - 85	39 - 88
Gender: n (%)		
Male	78 (57·8)	87 (64·4)
Female	57 (42·2)	48 (35·6)
Ethnicity: n (%)		
White British	135 (100)	135 (100)
Body Mass Index (kg.m^{-2})		
Mean ± SD	30·5 ± 5·6	30·4 ± 6·1
Range (Min – Max)	19·0 - 45·4	19·3 - 52·0
EuroSCORE: Mean ± SD (Min-Max)		
Logistic	5·2 ± 3·5 (1·5 - 29·5)	5·1 ± 3·5 (1·5 - 21·0)
II – Mean	1·5 ± 1·1 (0·5 - 10·2)	1·5 ± 1·2 (0·5 - 10·0)
Diagnosis echocardiogram: n (%)		
Regurgitation	3 (2·2)	8 (5·9)
Stenosis	132 (97·8)	127 (94·1)
NYHA class: n (%)		
I	24 (17·8)	18 (13·3)
II	68 (50·4)	66 (48·9)
III	40 (29·6)	46 (34·1)
IV	3 (2·2)	5 (3·7)
***Haemoglobin prior to randomisation: g/dl**		
Mean ± SD	137·9 ± 14·3	137·1 ± 16·1
Range (Min – Max)	97 -173	90 -175
Surgery type: n (%)		
Elective	111 (82·2)	112 (82·6)
In-house urgent	24 (17·8)	23 (17·4)

*One patient had a baseline hemoglobin (Hb) of 95 g/L at randomisation, which had fallen to 83 immediately prior to surgery. This Hb drop was not identified until after surgery and the patient continued in the trial with their data included in the analyses based on the intention to treat principle.

Table 2. The number and proportion of patients receiving a Red Cell Transfusion*, and the number of units received, to 7 days and to discharge following index surgery, by group.

	Mini-sternotomy group	Conventional sternotomy group	Odds Ratio (95% CI; p value)	Risk difference (95% CI; p value)
Red Cell Transfusions				
Post-operatively to 7 days number of patients (%)	23/135 (17·0)	23/135 (17·0)	1·0 (0·5, 2·0; p=0·9052)	0·0 (-0·1, 0·1; p=0·9999)
Post-operatively to discharge number of patients (%)	34/135 (25·2)	29/135 (21·5)	1·4 (0·7, 2·7)	
Red Cell Units – post operatively to 7 days				
Number of patients	23/135	23/135		
Mean ± SD	1·6 ± 0·7	2·3 ± 1·7		
Range (Min – Max)	1 - 3	1 - 9		
Red Cell Units – post operatively to discharge				
Number of patients	34/135	29/135		
Mean ± SD	2·5 ± 2·5	2·6 ± 2·0		
Range (Min – Max)	1 - 13	1 - 11		

*Reprinted from Journal of the American College of Cardiology Vol 73 (19); Hancock HC, Maier RH, Kasim AS, Mason JM, Murphy GJ, Goodwin AT, Owens WA, Kirmani BH, Akowuah EF. Mini-Sternotomy Versus Conventional Sternotomy for Aortic Valve Replacement. pp. 2491-2492. 2019[28], with permission from Elsevier.

Table 3. The number and proportion of patients receiving a Non-Red Cell Transfusion, and the number of units received, to 7 days and to discharge following index surgery, by group.

	Mini-sternotomy group	Conventional sternotomy group	Odds Ratio (95% CI; p value)
Non-Red Cell Transfusions			
Post-operatively to 7 days number of patients (%)	6/135 (4·4)	18/135 (13·3)	0·3 (0·1, 0·8; p=0·0137)
Post-operatively to discharge number of patients (%)	13/135 (9·6)	21/135 (15·6)	0·6 (0·3, 1·2)
Non-Red Cell Component Units – Post operatively to 7 days			
Number of patients	6	18	
Mean ± SD	3·2 ± 0·9	4·6 ± 1·6	
Range (Min – Max)	2 - 5	1 - 7	
Non-red Blood Cell Units – post operatively to discharge			
Number of patients	13	21	
Mean ± SD	4·8 ± 2·3	4·9 ± 2·3	
Range (Min – Max)	1 - 8	1 - 12	
Non-red Cell Component Transfusions			
Post-operatively to 7 days number of patients (%)	6 (4·4)	18 (13·3)	0·3 (0·1, 0·8)
Post-operatively to discharge number of patients (%)	13 (9·6)	21 (15·6)	0·6 (0·3, 1·2)

Table 4. Outcomes during index hospital stay for cardiopulmonary bypass and aortic cross clamp times, drain losses, valve size and type, and for valve function and regurgitation to 6 weeks by group.

	Mini-sternotomy group (n=135)	Conventional sternotomy group (n=135)	Mean Difference (95% CI; p value)
Cardio Pulmonary Bypass time (minutes)			
Mean ± SD	82·7 ± 23·5	59·6 ± 15·1	
Range (Min – Max)	41·0 - 199	37·0 -170·0	
Aortic cross clamp time (minutes)			
Mean ± SD	64·1 ± 17·1	46·3 ± 10·7	
Range (Min – Max)	32·0 - 132·0	32·0 -97·0	
Drain losses at 12 hours			
Mean ± SD	181·6 ± 138·7	306·9 ± 348·6	-127·7 (-191·7,-63·8; p=0·0001)
Range (Min – Max)	25 - 925	25 - 3000	
Drain losses at drain removal			
Mean ± SD	251·7 ± 198·4	393·7 ± 378·7	-145·3 (-218·1,-72·3; p=0·0001)
Range (Min – Max)	25 - 1425	50 - 3000	
Valve Characteristics			
Valve size: mm			
Mean ± SD	23·1 ± 2·1	23·6 ± 2·5	
Range (Min – Max)	19·0 - 29·0	19·0 - 31·0	
Valve type: n (%)			
Biological and sutureless	4 (3·0)	3 (2·2)	
Biological prosthesis	96 (71·1)	98 (72·6)	
Mechanical prosthesis	35 (25·9)	34 (25·2)	
Valve function			
Mean Gradient			
Baseline			
n	111*	110*	
Mean ± SD	47·9± 15·7	47·7 ± 20·2	0·2 (-4·6,5·0)
Min - Max	10-93	8-110	
6 weeks			
n	120*	126*	
Mean ± SD	15·7 ± 5·5	15·7 ± 5·8	0·5** (-1·0,2·1)
Min - Max	6-33	4-34	
Peak Gradient			
Baseline			
n	125*	124*	
Mean ± SD	82·3 ± 25·9	77·1 ± 29·1	5·2 (-1·7,2·3)
Min - Max	16-152	8-173	
6 weeks			
n	130*	130*	
Mean ± SD	29·9 ± 10·5	29·7 ± 10·8	-0·3** (-2·9,2·3)
Min - Max	12-62	11-61	
* It was not possible to quantify valve function in all patients			
**After adjusting for randomisation factors and baseline data			
Aortic Valve Regurgitation			
Nil/trivial			
n/n (%)	109/134* (81·3)	109/130* (83·8)	218/264 (82·6)
Mild			
n/n (%)	19/134* (14·2)	18/130* (13·9)	37/264 (14·0)
Moderate			
n/n (%)	5/134* (3·7)	2/130* (1·5)	7/264 (2·7)

Severe			
n/n (%)	1/134* (0·8)	1/130* (0·8)	2/264 (0·8)

* It was not possible to record valve regurgitation in all patients

Table 5. Cost-effectiveness, cost/QALY (£): mini-sternotomy versus conventional surgery

1 probability cost-effective or net monetary benefit if willing to pay £20,000/QALY
2 probability cost-effective or net monetary benefit if willing to pay £30,000/QALY
3 dominance indicates average costs were less and average benefit greater for conventional surgery
4 regression estimates adjusted for trial stratifying covariates and baseline EQ-5D

	Model	Incremental cost (95%CI)	Incremental QALYs (95%CI)	ICER (95%CI)	p[1]	p[2]
1	Multiple imputation, covariate adjusted[4]	508 (-202 to 1217)	-0·007 (-0·016 to 0·002)	Dominated[3]	0·058	0·052
2	Multiple imputation, unadjusted	859 (-116 to 1833)	-0·008 (-0·018 to 0·003)	Dominated	0·023	0·021
3	Complete case, covariate adjusted[4]	630 (25 to 1224)	-0·007 (-0·016 to 0·002)	Dominated	0·013	0·011
4	Complete case, unadjusted	544 (-99 to 1142)	-0·009 (-0·02 to 0·002)	Dominated	0·027	0·022

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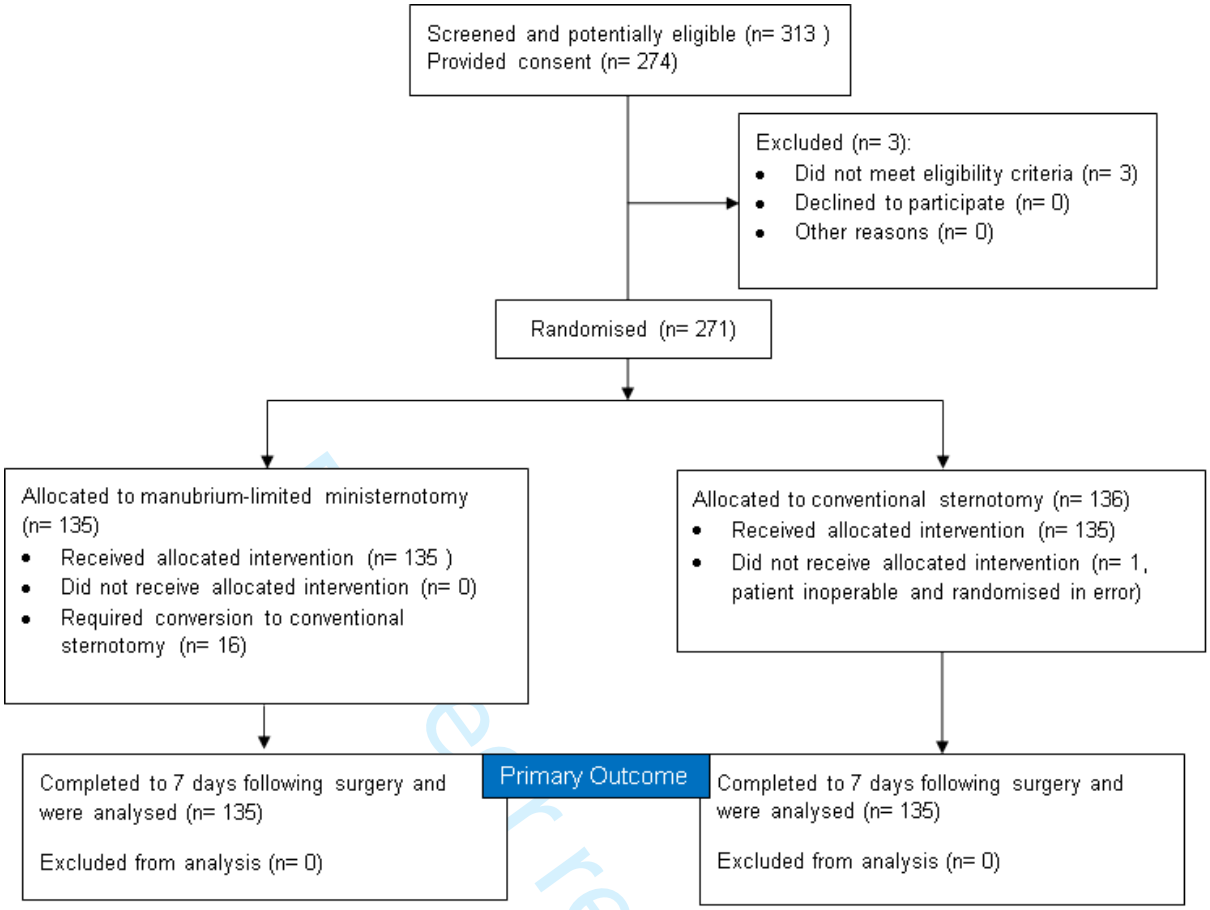
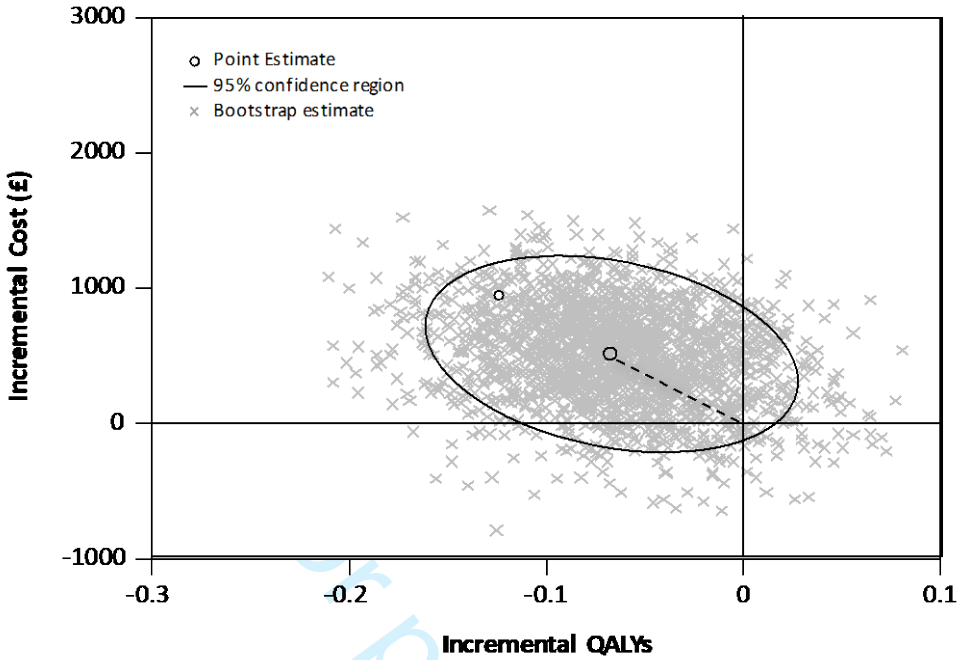
Figure 1. CONSORT Diagram. Flow of participants through trial.

