

# BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email [info.bmjopen@bmj.com](mailto:info.bmjopen@bmj.com)

# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-041398
Article Type:	Original research
Date Submitted by the Author:	08-Jun-2020
Complete List of Authors:	Hancock, Helen; Newcastle University, Newcastle Clinical Trials Unit Maier, Rebecca; Newcastle University, Newcastle Clinical Trials Unit Kasim, Adetayo; Durham University, Wolfson Research Institute for Health and Wellbeing Mason, James; University of Warwick, Warwick Medical School Murphy, Gavin; University of Leicester, Department of Cardiovascular Sciences and NIHR Leicester Biomedical Research Unit in Cardiovascular Medicine Goodwin, Andrew; South Tees Hospitals NHS Foundation Trust, James Cook Hospital Owens, W; South Tees Hospitals NHS Foundation Trust, James Cook Hospital Akowuah, Enoch; South Tees Hospitals NHS Foundation Trust, James Cook Hospital
Keywords:	Valvular heart disease < CARDIOLOGY, HEALTH ECONOMICS, Adult cardiology < CARDIOLOGY

SCHOLARONE™  
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1  
2  
3 1 **Title**

4  
5 2 Mini-sternotomy versus conventional sternotomy for aortic valve replacement: a randomised  
6  
7 3 controlled trial

8  
9  
10 4 **Authors**

11  
12 5 Helen C Hancock, PhD<sup>1</sup>, Rebecca H Maier<sup>1</sup>, MSc, Adetayo S Kasim, PhD<sup>2</sup>, James M Mason, DPhil<sup>3</sup>,  
13  
14 6 Gavin J. Murphy, FRCS (C.Th)<sup>4</sup>, Andrew T Goodwin, FRCS (C.Th)<sup>5</sup>, W Andrew Owens, FRCS (C.Th)<sup>5</sup>,  
15  
16 7 Enoch F Akowuah, FRCS (C.Th)<sup>5</sup>.

17  
18  
19 8 1. Newcastle Clinical Trials Unit, Newcastle University; 2. Durham Research Methods Centre,

20  
21 9 Durham University; 3. Warwick Medical School, University of Warwick; 4. Department of

22  
23 10 Cardiovascular Sciences, University of Leicester; 5. Cardiothoracic Services, South Tees Hospitals NHS

24  
25 11 Foundation Trust, The James Cook University Hospital.

26  
27  
28  
29 12

30  
31 13 **Word count 2925**

32  
33 14

34 15 **Corresponding author:** Enoch Akowuah

35  
36 16 Cardiothoracic Services, South Tees Hospitals NHS Foundation Trust, The James Cook  
37 17 University Hospital, Marton Road, Middlesbrough. TS3 4BW.

38 18 E mail Enoch.Akowuah@nhs.net

39  
40 19  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 20 **Abstract**  
4

5 21

6  
7  
8 22 **Objective**  
9

10 23

11 24 **To compare clinical and health economic outcomes after manubrium-limited mini-sternotomy**  
12  
13 25 **(intervention) and conventional median sternotomy (usual care)**  
14

15 26

16 27 **Design**  
17

18 28  
19 29 A single blind, randomised controlled trial.  
20

21 30 **Setting**  
22

23 31 Single centre UK National Health Service tertiary hospital  
24

25 32 **Participants**  
26

27 33 Adult patients undergoing aortic valve replacement surgery  
28  
29

30 34 **Interventions**  
31

32 35 Intervention was manubrium-limited mini-sternotomy performed using a 5-7cm midline incision.  
33

34 36 Usual care was median sternotomy performed using a midline incision from the sternal notch to the  
35  
36 37 xiphisternum.  
37  
38

39 38 **Primary and secondary outcome measures**  
40

41 39 The primary outcome was the proportion of patients who received a red cell transfusion post-  
42  
43 40 operatively and within 7 days of index surgery. Secondary outcomes included proportion of patients  
44  
45 41 receiving a non-red cell blood component transfusion and number of units transfused within 7 days  
46  
47 42 and during index hospital stay, quality of life and cost effectiveness analyses.  
47  
48  
49

50 43 **Results**  
51

52 44  
53 45 270 patients were randomised, received surgery and contributed to the intention to treat analysis.  
54

55 46 No difference between mini and conventional sternotomy in red-cell transfusion within 7 days was  
56  
57 47 found; 23/135 patients in each arm received a transfusion, odds ratio 1.0 (95% CI: 0.5, 2.0) and risk  
58  
59  
60

1  
2  
3 48 difference 0.0 (95% CI: -0.1, 0.1). Mini-sternotomy reduced chest drain losses (mean 181.6ml (SD  
4  
5 49 138.7) vs conventional, mean 306.9ml (SD 348.6)); this did not reduce red-cell transfusions. Mean  
6  
7 50 valve size and post-operative valve function were comparable between mini-sternotomy and  
8  
9 51 conventional groups; 23mm vs 24mm, and 6/134 moderate or severe aortic regurgitation vs 3/130,  
10  
11 52 respectively. Mini-sternotomy resulted in longer bypass (82.7 minutes (SD 23.5) vs 59.6 minutes (SD  
12  
13 53 15.1)) and cross clamp times (64.1 minutes (SD 17.1) vs 46.3 minutes (SD 10.7)). Conventional  
14  
15 54 sternotomy was more cost-effective with only a 5.8% probability of mini-sternotomy being cost-  
16  
17 55 effective at a willingness to pay of £20,000/QALY.  
18  
19  
20

## 21 56 **Conclusions**

22  
23 57  
24 58 AVR via mini-sternotomy did not reduce red blood cell transfusion within 7 days following surgery  
25  
26 59 when compared to conventional sternotomy.  
27  
28  
29

30  
31 61 **Clinical Trials Registry:** ISRCTN29567910  
32  
33  
34

35  
36 63  
37 64 Key word: minimally invasive, aortic valve  
38  
39  
40

41 65

42 66

43 67

44 68

45 69

46 70

47 71

48 72

49 73

50 74

1  
2  
3 75  
4  
5 76  
6  
7 77  
8  
9  
10 78  
11  
12 79  
13  
14 80  
15  
16 81  
17  
18  
19 82  
20  
21 83  
22  
23 84  
24  
25 85  
26  
27  
28 86  
29  
30 87  
31  
32 88  
33  
34 89  
35  
36 90  
37  
38  
39 91  
40  
41 92  
42  
43 93  
44  
45 94  
46  
47  
48 95  
49  
50 96  
51  
52 97  
53  
54 98  
55  
56 99  
57  
58  
59  
60 100

#### 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.

## 101 **Objectives**

102 Aortic valve replacement (AVR) for severe symptomatic valvular disease is one of the most common  
103 cardiac surgical procedures performed worldwide. Outcomes are generally excellent with in-hospital  
104 observed mortality in the UK of 1.5% for first time elective procedures.<sup>1</sup>

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

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

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

## 122 **Patients and Methods**

### 123 **Trial Design**

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



1  
2  
3 126 Research Ethics Committee approved the trial, which was conducted in accordance with the  
4  
5 127 principles of the International Conference on Harmonisation of Good Clinical Practice.<sup>12</sup> South Tees  
6  
7 128 Hospitals NHS Foundation Trust was the Sponsor and recruiting centre.  
8  
9

### 10 129 **Patient Public Involvement**

11  
12  
13 130 In designing the study, we asked patients their view on what factors may affect whether they took  
14  
15 131 part in the study. This was done in an outpatient setting and via a postal questionnaire. They felt  
16  
17 132 expertise was important. Most patients felt that although the cosmetic benefit of the minimally  
18  
19 133 invasive approach was appealing, they expected some clinical benefit from minimally invasive  
20  
21 134 surgery as well. Importantly most patients said they would accept being blind to the type of surgery  
22  
23 135 they had received for 48 hours after the procedure.  
24  
25  
26

### 27 136 **Participants**

28  
29 137 Patients were eligible if they were aged 18 years or over; required first-time, non-emergency,  
30  
31 138 isolated AVR surgery; and were willing to provide written informed consent. Full details of the  
32  
33 139 eligibility criteria are in the **Supplementary Material**.  
34  
35

### 36 140 **Randomisation**

37  
38  
39 141 Eligible patients were randomised by members of the research team using a 24-hour, central,  
40  
41 142 secure, web-based randomisation system with concealed allocation, managed by the Clinical Trials  
42  
43 143 Unit; randomisation was in a 1:1 ratio between mini and conventional sternotomy and stratified by  
44  
45 144 baseline logistic EuroSCORE and pre-operative Hemoglobin (Hb).  
46  
47

### 48 145 **Interventions**

49  
50 146 Manubrium-limited mini-sternotomy was performed using a 5-7cm midline skin incision dividing the  
51  
52 147 manubrium from the sternal notch to 1cm below the manubrium-sternal junction. Cardiopulmonary  
53  
54 148 bypass was established with an ascending aortic cannula and percutaneous femoral venous  
55  
56  
57 149 cannulation. Conventional median sternotomy was performed using a midline incision from the  
58  
59  
60

1  
2  
3 150 sternal notch to the xiphisternum. Key aspects of anaesthesia were standardised, and are detailed in  
4  
5 151 the protocol.<sup>13</sup>  
6  
7

## 8 152 **Blinding**

9  
10 153 All patients were blinded to type of sternotomy received until after their day 2 Quality of Life and  
11  
12 154 pain assessments. All patients had trial-specific opaque dressings applied to their sternal wound, and  
13  
14  
15 155 groin before leaving theatre.  
16

## 17 156 **Transfusion Protocol**

18  
19 157 The post-operative period, and trial protocol in relation to red cell and non-red cell transfusion,  
20  
21 158 began on admission to the Cardiothoracic Intensive Care Unit (CICU); it specified that patient's  
22  
23 159 should receive a red cell transfusion if their Hb dropped below 80 g/L; or were bleeding by 400ml/h  
24  
25 160 or more, or were bleeding 100ml/h or more for 4 or more hours with a Hb equal to or greater than  
26  
27 161 80g/L; or had blood loss with haemodynamic instability irrespective of thromboelastography (TEG)  
28  
29 162 and/or clotting profile results. One unit of red cells was transfused and Hb level checked before  
30  
31 163 transfusing another unit.  
32  
33