Figure 2. Cost-effectiveness plane, cost/QALY (£): mini-sternotomy versus conventional surgery.





Supplementary Material

Study Investigators: trial site, trials unit, statistics, health economics, committees

Trial Site
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Research Team
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Investigator
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Committees
Data Monitoring Committee Membership
- Mr Graham Cooper (Chair)
- Mr Heyman Luckraz
- Professor Chris Rogers

Trial Steering Committee Membership
- Mr Sukumaran Nair (Chair until Sep 2014)
- Professor Gavin Murphy (Acting Chair Oct 2014 to June 2015)
- Mr Peter Braidley (Chair, from July 2015)
- Mr Paul Modi
- Mr Brendan Ellis

Table 1. Eligibility criteria

Inclusion Criteria

- Aged 18 years or older at the time of consent
- Requiring first-time, non-emergency, isolated Aortic Valve Replacement surgery
- Able and willing to provide written informed consent

Exclusion Criteria

- requiring concomitant cardiac procedure(s) including redo surgery, emergency or salvage surgery,
- only conventional median sternotomy indicated*,
- haemoglobin level < 90g/L,
- pregnant**,
- currently participating in another interventional clinical trial,
- previous cardiac surgery,
- are unable to stop currently prescribed treatment affecting clotting (e·g·, heparin, warfarin), ***
- a history of thrombophilia, thrombocytopenia or other haematological conditions that would affect participation in the trial as determined by one of the three operating surgeons,
- infective endocarditis,
- prevented from having red blood cells and blood products according to a system of beliefs (e·g· Jehovah's Witnesses),
- having any other medical, psychiatric and or social reason as determined by the consenting surgeon that precludes participation.

* patients were excluded if only conventional median sternotomy was indicated, for example in the presence of significant skeletal abnormalities like kyphosis. They were also excluded if transoesophageal echocardiography could not be performed, as this was mandatory to perform safe peripheral venous cannulation. All 3 surgeons used consistent criteria.

** in women of child bearing age (18 – 50) a pregnancy test was be performed within 14 days of surgery prior to randomisation.

***for patients in both trial arms, pre-operative antiplatelet drugs (including clopidogrel and ticagrelor), and anti-coagulants (including warfarin and heparin) were discontinued 5 days prior to surgery. These drugs were re-started following surgery at the discretion of the clinical team· The exception to this was aspirin, which was stopped 5 days prior to surgery where possible, however continuation until the day of surgery did not exclude a patient from the trial.

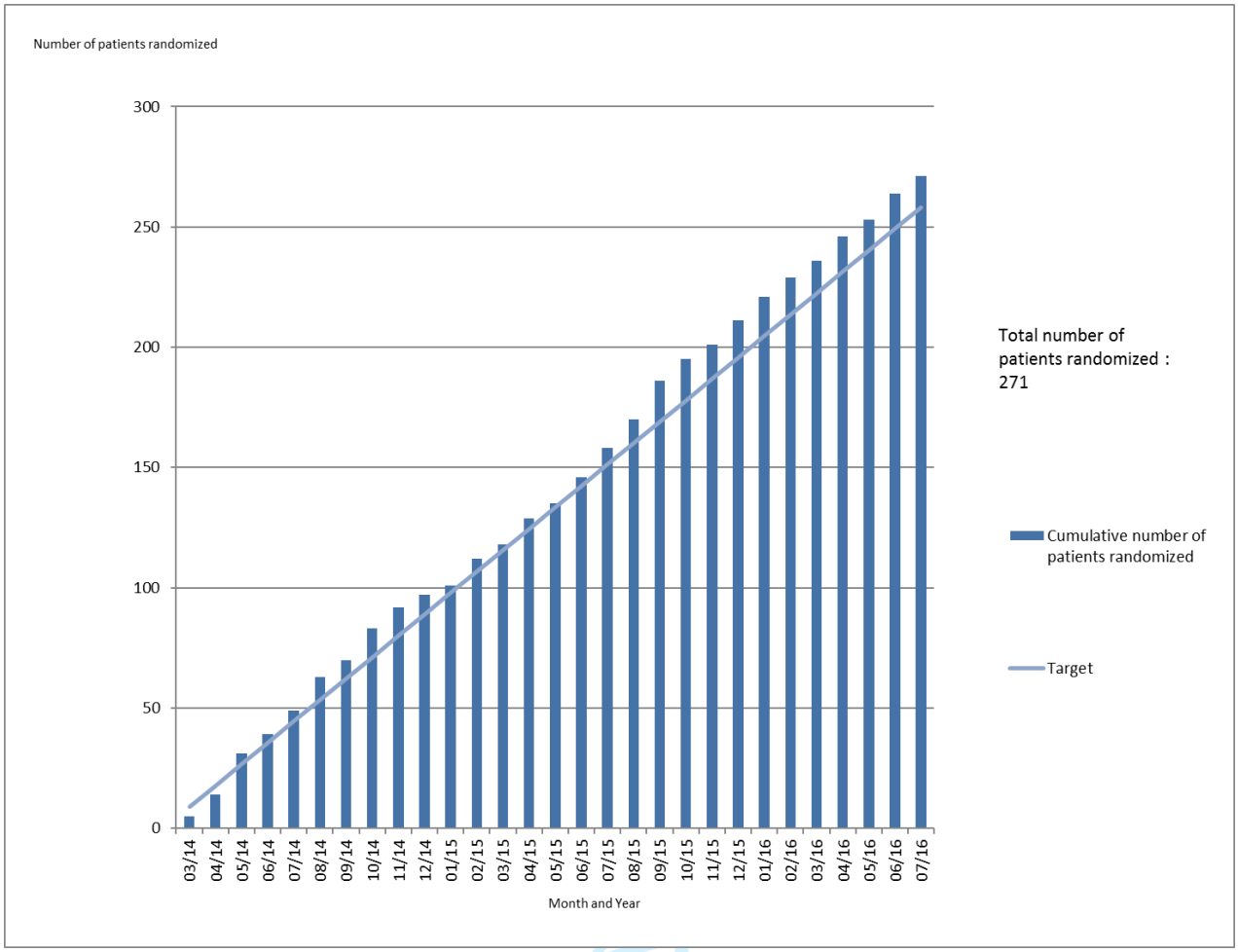

Figure 1. Trial recruitment by month.

Table 2. Conversion from mini-sternotomy to conventional sternotomy

Reason for conversion	Number of patients	Details
Anaesthetic emergency	**2**	• Patient became unstable as they were transferred into theatre and BP dropped – required conventional to re-stabilise • Anaphylactic reaction on induction needing CPR· Operation cancelled, patient taken to ITU· Widespread rash· Decision made the following morning to proceed to AVR (via full sternotomy)
Difficult vascular access (venous or arterial)	**9**	Venous • Femoral vessels unsuitable for cannulation • Poor venous drainage • Unable to pass venous dilators • Unable to insert pipe· Resistance felt, no back flow of blood· Femoral cannulation abandoned • Impossible to dilate femoral vein· Despite re-wiring, guide wire coiling within pelvic venous system Arterial • Difficulties cannulating femoral artery leading to haemodynamic instability • Poor access, unable to clamp aorta • Severe calcification of ascending aorta • Difficult access; aorta displaced to the left· Body habitus limited access
Intra-operative complications	**5**	• Bleeding from aortotomy site • Bleeding • Intra-operative decision to performed bypass graft to LAD • Post implant TOE showed small paravalvular leak and bleeding from aortotomy incision • Mild/moderate paravalvar leak on TOE· Required valve re-implant
TOTAL	**16**	

Table 3. Number of operations performed by Consultant Surgeon

	Mini-sternotomy group n=patients (%)	Conventional sternotomy group n=patients (%)	Total n=patients (%)
Consultant Surgeon A	58 (43·0)	58 (43··0)	116 (43·0)
Consultant Surgeon B	43 (31·9)	35 (25·9)	78 (28·9)
Consultant Surgeon C	34 (25·1)	42 (31·1)	76 (28·1)

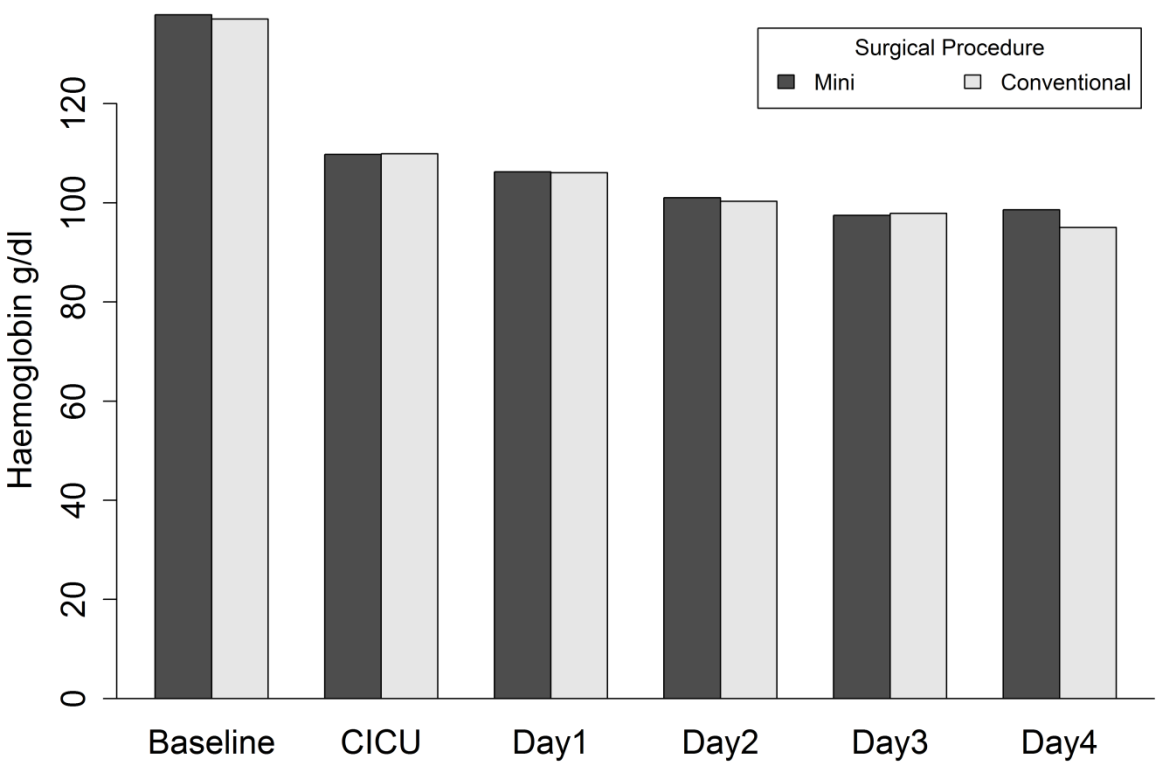

Figure 2. Haemoglobin profiles at Baseline, during CICU stay, and day 1 to day 4 post index surgery, by group

Table 4. Analgesic use and pain scores

Medication	Mini-sternotomy Group (135 patients) n = patients (%)	Conventional Sternotomy Group (135 patients) n = patients (%)	Total (270 patients) n = patients (%)
Analgesic use at baseline			
Buprenorphine patch	3 (2·2)	1 (0·7)	4 (1·5)
Codeine Phosphate	4 (3·0)	3 (0·7)	7 (2·6)
Dihydrocodeine Tartrate	0 (0·0)	1 (0·7)	1 (0·4)
Durogesic patch	0	1 (0·7)	1 (0·4)
Fentanyl	1 (0·7)	0 (0·0)	1 (0·4)
Gabapentin	1 (0·7)	0 (0·0)	1 (0·4)
Morphine Sulfate	0·0	1 (0·7)	1 (0·4)
Naxoproxen	1 (0·7)	0 (0·0)	1 (0·4)
Paracetamol	13 (9·6)	8 (5·9)	21 (7·8)
Tramadol Hydrochloride	0 (0·0)	2 (1·5)	2 (0·7)
At least one med at baseline	**16 (11·9)**	**12 (8·9)**	**28 (10·4)**
Analgesic use at day 2			
Buprenorphine patch	1 (0·7)	0 (0·0)	1 (0·4)
Codeine Phosphate	18 (13·3)	16 (11·9)	34 (12·6)
Dihydrocodeine Tartrate	4 (3·0)	6 (4·4)	10 (3·7)
Fentanyl	1 (0·7)	0 (0·0)	1 (0·4)
Gabapentin	1 (0·7)	0 (0·0)	1 (0·4)
Morphine Sulfate	13 (9·6)	13 (9·6)	26 (9·6)
Oramorph	1 (0·7)	1 (0·7)	2 (0·7)
Paracetamol	94 (69·6)	80 (59·3)	174 (64·4)
Pregabalin	1 (0·7)	0 (0·0)	1 (0·1)
Tramadol Hydrochloride	7 (5·2)	5 (3·7)	12 (4·4)
At least one med at day 2	**99 (73·3)**	**86 (63·7)**	**185 (68·5)**
Analgesic use at day 3			
Buprenorphine patch	1 (0·7)	0(0·0)	1 (0·4)
Codeine Phosphate	14 (10·4)	21 (15·6)	35 (13·0)
Dihydrocodeine Tartrate	4 (3·0)	7 (5·2)	11 (4·1)
Fentanyl	0 (0·0)	1 (0·7)	1 (0·4)
Gabapentin	1 (0·7)	1 (0·7)	2 (0·7)
Ibuprofen	0	1 (0·7)	1 (0·4)
Morphine Sulfate	6 (4·4)	1 (0·7)	7 (2·6)
Nefopam Hydrochloride	0	1 (0·7)	1 (0·4)
Oramorph	0	3 (2·2)	3 (1·1)
Paracetamol	89 (65·9)	99 (73·3)	188 (69·6)
Pregabalin	1 (0·7)	0 (0·0)	1 (0·4)
Tramadol Hydrochloride	8 (5·9)	3 (2·2)	11 (4·1)
At least one med at day 3	**90 (66·7)**	**101 (74·8)**	**191 (70·7)**
Analgesic use at Day 4			
Buprenorphine patch	1 (0·7)	0 (0·0)	1 (0·4)
Codeine Phosphate	15 (11·1)	15 (11·1)	30 (11·1)
Dihydrocodeine Tartrate	4 (3·0)	9 (6·7)	13 (4·8)
Fentanyl	1 (0·7)	1 (0·7)	2 (0·7)
Gabapentin	1 (0·7)	1 (0·7)	2 (0·7)
Ibuprofen	0 (0·0)	1 (0·7)	1 (0·4)
Paracetamol	86 (63·7)	75 (55·6)	161 (59·6)
Morphine Sulfate	1 (0·7)	2 (1·5)	3 (1·1)
Pregabalin	1 (0·7)	0 (0·0)	1 (0·4)
Tramadol Hydrochloride	3 (2·2)	3 (2·2)	6 (2·2)
At least one med at day 4	**88 (65·2)**	**81 (60·0)**	**169 (62·6)**
Analgesic use at Week 6			
Buprenorphine Patch	3(2·2)	0(0·0)	3(1·1)
Codeine Phosphate	7(5·1)	5(3·7)	12(4·5)
Dihydrocodeine Tartrate	1(0·7)	3(2·2)	4(1·5)
Fentanyl	1(0·7)	0(0·0)	1(0·4)
Gabapentin	2(1·5)	1(0·7)	3(1·1)
Ibuprofen	0(0·0)	1(0·7)	1(0·4)
Morphine Sulfate	0(0·0)	1(0·7)	1(0·4)
Paracetamol	35(25·9)	38(28·1)	73(27·0)
Pregabalin	1(0·7)	0(0·0)	1(0·4)
Tramadol Hydrochloride	2(1·5)	2(1·5)	4(1·5)
At least one med at week 6	**41(30·4)**	**41(30·4)**	**82(30·4)**
Analgesic use at Week 12			
Buprenorphine Patch	3(2·2)	0(0·0)	3(1·1)
Codeine Phosphate	7(5·2)	4(3·0)	11(4·1)