34  
35 164 Participants received a non-red cell transfusion if both of the following criteria were met: bleeding  
36  
37 165 defined by 400ml/h or more, or blood loss of 100ml/h or more for 4 hours or more; TEG or  
38  
39 166 coagulation guided transfusion indicated.  
40  
41

## 42 167 **Outcomes**

43  
44 168 All outcomes were measured from index surgery.  
45

### 46 169 **Primary Outcome**

47 170  
48  
49 171 The primary outcome was the proportion of patients who received a red cell transfusion post-  
50  
51 172 operatively and within 7 days of index surgery.  
52  
53

### 54 173 **Secondary Outcomes:**

- 55  
56 174
  - proportion of patients receiving a red cell transfusion and number of units transfused within  
57  
58 175 7 days and during index hospital stay;  
59  
60

- 1  
2  
3 176 • proportion of patients receiving a non-red cell blood component transfusion and number of  
4  
5 177 units transfused within 7 days and during index hospital stay;  
6  
7  
8 178 • volume in chest drains at 6 and 12 hours, and drain removal;  
9  
10  
11 179 • degree of aortic regurgitation using echocardiogram within 6 weeks;  
12  
13  
14 180 • re-operation rates;  
15  
16 181 • conversion to conventional AVR during surgery;  
17  
18  
19 182 • changes in lung function at 4 days and 6 weeks;  
20  
21  
22 183 • Quality of life EuroQol (EQ-5D-3L, EQ-VAS) at 2 days, 6 and 12 weeks;  
23  
24  
25 184 • time patients are deemed 'fit for discharge';  
26  
27  
28 185 • health care utilisation to 12 weeks;  
29  
30  
31 186 • cost and cost effectiveness analyses;  
32  
33 187 • adverse events to 12 weeks.

### 188 **Statistical Analysis**

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

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

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

1  
2  
3 199 predictors. Odds ratios and their associated 95% confidence interval are reported in the primary  
4  
5 200 analysis. Sensitivity analysis using alternating logistic regression was performed for the primary  
6  
7 201 endpoint to sensitise for surgeon effects; the odds of receiving a red cell transfusion for two patients  
8  
9 202 treated by the same surgeon was compared to two patients treated by different surgeons.

10  
11  
12 203 All analyses of secondary continuous efficacy endpoints at single time points were based on linear  
13  
14 204 models where, if appropriate, a log normal model was fitted to sensitise the linearity assumption.

15  
16  
17 205 Longitudinal analysis was performed for all endpoints with repeated data over time to investigate  
18  
19 206 changes in trends over the trial period. The trial period was defined as baseline, up to 7 days (post-  
20  
21 207 operative period), 6 week follow-up and 12 week follow-up. All analyses of binary endpoints at a  
22  
23 208 single time point were based on logistic regression. Generalised estimating equation was used to  
24  
25 209 analyse repeated binary data per patient to account for intra-patient correlation.

26  
27  
28 210 Further exploratory analysis was conducted to investigate the association between the treatment  
29  
30 211 group and other clinical factors. All analyses were performed using R 3.3.3 (The R Foundation) and  
31  
32 212 SAS 9.4 (SAS Institute Inc).

### 33 34 35 213 **Economic Evaluation**

36  
37  
38 214 A prospective economic evaluation applying a NHS perspective, following National Institute for  
39  
40 215 Health and Care Excellence (NICE) reference case guidance,<sup>14</sup> was employed. Health care utilisation  
41  
42 216 was captured up to three months following discharge from index surgery. Resource use was valued  
43  
44 217 in 2016 pounds sterling using national sources,<sup>15,16</sup> and where necessary, local micro-costing  
45  
46 218 (£1=\$1.50). Resources included surgery, transfusions, length of hospital stay (by level of care),  
47  
48 219 complications and further surgery, and community care following discharge.

49  
50  
51 220 Mechanisms of missingness within the data were explored and multiple imputation methods were  
52  
53 221 applied to impute missing data and minimise bias, using chained equations and predictive mean  
54  
55 222 matching. Imputation sets were analysed within a bivariate analysis of costs and QALYS, to generate  
56  
57 223 incremental within-trial cost per QALY estimates and credible intervals. Findings were presented on  
58  
59  
60

1  
2  
3 224 the ICER plane and with Cost-Effectiveness Acceptability Curves, using the net monetary benefit  
4  
5 225 approach.

## 8 226 **Results**

### 10 227 **Trial Population**

12 228 MAVRIC recruited to time and target; 313 patients were considered for the trial; 274 patients  
14  
15 229 consented between 20<sup>th</sup> March 2014 and 25<sup>th</sup> July 2016. The analysis population was 270 eligible  
16  
17 230 patients; 135 allocated to the AVR via mini-sternotomy group and 135 allocated to the AVR via  
18  
19 231 conventional sternotomy group (**Figure 1**).

22 232 All 270 patients underwent surgery. Sixteen patients required cross-over from minimally-invasive to  
23  
24 233 a conventional sternotomy due to anaesthetic emergency (n=2), difficulties due to vascular access  
25  
26 234 (n=9), and intra-operative complications (n=5); further details and the number of operations  
27  
28 235 performed by surgeon are in the Supplementary Material.

31 236 Baseline characteristics were similar between groups (**Table 1**).

### 34 237 **Primary Outcome**

37 238 There was no difference between groups in relation to the primary outcome (**Table 2**). The  
38  
39 239 proportion of patients receiving red cell transfusion transfusions was 23 of 135 in both groups, Odds  
40  
41 240 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).

### 44 241 **Secondary Outcomes**

#### 47 242 **Red cell and non-red cell transfusion**

49 243 There was no significant difference between groups with respect to any red cell transfusion at  
50  
51 244 discharge (**Table 2**). There was no difference between groups in Hb from baseline to 4 days following  
52  
53 245 index surgery (**Supplementary Material**). There was a statistically significant difference in the  
54  
55 246 proportion of patients receiving any non-red cell transfusion within 7 days of surgery; mini 6/135  
56  
57 247 versus conventional 18/135, Odds ratio: 0.3 (95% CI 0.1, 0.8; p=0.0137) (**Table 3**).

1  
2  
3 248 **Cross clamp time and cardiopulmonary bypass time**  
4

5  
6 249 Mini-sternotomy resulted in longer Cardio Pulmonary Bypass times; mini group 82.7 minutes (SD  
7  
8 250 23.5), conventional 59.6 minutes (SD 15.1). Aortic cross clamp times were also longer; mini group  
9  
10 251 64.1 minutes (SD 17.1), conventional 46.3 minutes (SD 10.7) (**Table 4**).

11  
12  
13 252 **Chest drain losses**  
14

15  
16 253 Mini-sternotomy resulted in a 40.8% reduction in chest drain losses at 12 hours, the mini group  
17  
18 254 mean was 181.6ml (SD 138.7), conventional group mean was 306.9ml (SD 348.6); the mean  
19  
20 255 difference was -127.7ml (95% CI -191.7, -63.8, p=0.0001). At drain removal mean difference was -  
21  
22 256 145.3ml (95% CI -218.1, -72.3; p=0.0001) (**Table 4**).

23  
24  
25 257 **Ventilation time**  
26

27  
28 258 Ventilation time between the groups was similar; 9.6 hours (SD 5.6) in the mini group and 9.8 hours  
29  
30 259 (SD 6.9) in the conventional (**Table 4**).

31  
32  
33 260 **Intensive care unit length of stay**  
34

35  
36 261 There was no difference in intensive care unit length of stay between groups (**Supplementary**  
37  
38 262 **Material**).

39  
40  
41 263 **Post-operative pain**  
42

43  
44 264 There was no difference in pain scores between groups (**Supplementary Material**).

45  
46 265 **Lung function**  
47

48  
49 266 There was no difference between groups in lung function at baseline. At 4 days post-surgery, mean  
50  
51 267 Forced Expiratory Volume 1 (FEV1) 1123mls (SD 433) and Forced Vital Capacity, FVC 1479mls (SD  
52  
53 268 583) were significantly reduced in the mini group, compared to the conventional; FEV1 1321 (SD  
54  
55 269 524), FVC 1698 (SD 707). Mean differences for FEV1 and FVC were statistically significant at 4 days  
56  
57 270 post-surgery; -171mls (95% CI -265, -77; p=0.0004) and -130mls (95% CI -269, 0; p=0.0498)  
58  
59  
60

1  
2  
3 271 respectively, after adjusting for baseline FEV1, FVC, and randomisation factors (**Supplementary**  
4  
5 272 **Material**).

### 8 273 **Hospital length of stay**

10 274 The mean time to patients being fit for hospital discharge following index surgery was similar  
11  
12  
13 275 between groups. The mean post-operative hospital length of stay was 7.4 (SD 7.5, range 3-79) in the  
14  
15 276 mini group, and 6.3 days (SD 3.2, range 3-31) in the conventional (**Supplementary Material**).

### 18 277 **Post-operative valve function**

20 278 The distribution of valve types and valve sizes were similar; mean valve size inserted was 23mm in  
21  
22 279 the mini group and 24mm in the conventional (**Table 4**). Over 70% of patients in each group received  
23  
24 280 a tissue valve, over 25% received a mechanical valve and 2-3% received a sutureless tissue valve.  
25  
26 281 Post operative transthoracic echo showed a similar decrease in mean aortic valve gradient in both  
27  
28 282 groups to 16mmHg; peak gradient decreased to 30mmHg in both groups (**Table 4**). 6/134 patients  
29  
30 283 had moderate or severe aortic regurgitation in the mini group compared to 3/130 in the  
31  
32 284 conventional (**Table 4**).

### 36 285 **Adverse events**

38 286 Adverse events in each group were broadly similar and within acceptable clinical limits. By 12 weeks,  
39  
40 287 4/135 patients in the mini-sternotomy group and 1/135 in the conventional group had suffered a  
41  
42 288 stroke (defined as a persistent neurological deficit). Atrial arrhythmias were identified in 61/135  
43  
44 289 patients in the mini group and 51/135 in the conventional. By 12 weeks, 11/135 patients in the mini  
45  
46 290 group and 3/135 patients in the conventional had a sternal wound infection (**Supplementary**  
47  
48 291 **Material**).