Dihyrocodeine Tartrate	0(0·0)	1(0·7)	1(0·4)
Gabapentin	2(1·5)	0(0·0)	2(0·7)
Ibuprofen	1(0·7)	0(0·0)	1(0·4)
Morphine Sulfate	1(0·7)	1(0·7)	2(0·7)
Naproxen	1(0·7)	0(0·0)	1(0·4)
Paracetamol	19(14·1)	20(14·8)	39(14·4)
Tramadol Hydrochloride	1(0·7)	1(0·7)	2(0·7)
At least one med at week 12	**23(17·0)**	**22(16·3)**	**45(16·7)**

	Mini-sternotomy Group (n=135 patients)	**Conventional sternotomy group (n=135)**
Baseline pain score		
n	128*	130*
Mean± SD	1·3 ± 2·1	0·9 ± 1·9
(min-max)	0 - 10	0 - 8
Day 2 pain score**		
n	123*	126*
Mean± SD	3·4 ± 2·4	3·7 ± 2·7
(min-max)	0 - 10	0 - 10
Day 3 pain score		
n	120*	129*
Mean± SD	2·8 ± 2·5	2·7 ± 2·3
(min-max)	0 - 9	0 - 8
Day 4 pain score		
n	116*	120*
Mean± SD	2·5 ± 2·2	2·1 ± 2·3
(min-max)	0 - 8	0 - 10
6 week pain score		
n	112*	118*
Mean± SD	1·5 ± 1·9	1·2 ± 1·8
(min-max)	0 - 8	0 - 8
12 week pain score		
n	128*	122*
Mean± SD	1·1 ± 1·9	1·0 ± 1·7
(min-max)	0 - 8	0 – 6

*Pain scores were assessed wherever possible
**Assessment on Day 2 was conducted with the patient blinded to their surgical allocation

Table 5. Adverse Events

Adverse Event	Mini-sternotomy Group n = patients (%)	Conventional Sternotomy Group n = patients (%)	Total n = patients (%)
Death			
In hospital	0/135 (0·0)	0/135 (0·0)	0/270 (0·0)
12 weeks	2/135 (1·5)	2/135 (1·5)	4/270 (1·5)
Stroke			
In hospital	3/135 (3·0)	1/135 (0·7)	4/270 (1·5)
12 weeks	4/135 (3·0)	1/135 (0·7)	5/270 (1·9)
Transient Ischaemic Attack			
In hospital	0/135 (0·0)	1/135 (0·7)	1/270 (0·4)
12 weeks	3/135 (2·2)	1/135 (0·7)	4/270 (1·5)
Renal failure			
In hospital	4/135 (2·3)	0/135 (0·0)	4/270 (1·5)
12 weeks	4/135 (2·3)	1/135 (0·7)	5/270 (1·9)
Atrial Arrhythmias			
In hospital	51/135 (37·8)	42/135 (31·1)	93/270 (34·4)
12 weeks	61/135 (45·2)	51/135 (37·8)	112/270 (41·5)
Ventricular Arrhythmias			
In hospital	2/135 (1·5)	2/135 (1·5)	4/270 (1·5)
12 weeks	2/135 (1·5)	2/135 (1·5)	4/270 (1·5)
Pericardial Effusion			
In hospital	4/135 (2·3)	1/135 (0·7)	5/270 (1·9)
12 weeks	9/135 (6·7)	6/135 (4·4)	15/270 (5·6)
Pulmonary Embolism			
In hospital	0/135 (0·0)	0/135 (0·0)	0/270 (0·0)
12 weeks	0/135 (0·0)	2/135 (1·5)	2/270 (0·7)
Chest Infection			
In hospital	7/135 (5·2)	10/135 (7·4)	17/270 (6·3)
12 weeks	18/135 (13·3)	26/135 (19·3)	44/270 (16·3)
Sternal wound infection			
In hospital	3/135 (2·2)	1/135 (0·7)	4/270 (1·5)
12 weeks	11/135 (8·1)	3/135 (2·2)	14/270 (5·2)
Re-operation for bleeding	3/135 (2·2)	5/135 (3·7)	8/270 (3·0)

Table 6. Health status, resource use and cost (complete cases)

	Conventional [C]			Mini-sternotomy [M]			[M]-[C][1]	
	mean	(SD)	N	mean	(SD)	N	mean	(95%CI)
Health status[2]								
EQ-5D Baseline	0·764	0·245	130	0·763	0·235	128	-0·001	(-0·060 to 0·057)
EQ-5D 2 days	0·349	0·349	133	0·353	0·291	128	0·004	(-0·074 to 0·082)
EQ-5D 6 weeks	0·798	0·194	118	0·751	0·221	112	-0·048	(-0·101 to 0·006)
EQ-5D 12 weeks	0·838	0·207	124	0·782	0·248	127	-0·056	(-0·112 to 0·001)
EQ-5D AUC (0-12 weeks)	0·162	0·041	105	0·153	0·040	98	-0·009	(-0·020 to 0·002)
Resource use								
Index Admission								
Length of stay (d)[3]	8·26	4·28	135	9·29	7·88	135	1·03	(-0·48 to 2·54)
CICU (d)	1·21	0·99	135	1·61	5·52	135	0·39	(-0·55 to 1·34)
HDU (d)	1·27	1·52	135	1·60	1·75	135	0·33	(-0·07 to 0·72)
Cardiac ward (d)	5·67	3·52	135	5·70	3·18	135	0·03	(-0·77 to 0·83)
Stroke ward (d)	0·03	0·34	135	0·11	1·00	135	0·08	(-0·10 to 0·26)
Time in first surgery (h)	2·24	0·51	135	2·98	0·69	135	0·74	(0·60 to 0·89)
Time in further surgery (h)[4]	0·08	0·34	135	0·03	0·17	135	-0·05	(-0·11 to 0·02)
Time in surgery (h)[4]	2·32	0·63	135	3·01	0·71	135	0·69	(0·53 to 0·85)
RBC (u)[4]	0·59	1·45	135	0·55	1·28	135	-0·04	(-0·37 to 0·28)
FFP (u)[4]	0·57	1·43	135	0·34	1·21	135	-0·23	(-0·55 to 0·09)
Platelets (u)[4]	0·22	0·64	135	0·12	0·46	135	-0·10	(-0·24 to 0·03)
Cryoprecipitate (u)[4]	0·01	0·09	135	0·00	0·00	135	-0·01	(-0·02 to 0·01)
Post discharge contacts								
GP surgery	1·47	1·52	129	1·40	1·32	131	-0·07	(-0·41 to 0·28)
GP home	0·09	0·32	129	0·19	0·56	131	0·10	(-0·01 to 0·21)
GP telephone	0·12	0·45	129	0·15	0·63	131	0·03	(-0·10 to 0·16)
Nurse surgery	1·38	2·56	129	2·07	3·54	131	0·69	(-0·06 to 1·44)
Nurse home	0·43	1·30	129	0·56	1·87	131	0·12	(-0·27 to 0·51)
Nurse telephone	0·05	0·25	129	0·04	0·26	131	-0·01	(-0·07 to 0·05)
Outpatient hospital	0·40	0·78	129	0·57	1·98	131	0·17	(-0·20 to 0·53)
Inpatient hospital	0·30	0·68	129	0·27	0·60	131	-0·03	(-0·18 to 0·13)
Inpatient hospital (d)	2·09	7·79	129	1·09	2·69	131	-1·00	(-2·42 to 0·42)
Total Contacts	4·29	3·53	129	5·47	4·90	131	1·18	(0·14 to 2·22)
Cost[5]								
Cost of index admission	7674	2055	135	8815	4517	135	1140	(303 to 1977)
Cost post discharge	824	2485	129	547	925	131	-277	(-734 to 180)
Cost	8527	3558	129	9274	4542	131	746	(-245 to 1737)

1 OLS regression-estimated means and 95% confidence intervals
2 EQ-5D-3L index score
3 Length stay by ward does not sum to length of stay due to theatre and transit time, and rounding
4 Item includes index and post-discharge usage
5 Resource items were costed using national reference costs except for the index procedures which were costed by South Tees Hospitals NHS Foundation Trust

Table 7. ICU Length of Stay, Fitness for Discharge and Hospital Length of Stay

	Mini-sternotomy group (n=135)	Conventional sternotomy group (n=135)
ICU stay (days)		
n	135	135
Mean ± SD	1·9 ± 5·8	1·3 ± 1·1
Min-Max	0 - 64*	0 - 7
Fitness for discharge (days)		
n	129**	133**
Mean ± SD	6·5 ± 3·7	6·3 ± 3·2
Min - Max	3 - 36	3 - 31
Post-operative length of stay (days)		
n	135	135
Mean ± SD	7·4 ± 7·5	6·3 ± 3·1
Min - Max	3 - 79	3 - 31

*3 patients in the mini-sternotomy group were in ICU for more than 7 days· Excluding these patients, the range would have been 0-5 days for the mini-sternotomy group.

**Fitness for discharge was assessed by the surgical and physiotherapy teams. For 6 patients in the mini-sternotomy group and 2 patients in the conventional sternotomy group this was not possible due staff availability at the point of discharge.

Table 8. Pulmonary Function Tests

		Mini-sternotomy group (n=135)	Conventional sternotomy group (n=135)	Mean Difference (95% CI; p value)
FEV1				
Baseline				
	n	123*	123*	
	Mean ± SD	2196·2 ± 712·2	2207·7 ± 748·2	-15·4 (-169·2,138·4)
	Min - Max	1000- 4340	1020-4090	
Day 4				
	n	105*	110*	
	Mean ± SD	1122·6 ± 433·0	1320·7 ± 523·5	-171·3** (-265·3,-77·2; p=0·0004)
	Min - Max	99-2400	76-2910	
6 weeks				
	n	106*	97*	
	Mean ± SD	1962·0 ± 468·7	2018·1 ± 662·8	-7·3** (-104·3,89·6)
	Min - Max	650-3570	870-3570	
FVC				
Baseline				
	n	123*	123*	
	Mean ± SD	2908·5 ± 926·4	2929·2 ± 955·7	-31·6 (-238·8,175·7)
	Min - Max	1250-6060	1200-5650	
Day 4				
	n	105*	110*	
	Mean ± SD	1478·9 ± 583·3	1697·5 ± 706·8	-129·7** (-259·2,-0·1; p=0·0498)
	Min - Max	139-2910	109-3920	
6 weeks				
	n	106*	97*	
	Mean ± SD	2529·4 ± 824·0	2615·9 ± 864·0	-36·0** (-173·2,101·2)
	Min - Max	1180-4760	1000-4840	

*It was not possible for all patients to complete pulmonary function tests
**After adjusting for randomisation factors and baseline data

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	3,5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	3,4,5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	4 (+appendix)
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	4,5
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	7
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	2,4
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	2,4

Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	2,4
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	4
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	2,4,5
	11b	If relevant, description of the similarity of interventions	4
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	7
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	9
	13b	For each group, losses and exclusions after randomisation, together with reasons	9,17
Recruitment	14a	Dates defining the periods of recruitment and follow-up	9
	14b	Why the trial ended or was stopped	9
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Tables
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	9, Tables
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Tables
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	12
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	11
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	13,14

Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	13,14
Other information			
Registration	23	Registration number and name of trial registry	1,4
Protocol	24	Where the full trial protocol can be accessed, if available	4
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	4, 15

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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Mini-sternotomy versus conventional sternotomy for aortic valve replacement: a randomised controlled trial

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Title

Mini-sternotomy versus conventional sternotomy for aortic valve replacement: a randomised controlled trial

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Abstract

Objective

To compare clinical and health economic outcomes after manubrium-limited mini-sternotomy (intervention) and conventional median sternotomy (usual care)

Design

A single blind, randomised controlled trial.