### 52 292 **Quality of Life, Costs and Cost-Effectiveness**

54 293 Costs during the index admission were significantly greater for the mini group (mini-conventional:  
55  
56 294 mean difference £1140; 95% CI 303, 1977), primarily reflecting the additional cost of theatre time  
57  
58 295 (**Supplementary Material**). Overall costs were not significantly different (mini-conventional: mean  
59  
60

1  
2  
3 296 difference £746; 95% CI -245, 1737). There was no significant difference in quality of life between  
4  
5 297 groups up to 12 weeks (mini-conventional: mean difference area under curve -0.009 QALYs; 95% CI  
6  
7 298 0.020, 0.002). Although differences in costs and quality-of-life were not individually significant, the  
8  
9 299 bivariate cost-QALY distribution (combining these two) suggests conventional surgery might be more  
10  
11 300 cost-effective (**Figure 2**). In the base-case model, mini was dominated by conventional surgery (due  
12  
13 301 to greater cost and less benefit), with only a 5.8% probability of being cost-effective at a willingness  
14  
15 302 to pay of £20,000/QALY (**Table 5**).

### 19 303 **Sensitivity and Subgroup Analyses**

21 304 There was no significant surgeon effect; the odds of receiving a red cell transfusion for two patients  
22  
23 305 treated by the same surgeon compared to two patients treated by different surgeons was 1.2 (95%  
24  
25 306 CI 0.9, 1.6; p=0.1379).

27  
28 307 Protocol deviations in respect of cell transfusions did not affect the results of the primary analysis;  
29  
30 308 excluding these patients produced the same results as those from the intention-to-treat analysis.

### 33 309 **Discussion**

#### 35 310 ***Main findings***

36 311 Mini-sternotomy was not superior to conventional sternotomy with respect to red cell transfusion  
37  
38 312 requirements within 7 days of surgery. Analysis of secondary endpoints showed a statistically  
39  
40 313 significant difference in transfusion volumes of non-red cell blood components. Aortic valve size and  
41  
42 314 post-operative function were comparable in the 2 groups. Mini-sternotomy resulted in a relative  
43  
44 315 reduction in chest drain losses however, higher blood loss in the conventional group did not  
45  
46 316 translate into red cell transfusions. Mini patients had substantially longer bypass and cross clamp  
47  
48 317 times and worse lung function at 4 days post-surgery. Lung function at twelve weeks, and adverse  
49  
50 318 event rates were otherwise not different between groups. Conventional sternotomy was found to be  
51  
52 319 more cost-effective. MAVRIC findings contradict those from other trials.<sup>17,18</sup>



1  
2  
3 320 *Strengths and limitations*  
4

5 321 This is the largest single trial to have compared minimally invasive sternotomy to conventional  
6  
7 322 median sternotomy for AVR. A recent Cochrane review identified 511 patients from 7 previous  
8  
9 323 RCTs.<sup>5</sup> In MAVRIC, the mini-sternotomy technique divided only the manubrium and is therefore less  
10  
11 324 invasive than other minimally invasive techniques. The trial was undertaken by three experienced  
12  
13 325 minimally invasive surgeons who were expert at both techniques. Patients were blinded to group  
14  
15 326 allocation until two days following index surgery, reducing the likelihood of bias. The trial recruited a  
16  
17 327 significant proportion of eligible patients; 274/313 (86%), with few requiring conversion to  
18  
19 328 conventional sternotomy, increasing the likelihood that the trial findings are generalisable. A further  
20  
21 329 strength was the detailed health economic evaluation; this has not been performed previously.  
22  
23

24  
25 330 The trial had some limitations, including the single centre design. This will tend to have biased  
26  
27 331 treatment effect estimates away from the null, which is at odds with our observed effect. There  
28  
29 332 were no significant levels of protocol non-adherence, with no effect on the main trial finding. The  
30  
31 333 event rate for the primary outcome, was much lower than expected at 17%; nationally red cell  
32  
33 334 transfusion rates following valve surgery are 46-4%.<sup>19</sup> In our pre-trial audit, 30% of mini-sternotomy  
34  
35 335 patients received a red cell transfusion. We attribute the observed transfusion rate in MAVRIC to the  
36  
37 336 restrictive red cell transfusion threshold applied; this followed evidence at the time of trial design.  
38  
39 337 The consultant (expert) led nature of the trial interventions is also likely to have reduced the need  
40  
41 338 for transfusions post-operatively and to have biased trial results towards the null.  
42  
43

44  
45  
46 339 *Clinical importance*  
47

48  
49 340 MAVRIC contributes important evidence to the minimally invasive AVR evidence base, summarised  
50  
51 341 in a Cochrane review.<sup>5</sup> MAVRIC demonstrated longer cross-clamp and bypass times with the  
52  
53 342 manubrium-limited mini-sternotomy, attributed to known differences between the interventions.  
54  
55 343 Minimally-invasive techniques in MAVRIC required a number of surgical steps to be performed with  
56  
57 344 the aortic clamp in place (drain insertion and pacing wire insertion for example), meaning cross-  
58  
59 345 clamp and bypass were longer. This is not an absolute requirement in other minimally invasive  
60

1  
2  
3 346 approaches; for example, where the incision is extended into the body of the sternum, or where  
4  
5 347 rapid deployment valves are used, there are no differences in cross clamp and bypass times.<sup>5</sup>  
6  
7 348 The size of MAVRIC and event rate prevents formal comparison of adverse events between the  
8  
9 349 groups, of note is the difference in stroke rate; this would benefit from exploration in a future trial.  
10  
11  
12 350 The cost-effectiveness plane indicates that conventional surgery is less costly and more beneficial  
13  
14 351 than minimally-invasive surgery; contact with healthcare professionals was greater in the mini  
15  
16 352 group, although there was no clear pattern of use. Wide confidence intervals mean that differences  
17  
18 353 are imprecise. MAVRIC does not support the use of funds to expand AVR via manubrium-limited  
19  
20 354 mini-sternotomy practice.  
21  
22  
23  
24 355 MAVRIC, the world's largest RCT at low risk of bias, found no additional clinical benefit of minimally  
25  
26 356 invasive AVR. Results are in agreement with the findings of a Cochrane review of trials that have  
27  
28 357 evaluated mini-sternotomy AVR.<sup>5</sup> This information should be disseminated to patients, clinicians and  
29  
30 358 commissioners to inform decisions about AVR surgery including commissioning.  
31  
32  
33  
34 359  
35  
36 360  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 361 **Role of funding source**  
4

5 362 This work was supported by the NIHR Research for Patient Benefit Programme (grant number PB-  
6  
7 363 PG-1112-29035). GJM is supported by the British Heart Foundation (CH/12/1/29419) and the NIHR  
8  
9 364 Leicester Biomedical Research Centre.  
10

11  
12 365 The views and opinions expressed are those of the authors and do not necessarily reflect those of  
13  
14 366 the National Institute for Health Research (NIHR) Research for Patient Benefit Programme, the  
15  
16 367 National Health Service or the Department of Health and Social Care.  
17  
18

19  
20 368 **Declaration of Interests**  
21

22 369 Helen C Hancock (HCH): None  
23

24  
25 370 Rebecca H Maier (RHM): None  
26

27 371 Adetayo S Kasim (ASK): None  
28

29  
30 372 James M Mason (JMM): None  
31

32  
33 373 Gavin J Murphy (GJM) declares research grant funding from Zimmer Biomet for a trial of blood  
34  
35 374 transfusion.  
36

37  
38 375 Andrew T Goodwin (ATG): None  
39

40 376 W Andrew Owens (WAO): None  
41

42  
43 377 Enoch F Akowuah (EFA): None  
44  
45

46 378 **Authors contributions**  
47

48 379 EFA, HCH, RHM, and JMM and GJM designed the trial, and sought funding. EFA, ATG and WAO  
49  
50 380 recruited patients to the trial and performed surgery. ASK conducted the statistical analysis and  
51  
52 381 JMM conducted the health economic analysis. All authors contributed to the final manuscript.  
53  
54

55 382 **Acknowledgements**  
56

57  
58 383 We are grateful to the patients who agreed to take part in the MAVRIC trial. This trial would not  
59  
60 384 have been possible without the support of all staff in the Cardiothoracic Services in The James Cook

1  
2  
3 385 University Hospital. We would like to thank Heather Robinson and Jonathan Broughton for their  
4  
5 386 assistance with recruitment, data collection and data entry. We would like to thank the team at the  
6  
7 387 Clinical Trials Unit, including Jennifer Wilkinson, Andrew Thorpe, Leanne Marsay and Catherine Frost  
8  
9  
10 388 for their work in managing the trial and its data.  
11

12  
13 389 **Data Sharing Statement**

14  
15 390 Anonymised data from this study may be available to the scientific community subject to  
16  
17 391 appropriate ethical approval. Requests for data should be directed to the senior author.  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

392 **Table 1 – Baseline Characteristics**

393

	Mini-sternotomy group (n=135)	Conventional sternotomy group (n=135)
<b>Baseline characteristics</b>		
<b>Age: (years)</b>		
Mean ± SD	69.3 ± 9.3	68.7 ± 8.4
Range	43 - 85	39 - 88
<b>Gender: n (%)</b>		
Male	78 (57.8)	87 (64.4)
Female	57 (42.2)	48 (35.6)
<b>Ethnicity: n (%)</b>		
White British	135 (100)	135 (100)
<b>Body Mass Index (kg.m<sup>-2</sup>)</b>		
Mean ± SD	30.5 ± 5.6	30.4 ± 6.1
Range (Min – Max)	19.0 - 45.4	19.3 - 52.0
<b>EuroSCORE: Mean ± SD (Min-Max)</b>		
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)
<b>Diagnosis echocardiogram: n (%)</b>		
Regurgitation	3 (2.2)	8 (5.9)
Stenosis	132 (97.8)	127 (94.1)
<b>NYHA class: n (%)</b>		
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)
<b>*Haemoglobin prior to randomisation: g/dl</b>		
Mean ± SD	137.9 ± 14.3	137.1 ± 16.1
Range (Min – Max)	97 -173	90 -175
<b>Surgery type: n (%)</b>		
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.