Setting

Single centre UK National Health Service tertiary hospital

Participants

Adult patients undergoing aortic valve replacement surgery

Interventions

Intervention was manubrium-limited mini-sternotomy performed using a 5-7cm midline incision. Usual care was median sternotomy performed using a midline incision from the sternal notch to the xiphisternum.

Primary and secondary outcome measures

The primary outcome was the proportion of patients who received a red cell transfusion post-operatively and within 7 days of index surgery. Secondary outcomes included proportion of patients receiving a non-red cell blood component transfusion and number of units transfused within 7 days and during index hospital stay, quality of life and cost effectiveness analyses.

Results

270 patients were randomised, received surgery and contributed to the intention to treat analysis. No difference between mini and conventional sternotomy in red-cell transfusion within 7 days was found; 23/135 patients in each arm received a transfusion, odds ratio 1·0 (95% CI: 0·5, 2·0) and risk difference 0·0 (95% CI: -0·1, 0·1). Mini-sternotomy reduced chest drain losses (mean 181·6ml (SD

138·7) vs conventional, mean 306·9ml (SD 348·6)); this did not reduce red-cell transfusions. Mean valve size and post-operative valve function were comparable between mini-sternotomy and conventional groups; 23mm vs 24mm, and 6/134 moderate or severe aortic regurgitation vs 3/130, respectively. Mini-sternotomy resulted in longer bypass (82·7 minutes (SD 23·5) vs 59·6 minutes (SD 15·1)) and cross clamp times (64·1 minutes (SD 17·1) vs 46·3 minutes (SD 10·7)). Conventional sternotomy was more cost-effective with only a 5·8% probability of mini-sternotomy being cost-effective at a willingness to pay of £20,000/QALY.

Conclusions

AVR via mini-sternotomy did not reduce red blood cell transfusion within 7 days following surgery when compared to conventional sternotomy.

Clinical Trials Registry: ISRCTN29567910

Key word: minimally invasive, aortic valve, clinical trial, cardiac surgery, replacement,

ARTICLE SUMMARY

1. Large proportion of eligible patients recruited, and all patient randomised contributed to the primary outcome
2. Clear protocols for transfusion of blood and blood products with high adherence throughout the trial
3. Patients were blinded to group allocation until two days following index surgery, reducing the likelihood of bias.
4. First randomised trial to perform detailed health economic evaluation of minimally invasive versus conventional sternotomy
5. The trial was undertaken by three experienced minimally invasive surgeons who were expert at both techniques.

Objectives

Aortic valve replacement (AVR) for severe symptomatic valvular disease is one of the most common cardiac surgical procedures performed worldwide. The current joint guidelines of the American College of Cardiology and American Heart Association (ACC/AHA) and the current European Society of Cardiology guidelines for the management of aortic valve disease, state that surgical AVR is recommended for symptomatic patients with severe aortic stenosis and asymptomatic patients with severe aortic stenosis who meet an indication for AVR when surgical risk is low or intermediate.[1]

In the UK, the National adult cardiac cardiac surgery audit published by NICOR (National Institute for Cardiac Outcome Reporting) reported 13,027 procedures for aotic valve disease in the UK from April 2018 to March 2019.[2] Outcomes are generally excellent with in-hospital observed mortality in the UK of 1·5% for first time elective procedures.[3] In low risk patients with a Euroscore 2 of less than 4, a mortality of less than 0.7% was observed in over 15,000 patients undergoing AVR surgery in the UK between 2016 and 2019.[2]

These results are not observed in all patients; in high risk groups, conventional surgery risks perioperative organ injury and prolonged recovery, with death in up to 31% of patients within 1 year.[4] Minimally invasive surgery combines the durability of surgical repair with reductions in surgical trauma that should reduce perioperative morbidity. Observational analyses demonstrating reductions in morbidity and resource use[5,6] may be confounded by multiple sources of bias and are at odds with limited evidence from RCTs that have not shown improved outcomes.[7] This uncertainty is reflected by variations in uptake internationally.[8,9,10]

The move towards minimally invasive surgery is also driven by patient perceptions of pain reduction and rapid recovery. However, minimally invasive cardiac surgery is not without risks; limiting access to the heart can result in technically sub-optimal surgery, including concern about the size of the prosthesis that can be inserted, and paravalvular leak rates.

This trial evaluated Manubrium-limited Mini-sternotomy versus Conventional Sternotomy for Aortic Valve Replacement (MAVRIC). We hypothesised that mini-sternotomy would reduce red cell

transfusion rates, a contemporary marker of surgical trauma and indicator of adverse outcomes;[11] this has been contested,[12] though the evidence is not conclusive.[13] An embedded cost effectiveness analysis evaluated whether the intervention was cost effective in a UK National Health Service (NHS) setting.

Patients and Methods

Trial Design

MAVRIC was a single centre, single-blind, RCT comparing AVR via manubrium-limited mini-sternotomy group (intervention) and AVR via conventional sternotomy group (usual care). A NHS Research Ethics Committee approved the trial, which was conducted in accordance with the principles of the International Conference on Harmonisation of Good Clinical Practice.[14] South Tees Hospitals NHS Foundation Trust was the Sponsor and recruiting centre.

Patient Public Involvement

In designing the study, we asked patients their view on what factors may affect whether they took part in the study. This was done in an outpatient setting and via a postal questionnaire. They felt expertise was important. Most patients felt that although the cosmetic benefit of the minimally invasive approach was appealing, they expected some clinical benefit form minimally invasive surgery as well. Importantly most patients said they would accept being blind to the type of surgery they had received for 48 hours after the procedure.

Participants

Patients were eligible if they were aged 18 years or over; required first-time, non-emergency, isolated AVR surgery; and were willing to provide written informed consent. Full details of the eligibility criteria are in the **Supplementary Material**.

Randomisation

Eligible patients were randomised by members of the research team using a 24-hour, central, secure, web-based randomisation system with concealed allocation, managed by the Clinical Trials

Unit; randomisation was in a 1:1 ratio between mini and conventional sternotomy and stratified by baseline logistic EuroSCORE and pre-operative Hemoglobin (Hb).

Interventions

Manubrium-limited mini-sternotomy was performed using a 5-7cm midline skin incision dividing the manubrium from the sternal notch to 1cm below the manubrium-sternal junction. Cardiopulmonary bypass was established with an ascending aortic cannula and percutaneous femoral venous cannulation. Conventional median sternotomy was performed using a midline incision from the sternal notch to the xiphisternum. Key aspects of anaesthesia were standardised, and are detailed in the protocol.[15]

Blinding

All patients were blinded to type of sternotomy received until after their day 2 Quality of Life and pain assessments. All patients had trial-specific opaque dressings applied to their sternal wound, and groin before leaving theatre.

Transfusion Protocol

The post-operative period, and trial protocol in relation to red cell and non-red cell transfusion, began on admission to the Cardiothoracic Intensive Care Unit (CICU); it specified that patient's should receive a red cell transfusion if their Hb dropped below 80 g/L; or were bleeding by 400ml/h or more, or were bleeding 100ml/h or more for 4 or more hours with a Hb equal to or greater than 80g/L; or had blood loss with haemodynamic instability irrespective of thromboelastography (TEG) and/or clotting profile results. One unit of red cells was transfused and Hb level checked before transfusing another unit.

Participants received a non-red cell transfusion if both of the following criteria were met: bleeding defined by 400ml/h or more, or blood loss of 100ml/h or more for 4 hours or more; TEG or coagulation guided transfusion indicated.

Outcomes

All outomes were measured from index surgery.

Primary Outcome

The primary outcome was the proportion of patients who received a red cell transfusion post-operatively and within 7 days of index surgery.

Secondary Outcomes:

- proportion of patients receiving a red cell transfusion and number of units transfused within 7 days and during index hospital stay;
- proportion of patients receiving a non-red cell blood component transfusion and number of units transfused within 7 days and during index hospital stay;
- volume in chest drains at 6 and 12 hours, and drain removal;
- degree of aortic regurgitation using echocardiogram within 6 weeks;
- re-operation rates;
- conversion to conventional AVR during surgery;
- changes in lung function at 4 days and 6 weeks;
- Quality of life EuroQol (EQ-5D-3L, EQ-VAS) at 2 days, 6 and 12 weeks;
- time patients are deemed 'fit for discharge';
- health care utilisation to 12 weeks;
- cost and cost effectiveness analyses;
- adverse events to 12 weeks.

Statistical Analysis

Audit data had indicated 30% of patients undergoing AVR via conventional sternotomy (15 of 50 patients) received a red cell transfusion compared with 13% of patients (8 of 60 patients)

undergoing AVR via mini-sternotomy. Using Fisher's Exact test, 90% power, 5% alpha, we estimated that 260 patients would be required to detect a 17% reduction in the proportion of patients requiring a red cell transfusion (13% compared with 30%), using a two-sided test. Allowing for loss to follow up, the sample size was increased to 270.

The primary analysis was based on intention-to-treat principles, in accordance with a pre-specified statistical analysis plan.

The primary efficacy analysis was based on a logistic regression model with only group (minimally invasive and conventional) and stratifying factors (baseline logistic EuroSCORE and Hb) as the predictors. Odds ratios and their associated 95% confidence interval are reported in the primary analysis. Sensitivity analysis using alternating logistic regression was performed for the primary endpoint to sensitise for surgeon effects; the odds of receiving a red cell transfusion for two patients treated by the same surgeon was compared to two patients treated by different surgeons.

All analyses of secondary continuous efficacy endpoints at single time points were based on linear models where, if appropriate, a log normal model was fitted to sensitise the linearity assumption. Longitudinal analysis was performed for all endpoints with repeated data over time to investigate changes in trends over the trial period. The trial period was defined as baseline, up to 7 days (post-operative period), 6 week follow-up and 12 week follow-up. All analyses of binary endpoints at a single time point were based on logistic regression. Generalised estimating equation was used to analyse repeated binary data per patient to account for intra-patient correlation.

Further exploratory analysis was conducted to investigate the association between the treatment group and other clinical factors. All analyses were performed using R 3·3·3 (The R Foundation) and SAS 9·4 (SAS Institute Inc).

Economic Evaluation

A prospective economic evaluation applying a NHS perspective, following National Institute for Health and Care Excellence (NICE) reference case guidance,[16] was employed. Health care utilisation

was captured up to three months following discharge from index surgery. Resource use was valued in 2016 pounds sterling using national sources,[17,18] and where necessary, local micro-costing (£1=$1·50). Resources included surgery, transfusions, length of hospital stay (by level of care), complications and further surgery, and community care following discharge.

Mechanisms of missingness within the data were explored and multiple imputation methods were applied to impute missing data and minimise bias, using chained equations and predictive mean matching. Imputation sets were analysed within a bivariate analysis of costs and QALYS, to generate incremental within-trial cost per QALY estimates and credible intervals. Findings were presented on the ICER plane and with Cost-Effectiveness Acceptability Curves, using the net monetary benefit approach.

Imputation was conducted according to good practice guidance.[19,20] Multiple imputation provides unbiased estimates of treatment effect if data are missing at random (MAR) and the missingness process is adequately characterised : this assumption was explored in the data, for example by using logistic regression for missingness of costs and QALYs against baseline variables.[21] A regression model was used to generate multiple imputed datasets (or 'draws') for individual treatment groups, where missing values were predicted drawing on predictive covariates. Outcome measures and costs (at each time point) contributed as predictors and imputed variables. Each draw provided a complete dataset, reflecting the distributions and correlations between variables. Predictive mean matching drawn from the five nearest neighbours (knn=5) was used to enhance the plausibility and robustness of imputed values; normality was not assumed. The imputation model used fully conditional (MCMC) methods. Draws were analysed using bivariate regression (see below) within the Stata MI framework, capturing within and between variances for imputed samples.[22] After examining the fraction of missing information (FMI) from finite imputation sampling, 20 draws was taken in the final imputation model.

Results

Trial Population

MAVRIC recruited to time and target; 313 patients were considered for the trial; 274 patients consented between 20th March 2014 and 25th July 2016. The analysis population was 270 eligible patients; 135 allocated to the AVR via mini-sternotomy group and 135 allocated to the AVR via conventional sternotomy group (**Figure 1.**).

All 270 patients underwent surgery. Sixteen patients required cross-over from minimally-invasive to a conventional sternotomy due to anaesthetic emergency (n=2), difficulties due to vascular access (n=9), and intra-operative complications (n=5); further details and the number of operations performed by surgeon are in the Supplementary Material.

Baseline characteristics were similar between groups (**Table 1**).

Primary Outcome

There was no difference between groups in relation to the primary outcome (**Table 2**). The proportion of patients receiving a red cell transfusion was 23 of 135 in both groups, Odds ratio 1·0 (95% CI 0·5, 2·0; p=0·9052) and risk difference of 0·0 (95% CI -0·1, 0·1; p=0·9999).

Secondary Outcomes

Red cell and non-red cell transfusion

There was no significant difference between groups with respect to any red cell transfusion at discharge (**Table 2**). There was no difference between groups in Hb from baseline to 4 days following index surgery (**Supplementary Material**). There was a statistically significant difference in the proportion of patients receiving any non-red cell transfusion within 7 days of surgery; mini 6/135 versus conventional 18/135, Odds ratio: 0·3 (95% CI 0·1, 0·8; p=0·0137) (**Table 3**).