394

395 **Table 2 - Red Cell Transfusions\***

	<b>Mini-sternotomy group</b>	<b>Conventional sternotomy group</b>	<b>Odds Ratio (95% CI; p value)</b>	<b>Risk difference (95% CI; p value)</b>
<b>Red Cell transfusions</b>				
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)	
<b>Red Cell Units – post operatively to 7 days</b>				
Number of patients	23/135	23/135		
Mean ± SD	1.6 ± 0.7	2.3 ± 1.7		
Range (Min – Max)	1 - 3	1 - 9		
<b>Red Cell Units – post operatively to discharge</b>				
Number of patients	34/135	29/135		
Mean ± SD	2.5 ± 2.5	2.6 ± 2.0		
Range (Min – Max)	1 - 13	1 - 11		

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

	Mini-sternotomy group	Conventional sternotomy group	Odds Ratio (95% CI; p value)
<b>Non-Red Cell transfusions</b>			
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)
<b>Non-Red Cell Component Units – Post operatively to 7 days</b>			
Number of patients	6	18	
Mean ± SD	3.2 ± 0.9	4.6 ± 1.6	
Range (Min – Max)	2 - 5	1 - 7	
<b>Non-red Blood Cell Units – post operatively to discharge</b>			
Number of patients	13	21	
Mean ± SD	4.8 ± 2.3	4.9 ± 2.3	
Range (Min – Max)	1 - 8	1 - 12	
<b>Non-red Cell Component Transfusions</b>			
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)

399

400 Table 4 - Secondary Outcomes

	Mini-sternotomy group (n=135)	Conventional sternotomy group (n=135)	Mean Difference (95% CI; p value)
<b>Cardio Pulmonary Bypass time (minutes)</b>			
Mean $\pm$ SD	82.7 $\pm$ 23.5	59.6 $\pm$ 15.1	
Range (Min – Max)	41.0 - 199	37.0 - 170.0	
<b>Aortic cross clamp time (minutes)</b>			
Mean $\pm$ SD	64.1 $\pm$ 17.1	46.3 $\pm$ 10.7	
Range (Min – Max)	32.0 - 132.0	32.0 - 97.0	
<b>Drain losses at 12 hours</b>			
Mean $\pm$ SD	181.6 $\pm$ 138.7	306.9 $\pm$ 348.6	-127.7 (-191.7, -63.8; p=0.0001)
Range (Min – Max)	25 - 925	25 - 3000	
<b>Drain losses at drain removal</b>			
Mean $\pm$ SD	251.7 $\pm$ 198.4	393.7 $\pm$ 378.7	-145.3 (-218.1, -72.3; p=0.0001)
Range (Min – Max)	25 - 1425	50 - 3000	
<b>Valve Characteristics</b>			
<b>Valve size: mm</b>			
Mean $\pm$ SD	23.1 $\pm$ 2.1	23.6 $\pm$ 2.5	
Range (Min – Max)	19.0 - 29.0	19.0 - 31.0	
<b>Valve type: n (%)</b>			
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)	
<b>Valve function</b>			
<b>Mean Gradient</b>			
<b>Baseline</b>			
n	111*	110*	
Mean $\pm$ SD	47.9 $\pm$ 15.7	47.7 $\pm$ 20.2	0.2 (-4.6, 5.0)
Min - Max	10-93	8-110	
<b>6 weeks</b>			
n	120*	126*	
Mean $\pm$ SD	15.7 $\pm$ 5.5	15.7 $\pm$ 5.8	0.5** (-1.0, 2.1)
Min - Max	6-33	4-34	
<b>Peak Gradient</b>			
<b>Baseline</b>			
n	125*	124*	
Mean $\pm$ SD	82.3 $\pm$ 25.9	77.1 $\pm$ 29.1	5.2 (-1.7, 2.3)
Min - Max	16-152	8-173	
<b>6 weeks</b>			
n	130*	130*	
Mean $\pm$ SD	29.9 $\pm$ 10.5	29.7 $\pm$ 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			
<b>Aortic Valve Regurgitation</b>			
<b>Nil/trivial</b>			
n/n (%)	109/134* (81.3)	109/130* (83.8)	218/264 (82.6)
<b>Mild</b>			
n/n (%)	19/134* (14.2)	18/130* (13.9)	37/264 (14.0)
<b>Moderate</b>			
n/n (%)	5/134* (3.7)	2/130* (1.5)	7/264 (2.7)
<b>Severe</b>			



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

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

Model	Incremental cost (95%CI)	Incremental QALYs (95%CI)	ICER (95%CI)	p <sup>1</sup>	p <sup>2</sup>
1 Multiple imputation, covariate adjusted <sup>4</sup>	508 (-202 to 1217)	-0.007 (-0.016 to 0.002)	Dominated <sup>3</sup>	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 <sup>4</sup>	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