Cross clamp time and cardiopulmonary bypass time

Mini-sternotomy resulted in longer Cardio Pulmonary Bypass times; mini group 82·7 minutes (SD 23·5), conventional 59·6 minutes (SD 15·1). Aortic cross clamp times were also longer; mini group 64·1 minutes (SD 17·1), conventional 46·3 minutes (SD 10·7) (**Table 4**).

Chest drain losses

Mini-sternotomy resulted in a 40·8% reduction in chest drain losses at 12 hours, the mini group mean was 181·6ml (SD 138·7), conventional group mean was 306·9ml (SD 348·6); the mean difference was -127·7ml (95% CI -191·7, -63·8, p=0.0001). At drain removal mean difference was -145·3ml (95% CI -218·1, -72·3; p=0.0001) (**Table 4**).

Ventilation time

Ventilation time between the groups was similar; 9·6 hours (SD 5·6) in the mini group and 9·8 hours (SD 6·9) in the conventional (**Table 4**).

Intensive care unit length of stay

There was no difference in intensive care unit length of stay between groups (**Supplementary Material**).

Post-operative pain

There was no difference in pain scores between groups; analgesic use is also included to assist interpretation (**Supplementary Material**).

Lung function

There was no difference between groups in lung function at baseline. At 4 days post-surgery, mean Forced Expiratory Volume 1 (FEV1) 1123mls (SD 433) and Forced Vital Capacity, FVC 1479mls (SD 583) were significantly reduced in the mini group, compared to the conventional; FEV1 1321 (SD 524), FVC 1698 (SD 707). Mean differences for FEV1 and FVC were statistically significant at 4 days post-surgery; -171mls (95% CI -265, -77; p=0·0004) and -130mls (95% CI -269, 0; p=0·0498)

respectively, after adjusting for baseline FEV1, FVC, and randomisation factors (**Supplementary Material**).

Hospital length of stay

The mean time to patients being fit for hospital discharge following index surgery was similar between groups. The mean post-operative hospital length of stay was 7·4 (SD 7·5, range 3-79) in the mini group, and 6·3 days (SD 3·2, range 3-31) in the conventional (**Supplementary Material**).

Post-operative valve function

The distribution of valve types and valve sizes by group were similar; mean valve size inserted was 23mm in the mini group and 24mm in the conventional (**Table 5, Figure 2,3**). Over 70% of patients in each group received a tissue valve, over 25% received a mechanical valve and 2-3% received a sutureless tissue valve.

Post operative transthoracic echo showed a similar decrease in mean aortic valve gradient in both groups to 16mmHg; peak gradient decreased to 30mmHg in both groups (**Table 5**). 6/134 patients had moderate or severe aortic regurgitation in the mini group compared to 3/130 in the conventional (**Table 5**). Only 2 patients in the trial, 1 in each arm, suffered a paravalvular leak; both were severe. One of these patients, in the mini sternotomy arm had a sutureless valve prosthesis. 7 further patients had moderate regurgitation; these were all intravalvular leaks. Transoesophageal echo was performed in all patients prior to leaving the operating theatre.

Adverse events

There were no in-hospital deaths in either group. At 12 weeks follow up, there were 4 deaths; 2 in each arm of the study. Adverse events in each group were broadly similar and within acceptable clinical limits. By 12 weeks, 4/135 patients in the mini-sternotomy group and 1/135 in the conventional group had suffered a stroke (defined as a persistent neurological deficit). Atrial arrhythmias were identified in 61/135 patients in the mini group and 51/135 in the conventional. By

12 weeks, 11/135 patients in the mini group and 3/135 patients in the conventional had a sternal wound infection (**Supplementary Material**).

Quality of Life, Costs and Cost-Effectiveness

Costs during the index admission were significantly greater for the mini group (mini-conventional: mean difference £1140; 95% CI 303, 1977), primarily reflecting the additional cost of theatre time (**Supplementary Material**). Overall costs were not significantly different (mini-conventional: mean difference £746; 95% CI -245, 1737). There was no significant difference in quality of life between groups up to 12 weeks (mini-conventional: mean difference area under curve -0.009 QALYs; 95% CI 0.020, 0.002). Although differences in costs and quality-of-life were not individually significant, the bivariate cost-QALY distribution (combining these two) suggests conventional surgery might be more cost-effective (**Figure 4.**). In the base-case model, mini was dominated by conventional surgery (due to greater cost and less benefit), with only a 5.8% probability of being cost-effective at a willingness to pay of £20,000/QALY (**Table 6**).

Sensitivity and Subgroup Analyses

There was no significant surgeon effect; the odds of receiving a red cell transfusion for two patients treated by the same surgeon compared to two patients treated by different surgeons was 1·2 (95% CI 0·9, 1·6; p=0·1379).

Protocol deviations in respect of cell tranfusions did not affect the results of the primary analysis; excluding these patients produced the same results as those from the intention-to-treat analysis.

Discussion

Main findings

Mini-sternotomy was not superior to conventional sternotomy with respect to red cell transfusion requirements within 7 days of surgery. Analysis of secondary endpoints showed a statistically significant difference in transfusion volumes of non-red cell blood components. Aortic valve size and post-operative function were comparable in the 2 groups. Mini-sternotomy resulted in a relative

reduction in chest drain losses however, higher blood loss in the conventional group did not translate into red cell transfusions. Mini patients had substantially longer bypass and cross clamp times and worse lung function at 4 days post-surgery. Lung function at twelve weeks, and adverse event rates were otherwise not different between groups. Conventional sternotomy was found to be more cost-effective. MAVRIC findings contradict those from other trials that pre-date it.[23,24] Two 100 patient RCTs published since MAVRIC and the systematic review, do not alter the discussion.[25,26] Both found no difference in major clinical outcomes, and findings relating to shorter hospital stay in mini-sternotomy; a reduction in bleeding through chest drains, and mean difference in EQ-5D scores at baseline and at 6 weeks[25] are consistent with MAVRIC findings.

Strengths and limitations

This is the largest single trial to have compared minimally invasive sternotomy to conventional median sternotomy for AVR. A recent Cochrane review identified 511 patients from 7 previous RCTs.[7] In MAVRIC, the mini-sternotomy technique divided only the manubrium and is therefore less invasive than other minimally invasive techniques. The trial was undertaken by three experienced minimally invasive surgeons who were expert at both techniques. Patients were blinded to group allocation until two days following index surgery, reducing the likelihood of bias. The trial recruited a significant proportion of eligible patients; 274/313 (86%), with few requiring conversion to conventional sternotomy, increasing the likelihood that the trial findings are generalisable. A further strength was the detailed health economic evaluation; this has not been performed previously.

The trial had some limitations, including the single centre design. This will tend to have biased treatment effect estimates away from the null, which is at odds with our observed effect. There were no significant levels of protocol non-adherence, with no effect on the main trial finding. The event rate for the primary outcome, was much lower than expected at 17%; nationally red cell transfusion rates following valve surgery are 46·4%.[27] In our pre-trial audit conducted over 5 years , ending 2009, 30% of mini-sternotomy patients received a red cell transfusion. We attribute the

observed transfusion rate in MAVRIC to the restrictive red cell transfusion threshold applied; this followed evidence at the time of trial design. The consultant (expert) led nature of the trial interventions is also likely to have reduced the need for transfusions post-operatively and to have biased trial results towards the null.

Clinical importance

MAVRIC contributes important evidence to the minimally invasive AVR evidence base, summarised in a Cochrane review.[7] MAVRIC demonstrated longer cross-clamp and bypass times with the manubrium-limited mini-sternotomy, attributed to known differences between the interventions. Minimally-invasive techniques in MAVRIC required a number of surgical steps to be performed with the aortic clamp in place (drain insertion and pacing wire insertion for example), meaning cross-clamp and bypass were longer. This is not an absolute requirement in other minimally invasive approaches; for example, where the incision is extended into the body of the sternum, or where rapid deployment valves are used, there are no differences in cross clamp and bypass times.[7]

The size of MAVRIC and event rate prevents formal comparison of adverse events between the groups, of note is the difference in stroke rate; this would benefit from exploration in a future trial.

The cost-effectiveness plane indicates that conventional surgery is less costly and more beneficial than minimally-invasive surgery; contact with healthcare professionals was greater in the mini group, although there was no clear pattern of use. Wide confidence intervals mean that differences are imprecise. MAVRIC does not support the use of funds to expand AVR via manubrium-limited mini-sternotomy practice.

MAVRIC, the world's largest RCT at low risk of bias, found no additional clinical benefit, in terms of red blood cell transfusion rates of minimally invasive AVR. Results are in agreement with the findings of a Cochrane review of trials that have evaluated mini-sternotomy AVR.[7] This information should be disseminated to patients, clinicians and commissioners to inform decisions about AVR surgery including commissioning.

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Authors contributions

EA, HCH, RHM, and JM and GM designed the trial, and sought funding. EA, AG and WAO recruited patients to the trial and performed surgery. AK conducted the statistical analysis and JM conducted the health economic analysis. All authors contributed to the final manuscript.

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Data Sharing Statement

Anonymised data from this study may be available to the scientific community subject to appropriate ethical approval. Requests for data should be directed to the senior author.

Table 1. Baseline characteristics of participants by group

	Mini-sternotomy group (n=135)	Conventional sternotomy group (n=135)
Baseline characteristics		
Age: (years)		
Mean ± SD	69·3 ± 9·3	68·7 ± 8·4
Range	43 - 85	39 - 88
Gender: n (%)		
Male	78 (57·8)	87 (64·4)
Female	57 (42·2)	48 (35·6)
Ethnicity: n (%)		
White British	135 (100)	135 (100)
Body Mass Index (kg.m^{-2})		
Mean ± SD	30·5 ± 5·6	30·4 ± 6·1
Range (Min – Max)	19·0 - 45·4	19·3 - 52·0
EuroSCORE: Mean ± SD (Min-Max)		
Logistic	5·2 ± 3·5 (1·5 - 29·5)	5·1 ± 3·5 (1·5 - 21·0)
II – Mean	1·5 ± 1·1 (0·5 - 10·2)	1·5 ± 1·2 (0·5 - 10·0)
Diagnosis echocardiogram: n (%)		
Regurgitation	3 (2·2)	8 (5·9)
Stenosis	132 (97·8)	127 (94·1)
NYHA class: n (%)		
I	24 (17·8)	18 (13·3)
II	68 (50·4)	66 (48·9)
III	40 (29·6)	46 (34·1)
IV	3 (2·2)	5 (3·7)
***Haemoglobin prior to randomisation: g/dl**		
Mean ± SD	137·9 ± 14·3	137·1 ± 16·1
Range (Min – Max)	97 -173	90 -175
Surgery type: n (%)		
Elective	111 (82·2)	112 (82·6)
In-house urgent	24 (17·8)	23 (17·4)

*One patient had a baseline hemoglobin (Hb) of 95 g/L at randomisation, which had fallen to 83 immediately prior to surgery. This Hb drop was not identified until after surgery and the patient continued in the trial with their data included in the analyses based on the intention to treat principle.

Table 2. The number and proportion of patients receiving a Red Cell Transfusion*, and the number of units received, to 7 days and to discharge following index surgery, by group.

	Mini-sternotomy group	Conventional sternotomy group	Odds Ratio (95% CI; p value)	Risk difference (95% CI; p value)
Red Cell Transfusions				
Post-operatively to 7 days number of patients (%)	23/135 (17·0)	23/135 (17·0)	1·0 (0·5, 2·0; p=0·9052)	0·0 (-0·1, 0·1; p=0·9999)
Post-operatively to discharge number of patients (%)	34/135 (25·2)	29/135 (21·5)	1·4 (0·7, 2·7)	
Red Cell Units – post operatively to 7 days				
Number of patients	23/135	23/135		
Mean ± SD	1·6 ± 0·7	2·3 ± 1·7		
Range (Min – Max)	1 - 3	1 - 9		
Red Cell Units – post operatively to discharge				
Number of patients	34/135	29/135		
Mean ± SD	2·5 ± 2·5	2·6 ± 2·0		
Range (Min – Max)	1 - 13	1 - 11		

*Reprinted from Journal of the American College of Cardiology Vol 73 (19); Hancock HC, Maier RH, Kasim AS, Mason JM, Murphy GJ, Goodwin AT, Owens WA, Kirmani BH, Akowuah EF. Mini-Sternotomy Versus Conventional Sternotomy for Aortic Valve Replacement. pp. 2491-2492. 2019[28], with permission from Elsevier.

Table 3. The number and proportion of patients receiving a Non-Red Cell Transfusion, and the number of units received, to 7 days and to discharge following index surgery, by group.

	Mini-sternotomy group	Conventional sternotomy group	Odds Ratio (95% CI; p value)
Non-Red Cell Transfusions			
Post-operatively to 7 days number of patients (%)	6/135 (4·4)	18/135 (13·3)	0·3 (0·1, 0·8; p=0·0137)
Post-operatively to discharge number of patients (%)	13/135 (9·6)	21/135 (15·6)	0·6 (0·3, 1·2)
Non-Red Cell Component Units – Post operatively to 7 days			
Number of patients	6	18	
Mean ± SD	3·2 ± 0·9	4·6 ± 1·6	
Range (Min – Max)	2 - 5	1 - 7	
Non-red Blood Cell Units – post operatively to discharge			
Number of patients	13	21	
Mean ± SD	4·8 ± 2·3	4·9 ± 2·3	
Range (Min – Max)	1 - 8	1 - 12	
Non-red Cell Component Transfusions			
Post-operatively to 7 days number of patients (%)	6 (4·4)	18 (13·3)	0·3 (0·1, 0·8)
Post-operatively to discharge number of patients (%)	13 (9·6)	21 (15·6)	0·6 (0·3, 1·2)

Table 4. Outcomes during index hospital stay for cardiopulmonary bypass and aortic cross clamp times and drain losses.

	Mini-sternotomy group (n=135)	Conventional sternotomy group (n=135)	Mean Difference (95% CI; p value)
Cardio Pulmonary Bypass time (minutes)			
Mean ± SD	82·7 ± 23·5	59·6 ± 15·1	
Range (Min – Max)	41·0 - 199	37·0 -170·0	
Aortic cross clamp time (minutes)			
Mean ± SD	64·1 ± 17·1	46·3 ± 10·7	
Range (Min – Max)	32·0 - 132·0	32·0 -97·0	
Drain losses at 12 hours			
Mean ± SD	181·6 ± 138·7	306·9 ± 348·6	-127·7 (-191·7,-63·8; p=0·0001)
Range (Min – Max)	25 - 925	25 - 3000	
Drain losses at drain removal			
Mean ± SD	251·7 ± 198·4	393·7 ± 378·7	-145·3 (-218·1,-72·3; p=0·0001)
Range (Min – Max)	25 - 1425	50 - 3000	

Table 5. Outcomes during index hospital stay for valve size and type, and for valve function and regurgitation to 6 weeks by group.

Valve Characteristics	Mini-sternotomy group (n=135)	Conventional sternotomy group (n=135)	Mean Difference (95% CI; p value)
Valve size: mm			
19-21mm n (%)	40 (29.6)	38 (28.1)	
23-25mm n (%)	84 (62.2)	80 (59.3)	
27-29mm n (%)	11 (8.2)	17 (12.6)	
Mean ± SD	23·1 ± 2·1	23·6 ± 2·5	
Range (Min – Max)	19·0 - 29·0	19·0 - 31·0	
Valve type: n (%)			
Biological and sutureless	4 (3·0)	3 (2·2)	
Biological prosthesis	96 (71·1)	98 (72·6)	
Mechanical prosthesis	35 (25·9)	34 (25·2)	
Valve function			
Mean Gradient			
Baseline			
n	111*	110*	
Mean ± SD	47·9± 15·7	47·7 ± 20·2	0·2 (-4·6,5·0)
Min - Max	10-93	8-110	
6 weeks			
n	120*	126*	
Mean ± SD	15·7 ± 5·5	15·7 ± 5·8	0·5**(-1·0,2·1)
Min - Max	6-33	4-34	
Peak Gradient			
Baseline			
n	125*	124*	
Mean ± SD	82·3 ± 25·9	77·1 ± 29·1	5·2 (-1·7,2·3)
Min - Max	16-152	8-173	
6 weeks			
n	130*	130*	
Mean ± SD	29·9 ± 10·5	29·7 ± 10·8	-0·3** (-2·9,2·3)
Min - Max	12-62	11-61	
* It was not possible to quantify valve function in all patients			
**After adjusting for randomisation factors and baseline data			
Aortic Valve Regurgitation			
Nil/trivial			
n/n (%)	109/134* (81·3)	109/130* (83·8)	218/264 (82·6)
Mild			
n/n (%)	19/134* (14·2)	18/130* (13·9)	37/264 (14·0)
Moderate			
n/n (%)	5/134* (3·7)	2/130* (1·5)	7/264 (2·7)
Severe			
n/n (%)	1/134* (0·8)	1/130* (0·8)	2/264 (0·8)
* It was not possible to record valve regurgitation in all patients			

Table 6. Cost-effectiveness, cost/QALY (£): mini-sternotomy versus conventional surgery

1 probability cost-effective or net monetary benefit if willing to pay £20,000/QALY
2 probability cost-effective or net monetary benefit if willing to pay £30,000/QALY
3 dominance indicates average costs were less and average benefit greater for conventional surgery
4 regression estimates adjusted for trial stratifying covariates and baseline EQ-5D

	Model	Incremental cost (95%CI)	Incremental QALYs (95%CI)	ICER (95%CI)	p[1]	p[2]
1	Multiple imputation, covariate adjusted[4]	508 (-202 to 1217)	-0·007 (-0·016 to 0·002)	Dominated[3]	0·058	0·052
2	Multiple imputation, unadjusted	859 (-116 to 1833)	-0·008 (-0·018 to 0·003)	Dominated	0·023	0·021
3	Complete case, covariate adjusted[4]	630 (25 to 1224)	-0·007 (-0·016 to 0·002)	Dominated	0·013	0·011
4	Complete case, unadjusted	544 (-99 to 1142)	-0·009 (-0·02 to 0·002)	Dominated	0·027	0·022

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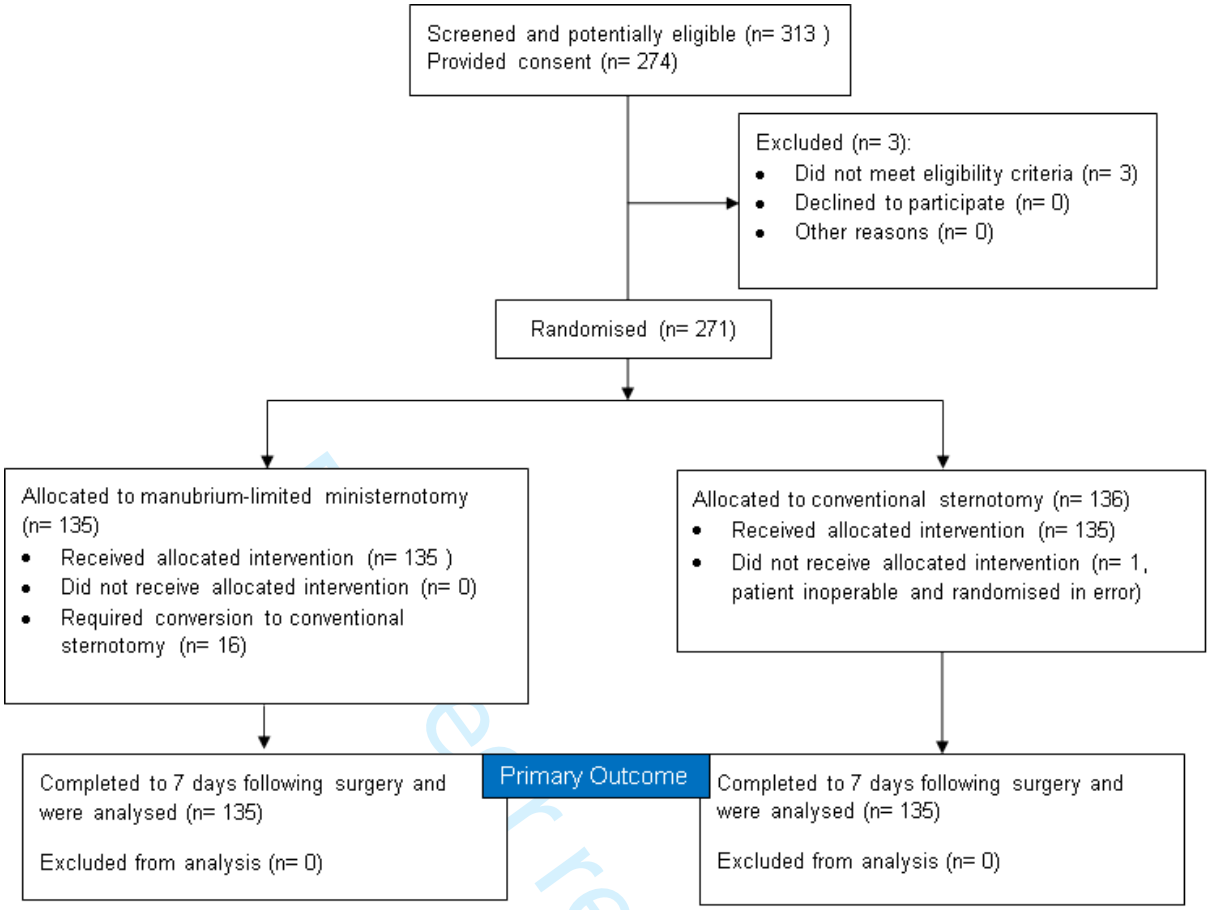
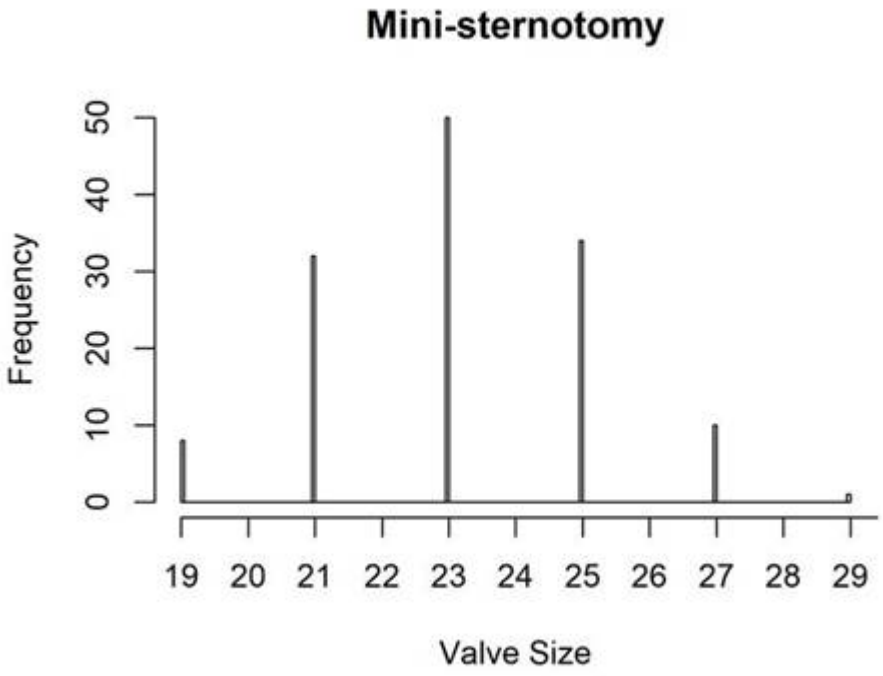
Figure 1. CONSORT Diagram. Flow of participants through trial.

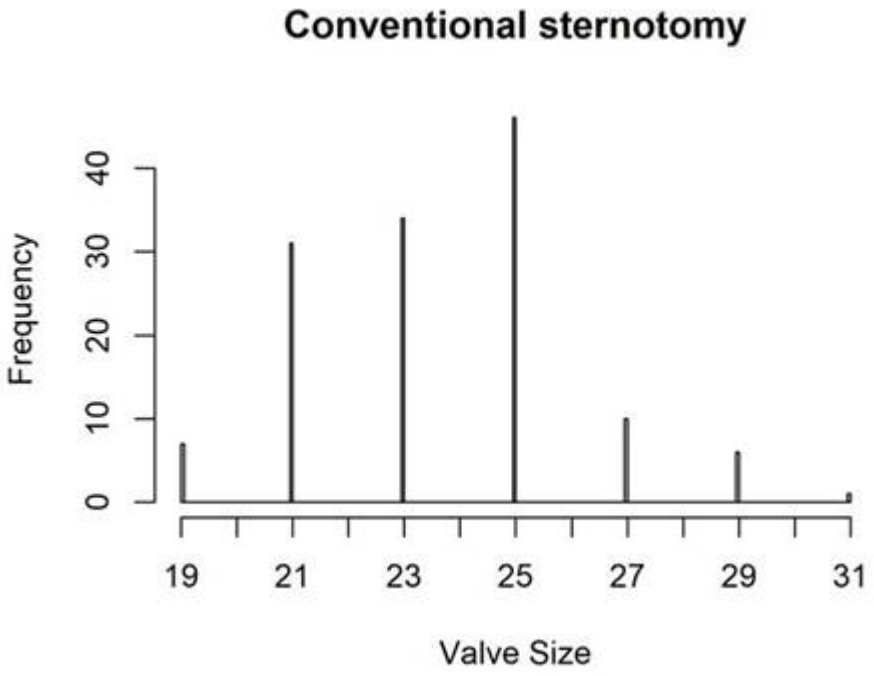
Figure 2. Valve size distribution: mini-sternotomy group

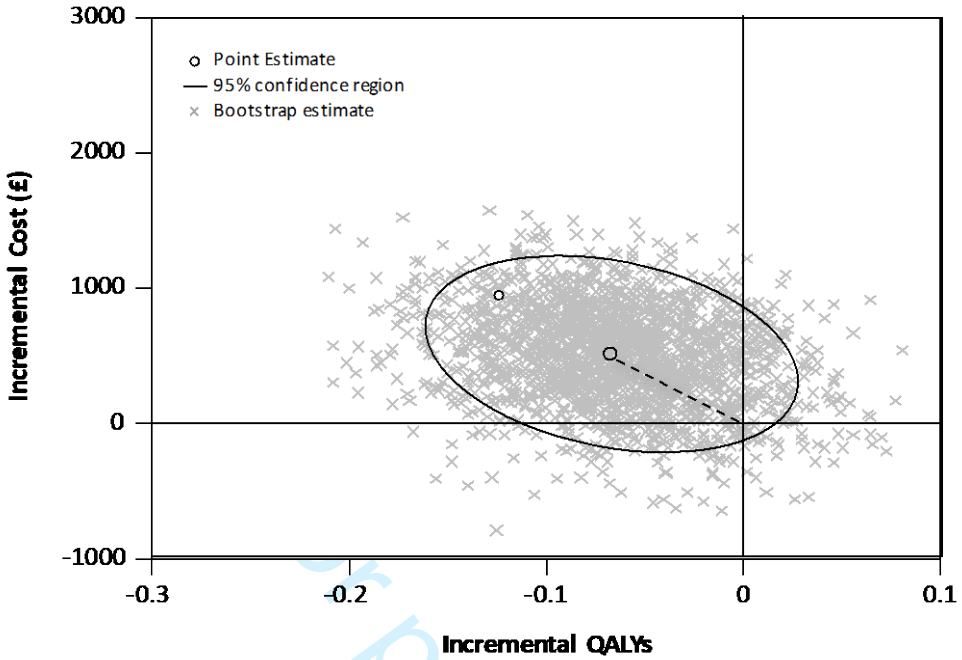
Figure 3. Valve size distribution: conventional sternotomy group

Figure 4. Cost-effectiveness plane, cost/QALY (£): mini-sternotomy versus conventional surgery.









Supplementary Material

Study Investigators: trial site, trials unit, statistics, health economics, committees

Trial Site
The James Cook University Hospital, South Tees Hospitals NHS Foundation Trust, Middlesbrough, United Kingdom

Investigators
- Mr Enoch Akowuah (Chief Investigator)
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Health Economics
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Investigator
- Professor James Mason (co-Investigator)

Committees
Data Monitoring Committee Membership
- Mr Graham Cooper (Chair)
- Mr Heyman Luckraz
- Professor Chris Rogers

Trial Steering Committee Membership
- Mr Sukumaran Nair (Chair until Sep 2014)
- Professor Gavin Murphy (Acting Chair Oct 2014 to June 2015)
- Mr Peter Braidley (Chair, from July 2015)
- Mr Paul Modi
- Mr Brendan Ellis

Table 1. Eligibility criteria

Inclusion Criteria

- Aged 18 years or older at the time of consent
- Requiring first-time, non-emergency, isolated Aortic Valve Replacement surgery
- Able and willing to provide written informed consent

Exclusion Criteria

- requiring concomitant cardiac procedure(s) including redo surgery, emergency or salvage surgery,
- only conventional median sternotomy indicated*,
- haemoglobin level < 90g/L,
- pregnant**,
- currently participating in another interventional clinical trial,
- previous cardiac surgery,
- are unable to stop currently prescribed treatment affecting clotting (e·g·, heparin, warfarin), ***
- a history of thrombophilia, thrombocytopenia or other haematological conditions that would affect participation in the trial as determined by one of the three operating surgeons,
- infective endocarditis,
- prevented from having red blood cells and blood products according to a system of beliefs (e·g· Jehovah's Witnesses),
- having any other medical, psychiatric and or social reason as determined by the consenting surgeon that precludes participation.

* patients were excluded if only conventional median sternotomy was indicated, for example in the presence of significant skeletal abnormalities like kyphosis. They were also excluded if transoesophageal echocardiography could not be performed, as this was mandatory to perform safe peripheral venous cannulation. All 3 surgeons used consistent criteria.

** in women of child bearing age (18 – 50) a pregnancy test was be performed within 14 days of surgery prior to randomisation.

***for patients in both trial arms, pre-operative antiplatelet drugs (including clopidogrel and ticagrelor), and anti-coagulants (including warfarin and heparin) were discontinued 5 days prior to surgery. These drugs were re-started following surgery at the discretion of the clinical team· The exception to this was aspirin, which was stopped 5 days prior to surgery where possible, however continuation until the day of surgery did not exclude a patient from the trial.

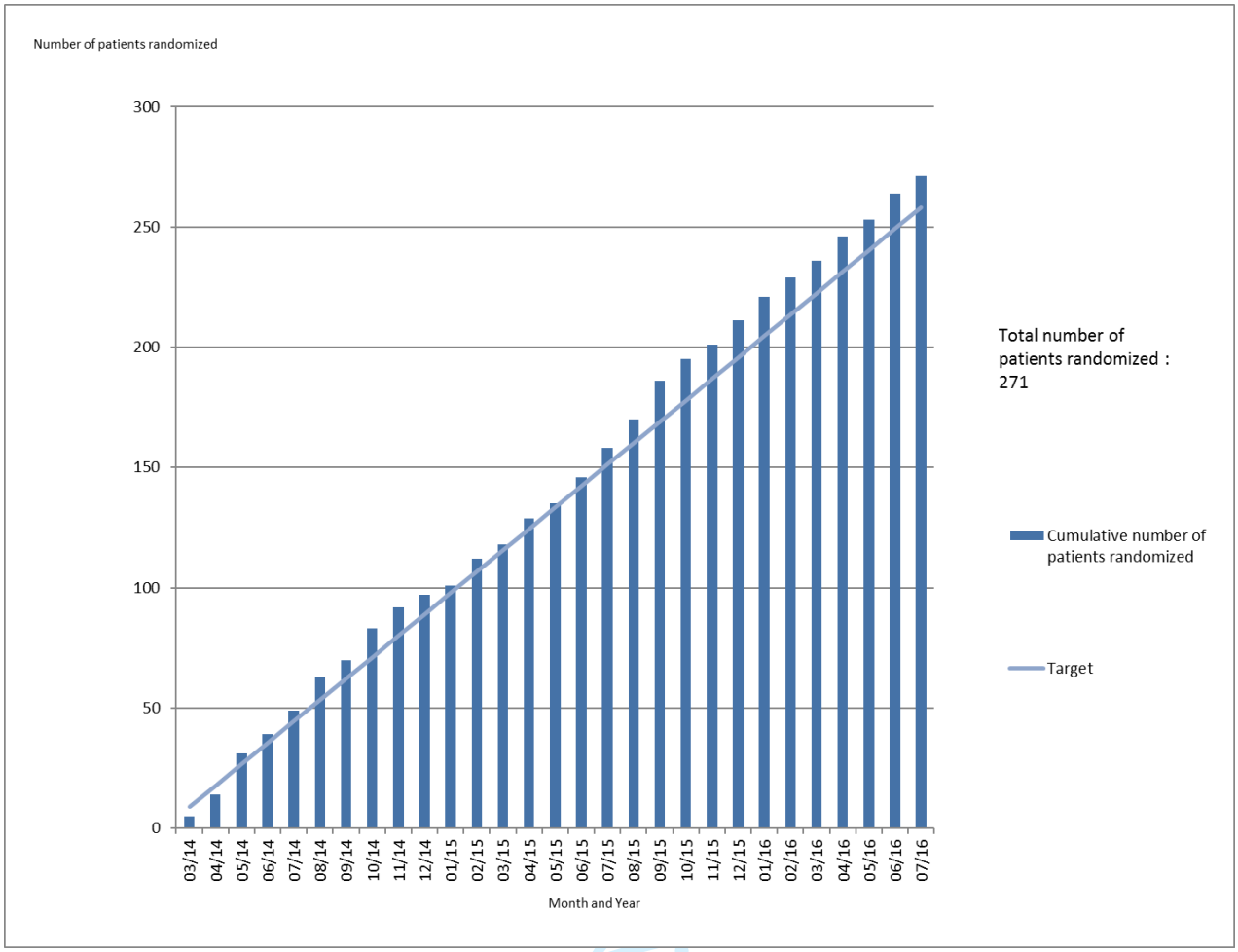

Figure 1. Trial recruitment by month.

Table 2. Conversion from mini-sternotomy to conventional sternotomy

Reason for conversion	Number of patients	Details
Anaesthetic emergency	**2**	• Patient became unstable as they were transferred into theatre and BP dropped – required conventional to re-stabilise • Anaphylactic reaction on induction needing CPR· Operation cancelled, patient taken to ITU· Widespread rash· Decision made the following morning to proceed to AVR (via full sternotomy)
Difficult vascular access (venous or arterial)	**9**	Venous • Femoral vessels unsuitable for cannulation • Poor venous drainage • Unable to pass venous dilators • Unable to insert pipe· Resistance felt, no back flow of blood· Femoral cannulation abandoned • Impossible to dilate femoral vein· Despite re-wiring, guide wire coiling within pelvic venous system Arterial • Difficulties cannulating femoral artery leading to haemodynamic instability • Poor access, unable to clamp aorta • Severe calcification of ascending aorta • Difficult access; aorta displaced to the left· Body habitus limited access
Intra-operative complications	**5**	• Bleeding from aortotomy site • Bleeding • Intra-operative decision to performed bypass graft to LAD • Post implant TOE showed small paravalvular leak and bleeding from aortotomy incision • Mild/moderate paravalvar leak on TOE· Required valve re-implant
TOTAL	**16**	

Table 3. Number of operations performed by Consultant Surgeon

	Mini-sternotomy group n=patients (%)	Conventional sternotomy group n=patients (%)	Total n=patients (%)
Consultant Surgeon A	58 (43·0)	58 (43··0)	116 (43·0)
Consultant Surgeon B	43 (31·9)	35 (25·9)	78 (28·9)
Consultant Surgeon C	34 (25·1)	42 (31·1)	76 (28·1)

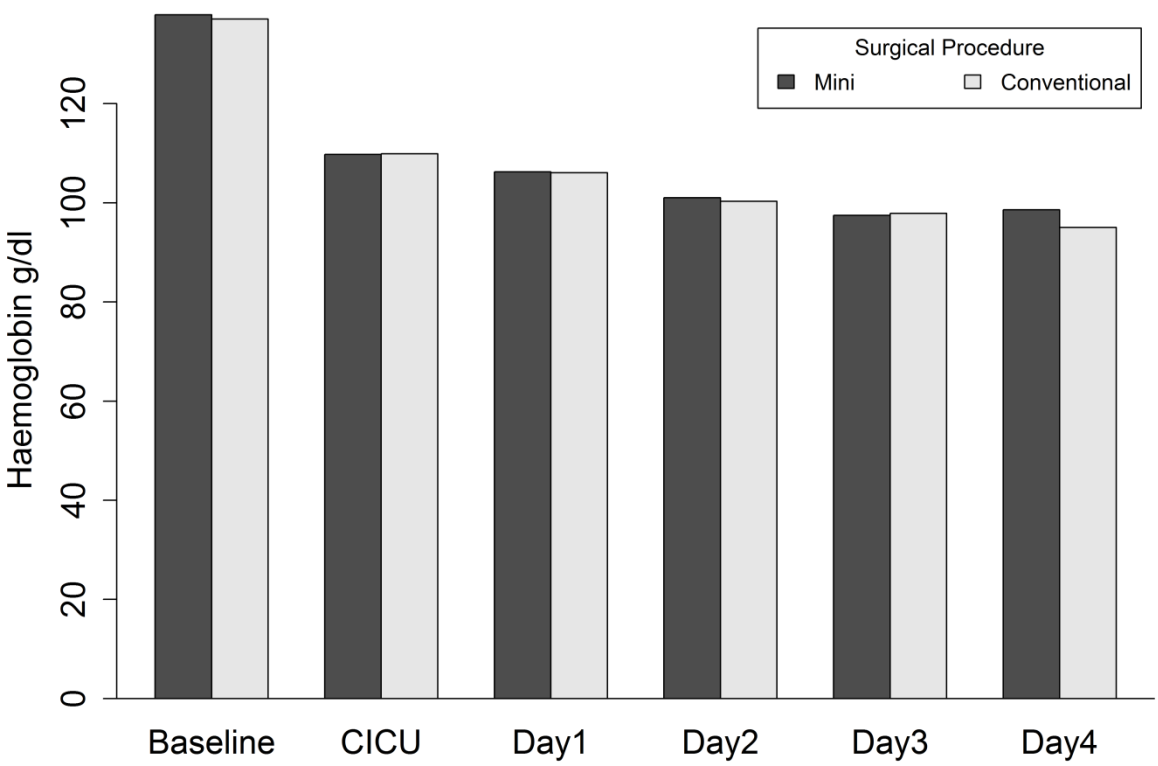

Figure 2. Haemoglobin profiles at Baseline, during CICU stay, and day 1 to day 4 post index surgery, by group

Table 4. Analgesic use and pain scores

Medication	Mini-sternotomy Group (135 patients) n = patients (%)	Conventional Sternotomy Group (135 patients) n = patients (%)	Total (270 patients) n = patients (%)
Analgesic use at baseline			
Buprenorphine patch	3 (2·2)	1 (0·7)	4 (1·5)
Codeine Phosphate	4 (3·0)	3 (0·7)	7 (2·6)
Dihydrocodeine Tartrate	0 (0·0)	1 (0·7)	1 (0·4)
Durogesic patch	0	1 (0·7)	1 (0·4)
Fentanyl	1 (0·7)	0 (0·0)	1 (0·4)
Gabapentin	1 (0·7)	0 (0·0)	1 (0·4)
Morphine Sulfate	0·0	1 (0·7)	1 (0·4)
Naxoproxen	1 (0·7)	0 (0·0)	1 (0·4)
Paracetamol	13 (9·6)	8 (5·9)	21 (7·8)
Tramadol Hydrochloride	0 (0·0)	2 (1·5)	2 (0·7)
At least one med at baseline	**16 (11·9)**	**12 (8·9)**	**28 (10·4)**
Analgesic use at day 2			
Buprenorphine patch	1 (0·7)	0 (0·0)	1 (0·4)
Codeine Phosphate	18 (13·3)	16 (11·9)	34 (12·6)
Dihydrocodeine Tartrate	4 (3·0)	6 (4·4)	10 (3·7)
Fentanyl	1 (0·7)	0 (0·0)	1 (0·4)
Gabapentin	1 (0·7)	0 (0·0)	1 (0·4)
Morphine Sulfate	13 (9·6)	13 (9·6)	26 (9·6)
Oramorph	1 (0·7)	1 (0·7)	2 (0·7)
Paracetamol	94 (69·6)	80 (59·3)	174 (64·4)
Pregabalin	1 (0·7)	0 (0·0)	1 (0·1)
Tramadol Hydrochloride	7 (5·2)	5 (3·7)	12 (4·4)
At least one med at day 2	**99 (73·3)**	**86 (63·7)**	**185 (68·5)**
Analgesic use at day 3			
Buprenorphine patch	1 (0·7)	0(0·0)	1 (0·4)
Codeine Phosphate	14 (10·4)	21 (15·6)	35 (13·0)
Dihydrocodeine Tartrate	4 (3·0)	7 (5·2)	11 (4·1)
Fentanyl	0 (0·0)	1 (0·7)	1 (0·4)
Gabapentin	1 (0·7)	1 (0·7)	2 (0·7)
Ibuprofen	0	1 (0·7)	1 (0·4)
Morphine Sulfate	6 (4·4)	1 (0·7)	7 (2·6)
Nefopam Hydrochloride	0	1 (0·7)	1 (0·4)
Oramorph	0	3 (2·2)	3 (1·1)
Paracetamol	89 (65·9)	99 (73·3)	188 (69·6)
Pregabalin	1 (0·7)	0 (0·0)	1 (0·4)
Tramadol Hydrochloride	8 (5·9)	3 (2·2)	11 (4·1)
At least one med at day 3	**90 (66·7)**	**101 (74·8)**	**191 (70·7)**
Analgesic use at Day 4			
Buprenorphine patch	1 (0·7)	0 (0·0)	1 (0·4)
Codeine Phosphate	15 (11·1)	15 (11·1)	30 (11·1)
Dihydrocodeine Tartrate	4 (3·0)	9 (6·7)	13 (4·8)
Fentanyl	1 (0·7)	1 (0·7)	2 (0·7)
Gabapentin	1 (0·7)	1 (0·7)	2 (0·7)
Ibuprofen	0 (0·0)	1 (0·7)	1 (0·4)
Paracetamol	86 (63·7)	75 (55·6)	161 (59·6)
Morphine Sulfate	1 (0·7)	2 (1·5)	3 (1·1)
Pregabalin	1 (0·7)	0 (0·0)	1 (0·4)
Tramadol Hydrochloride	3 (2·2)	3 (2·2)	6 (2·2)
At least one med at day 4	**88 (65·2)**	**81 (60·0)**	**169 (62·6)**
Analgesic use at Week 6			
Buprenorphine Patch	3(2·2)	0(0·0)	3(1·1)
Codeine Phosphate	7(5·1)	5(3·7)	12(4·5)
Dihydrocodeine Tartrate	1(0·7)	3(2·2)	4(1·5)
Fentanyl	1(0·7)	0(0·0)	1(0·4)
Gabapentin	2(1·5)	1(0·7)	3(1·1)
Ibuprofen	0(0·0)	1(0·7)	1(0·4)
Morphine Sulfate	0(0·0)	1(0·7)	1(0·4)
Paracetamol	35(25·9)	38(28·1)	73(27·0)
Pregabalin	1(0·7)	0(0·0)	1(0·4)
Tramadol Hydrochloride	2(1·5)	2(1·5)	4(1·5)
At least one med at week 6	**41(30·4)**	**41(30·4)**	**82(30·4)**
Analgesic use at Week 12			
Buprenorphine Patch	3(2·2)	0(0·0)	3(1·1)
Codeine Phosphate	7(5·2)	4(3·0)	11(4·1)

Dihyrocodeine Tartrate	0(0·0)	1(0·7)	1(0·4)
Gabapentin	2(1·5)	0(0·0)	2(0·7)
Ibuprofen	1(0·7)	0(0·0)	1(0·4)
Morphine Sulfate	1(0·7)	1(0·7)	2(0·7)
Naproxen	1(0·7)	0(0·0)	1(0·4)
Paracetamol	19(14·1)	20(14·8)	39(14·4)
Tramadol Hydrochloride	1(0·7)	1(0·7)	2(0·7)
At least one med at week 12	**23(17·0)**	**22(16·3)**	**45(16·7)**

	Mini-sternotomy Group (n=135 patients)	**Conventional sternotomy group (n=135)**
Baseline pain score		
n	128*	130*
Mean± SD	1·3 ± 2·1	0·9 ± 1·9
(min-max)	0 - 10	0 - 8
Day 2 pain score**		
n	123*	126*
Mean± SD	3·4 ± 2·4	3·7 ± 2·7
(min-max)	0 - 10	0 - 10
Day 3 pain score		
n	120*	129*
Mean± SD	2·8 ± 2·5	2·7 ± 2·3
(min-max)	0 - 9	0 - 8
Day 4 pain score		
n	116*	120*
Mean± SD	2·5 ± 2·2	2·1 ± 2·3
(min-max)	0 - 8	0 - 10
6 week pain score		
n	112*	118*
Mean± SD	1·5 ± 1·9	1·2 ± 1·8
(min-max)	0 - 8	0 - 8
12 week pain score		
n	128*	122*
Mean± SD	1·1 ± 1·9	1·0 ± 1·7
(min-max)	0 - 8	0 – 6

*Pain scores were assessed wherever possible
**Assessment on Day 2 was conducted with the patient blinded to their surgical allocation

Table 5. Adverse Events

Adverse Event	Mini-sternotomy Group n = patients (%)	Conventional Sternotomy Group n = patients (%)	Total n = patients (%)
Death			
In hospital	0/135 (0·0)	0/135 (0·0)	0/270 (0·0)
12 weeks	2/135 (1·5)	2/135 (1·5)	4/270 (1·5)
Stroke			
In hospital	3/135 (3·0)	1/135 (0·7)	4/270 (1·5)
12 weeks	4/135 (3·0)	1/135 (0·7)	5/270 (1·9)
Transient Ischaemic Attack			
In hospital	0/135 (0·0)	1/135 (0·7)	1/270 (0·4)
12 weeks	3/135 (2·2)	1/135 (0·7)	4/270 (1·5)
Renal failure			
In hospital	4/135 (2·3)	0/135 (0·0)	4/270 (1·5)
12 weeks	4/135 (2·3)	1/135 (0·7)	5/270 (1·9)
Atrial Arrhythmias			
In hospital	51/135 (37·8)	42/135 (31·1)	93/270 (34·4)
12 weeks	61/135 (45·2)	51/135 (37·8)	112/270 (41·5)
Ventricular Arrhythmias			
In hospital	2/135 (1·5)	2/135 (1·5)	4/270 (1·5)
12 weeks	2/135 (1·5)	2/135 (1·5)	4/270 (1·5)
Pericardial Effusion			
In hospital	4/135 (2·3)	1/135 (0·7)	5/270 (1·9)
12 weeks	9/135 (6·7)	6/135 (4·4)	15/270 (5·6)
Pulmonary Embolism			
In hospital	0/135 (0·0)	0/135 (0·0)	0/270 (0·0)
12 weeks	0/135 (0·0)	2/135 (1·5)	2/270 (0·7)
Chest Infection			
In hospital	7/135 (5·2)	10/135 (7·4)	17/270 (6·3)
12 weeks	18/135 (13·3)	26/135 (19·3)	44/270 (16·3)
Sternal wound infection			
In hospital	3/135 (2·2)	1/135 (0·7)	4/270 (1·5)
12 weeks	11/135 (8·1)	3/135 (2·2)	14/270 (5·2)
Re-operation for bleeding	3/135 (2·2)	5/135 (3·7)	8/270 (3·0)

Table 6. Health status, resource use and cost (complete cases)

	Conventional [C]			Mini-sternotomy [M]			[M]-[C][1]	
	mean	(SD)	N	mean	(SD)	N	mean	(95%CI)
Health status[2]								
EQ-5D Baseline	0·764	0·245	130	0·763	0·235	128	-0·001	(-0·060 to 0·057)
EQ-5D 2 days	0·349	0·349	133	0·353	0·291	128	0·004	(-0·074 to 0·082)
EQ-5D 6 weeks	0·798	0·194	118	0·751	0·221	112	-0·048	(-0·101 to 0·006)
EQ-5D 12 weeks	0·838	0·207	124	0·782	0·248	127	-0·056	(-0·112 to 0·001)
EQ-5D AUC (0-12 weeks)	0·162	0·041	105	0·153	0·040	98	-0·009	(-0·020 to 0·002)
Resource use								
Index Admission								
Length of stay (d)[3]	8·26	4·28	135	9·29	7·88	135	1·03	(-0·48 to 2·54)
CICU (d)	1·21	0·99	135	1·61	5·52	135	0·39	(-0·55 to 1·34)
HDU (d)	1·27	1·52	135	1·60	1·75	135	0·33	(-0·07 to 0·72)
Cardiac ward (d)	5·67	3·52	135	5·70	3·18	135	0·03	(-0·77 to 0·83)
Stroke ward (d)	0·03	0·34	135	0·11	1·00	135	0·08	(-0·10 to 0·26)
Time in first surgery (h)	2·24	0·51	135	2·98	0·69	135	0·74	(0·60 to 0·89)
Time in further surgery (h)[4]	0·08	0·34	135	0·03	0·17	135	-0·05	(-0·11 to 0·02)
Time in surgery (h)[4]	2·32	0·63	135	3·01	0·71	135	0·69	(0·53 to 0·85)
RBC (u)[4]	0·59	1·45	135	0·55	1·28	135	-0·04	(-0·37 to 0·28)
FFP (u)[4]	0·57	1·43	135	0·34	1·21	135	-0·23	(-0·55 to 0·09)
Platelets (u)[4]	0·22	0·64	135	0·12	0·46	135	-0·10	(-0·24 to 0·03)
Cryoprecipitate (u)[4]	0·01	0·09	135	0·00	0·00	135	-0·01	(-0·02 to 0·01)
Post discharge contacts								
GP surgery	1·47	1·52	129	1·40	1·32	131	-0·07	(-0·41 to 0·28)
GP home	0·09	0·32	129	0·19	0·56	131	0·10	(-0·01 to 0·21)
GP telephone	0·12	0·45	129	0·15	0·63	131	0·03	(-0·10 to 0·16)
Nurse surgery	1·38	2·56	129	2·07	3·54	131	0·69	(-0·06 to 1·44)
Nurse home	0·43	1·30	129	0·56	1·87	131	0·12	(-0·27 to 0·51)
Nurse telephone	0·05	0·25	129	0·04	0·26	131	-0·01	(-0·07 to 0·05)
Outpatient hospital	0·40	0·78	129	0·57	1·98	131	0·17	(-0·20 to 0·53)
Inpatient hospital	0·30	0·68	129	0·27	0·60	131	-0·03	(-0·18 to 0·13)
Inpatient hospital (d)	2·09	7·79	129	1·09	2·69	131	-1·00	(-2·42 to 0·42)
Total Contacts	4·29	3·53	129	5·47	4·90	131	1·18	(0·14 to 2·22)
Cost[5]								
Cost of index admission	7674	2055	135	8815	4517	135	1140	(303 to 1977)
Cost post discharge	824	2485	129	547	925	131	-277	(-734 to 180)
Cost	8527	3558	129	9274	4542	131	746	(-245 to 1737)

1 OLS regression-estimated means and 95% confidence intervals
2 EQ-5D-3L index score
3 Length stay by ward does not sum to length of stay due to theatre and transit time, and rounding
4 Item includes index and post-discharge usage
5 Resource items were costed using national reference costs except for the index procedures which were costed by South Tees Hospitals NHS Foundation Trust

Table 7. ICU Length of Stay, Fitness for Discharge and Hospital Length of Stay

	Mini-sternotomy group (n=135)	Conventional sternotomy group (n=135)
ICU stay (days)		
n	135	135
Mean ± SD	1·9 ± 5·8	1·3 ± 1·1
Min-Max	0 - 64*	0 - 7
Fitness for discharge (days)		
n	129**	133**
Mean ± SD	6·5 ± 3·7	6·3 ± 3·2
Min - Max	3 - 36	3 - 31
Post-operative length of stay (days)		
n	135	135
Mean ± SD	7·4 ± 7·5	6·3 ± 3·1
Min - Max	3 - 79	3 - 31

*3 patients in the mini-sternotomy group were in ICU for more than 7 days· Excluding these patients, the range would have been 0-5 days for the mini-sternotomy group.

**Fitness for discharge was assessed by the surgical and physiotherapy teams. For 6 patients in the mini-sternotomy group and 2 patients in the conventional sternotomy group this was not possible due staff availability at the point of discharge.

Table 8. Pulmonary Function Tests

		Mini-sternotomy group (n=135)	Conventional sternotomy group (n=135)	Mean Difference (95% CI; p value)
FEV1				
Baseline				
	n	123*	123*	
	Mean ± SD	2196·2 ± 712·2	2207·7 ± 748·2	-15·4 (-169·2,138·4)
	Min - Max	1000- 4340	1020-4090	
Day 4				
	n	105*	110*	
	Mean ± SD	1122·6 ± 433·0	1320·7 ± 523·5	-171·3** (-265·3,-77·2; p=0·0004)
	Min - Max	99-2400	76-2910	
6 weeks				
	n	106*	97*	
	Mean ± SD	1962·0 ± 468·7	2018·1 ± 662·8	-7·3** (-104·3,89·6)
	Min - Max	650-3570	870-3570	
FVC				
Baseline				
	n	123*	123*	
	Mean ± SD	2908·5 ± 926·4	2929·2 ± 955·7	-31·6 (-238·8,175·7)
	Min - Max	1250-6060	1200-5650	
Day 4				
	n	105*	110*	
	Mean ± SD	1478·9 ± 583·3	1697·5 ± 706·8	-129·7** (-259·2,-0·1; p=0·0498)
	Min - Max	139-2910	109-3920	
6 weeks				
	n	106*	97*	
	Mean ± SD	2529·4 ± 824·0	2615·9 ± 864·0	-36·0** (-173·2,101·2)
	Min - Max	1180-4760	1000-4840	

*It was not possible for all patients to complete pulmonary function tests
**After adjusting for randomisation factors and baseline data

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	3,5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	3,4,5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	4 (+appendix)
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	4,5
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	7
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	2,4
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	2,4

Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	2,4
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	4
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	2,4,5
	11b	If relevant, description of the similarity of interventions	4
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	7
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	9
	13b	For each group, losses and exclusions after randomisation, together with reasons	9,17
Recruitment	14a	Dates defining the periods of recruitment and follow-up	9
	14b	Why the trial ended or was stopped	9
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Tables
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	9, Tables
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Tables
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	12
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	11
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	13,14

Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	13,14
Other information			
Registration	23	Registration number and name of trial registry	1,4
Protocol	24	Where the full trial protocol can be accessed, if available	4
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	4, 15

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.