402

403 **References**

- 404  
405  
406  
407  
408  
409  
410  
411  
412  
413  
414  
415  
416  
417  
418  
419  
420  
421  
422  
423  
424  
425  
426  
427  
428  
429  
430  
431  
432  
433  
434  
435  
436  
437  
438  
439  
440  
441  
442  
443  
444  
445  
446  
447  
448  
449  
450  
451
1. Blue Book Online. The Society for Cardiothoracic Surgery in Great Britain & Ireland <http://bluebook.scts.org/#> (accessed 23<sup>rd</sup> July, 2018).
  2. Leontyev S, Walther T, Borger MA, et al. Aortic Valve Replacement in Octogenarians: Utility of Risk Stratification With EuroSCORE. *Ann Thorac Surg* 2009; **87**: 1440–5.
  3. Phan K, Xie A, Di Eusano M, Yan TD. The Collaborative Research (CORE) Group. Meta-Analysis of Minimally Invasive Versus Conventional Sternotomy for Aortic Valve Replacement. *Ann Thorac Surg* 2014; **98**: 1499–511.
  4. Ghanta RK, Lapar DJ, Kern JA, et al. Minimally invasive aortic valve replacement provides equivalent outcomes at reduced cost compared with conventional aortic valve replacement: A real-world multi-institutional analysis. *J Thorac Cardiovasc Surg* 2015; **149**: 1060–5.
  5. Kirmani BH, Jones SG, Malaisrie SC, Chung DA, Williams RJ. Limited versus full sternotomy for aortic valve replacement. *Cochrane Database Syst Rev* **2017**; 4: CD011793.
  6. Fujita B, Ensminger S, Bauer T, et al; GARY Executive Board. Trends in practice and outcomes from 2011 to 2015 for surgical aortic valve replacement: an update from the German Aortic Valve Registry on 42,776 patients. *Eur J Cardiothorac Surg*. **2018**; 53: 552–559.
  7. Lehmann S, Merk DR, Etz CD, et al. Minimally invasive aortic valve replacement: the Leipzig experience. *Ann Cardiothorac Surg* **2015**; 4: 49–56.
  8. Johnston DR, Roselli EE. Minimally invasive aortic valve surgery: Cleveland Clinic Experience. *Ann Cardiothorac Surg* 2015; **4**: 140–147.
  9. Patel NN, Avlonitis VS, Jones HE, Reevesw BC, Sterne JA, Murphy GJ. Indications for red blood cell transfusion in cardiac surgery: a systematic review and meta-analysis. *Lancet Haem* 2015; **12**: e543–53.
  10. Chen QH, Wang HL, Liu L, Shao J, Yu J, Zheng RQ. Effects of restrictive red blood cell transfusion on the prognoses of adult patients undergoing cardiac surgery: a meta-analysis of randomized controlled trials. *Crit Care* 2018; **22**: 142.
  11. Pagano D, Milojevic M, Meestersa MI, et al. The Task Force on Patient Blood Management for Adult Cardiac Surgery of the European Association for Cardio-Thoracic Surgery (EACTS) and the European Association of Cardiothoracic Anaesthesiology (EACTA). EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery. *Eur J Cardio-Thorac Surg* 2018; **53**: 79–111.
  12. Dixon JR. The International Conference on Harmonization Good Clinical Practice guideline. ICH GCP *Qual Assur* 1998; **6**: 65–74.
  13. Akowuah E, Goodwin AT, Owens WA, et al. Manubrium-limited ministernotomy versus conventional sternotomy for aortic valve replacement (MAVRIC): study protocol for a randomised controlled trial. <https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-016-1768-4> *Trials* 2017; **18**: 46.
  14. NICE. Guide to the methods of Technology Appraisal. London, National Institute for Health and Care Excellence, 2013.
  15. NHS Reference Costs 2015–16. London: Department of Health, 2016.
  16. Curtis L, Burns A. Unit costs of health and social care 2015. Canterbury: the University of Kent, 2015.
  17. Aris A, Camara ML, Montiel J Delgado LJ, Galan J, Litvan H. Ministernotomy versus median sternotomy for aortic valve replacement: a prospective, randomized study. *Ann Thor Surg* 1999; **67**: 1583–7.
  18. Moustafa MA, Abdelsamad AA, Zakaria G, Omarah MM. Minimal vs median sternotomy for aortic valve replacement. *Asian Cardiovasc Thorac Annals* 2007; **15**: 472–5.

- 1  
2  
3 452 19. National Comparative Audit of Blood Transfusion  
4 453 <http://hospital.blood.co.uk/media/26859/nca->  
5 454 [2011\\_use\\_of\\_blood\\_in\\_adult\\_cardiac\\_surgery\\_report.pdf](http://hospital.blood.co.uk/media/26859/nca-2011_use_of_blood_in_adult_cardiac_surgery_report.pdf) (accessed 23<sup>rd</sup> July, 2018).  
6 455  
7 456 20. Higgins JPT, Sterne JAC, Savović J, et al. A revised tool for assessing risk of bias in randomized  
8 457 trials In: Chandler J, McKenzie J, Boutron I, Welch V (editors). *Cochrane Methods. Cochrane*  
9 458 *Database Syst Rev* 2016; **10**: CD201601.  
10 459  
11 460 21. Brown ML, McKellar SH, Sundt TM, Schaff HV. Ministernotomy versus conventional  
12 460 sternotomy for aortic valve replacement: a cochranceand meta-analysis. *J Thorac Cardiovasc*  
13 *Surg* 2009; 137: 670–79.  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## MAVRIC Trial Figures

Figure 1 – CONSORT Diagram \_\_\_\_\_  
Figure 2 - Cost-effectiveness plane: mini-sternotomy vs. conventional surgery (cost/QALY) \_\_\_\_\_

For peer review only

Figure 1 – CONSORT Diagram

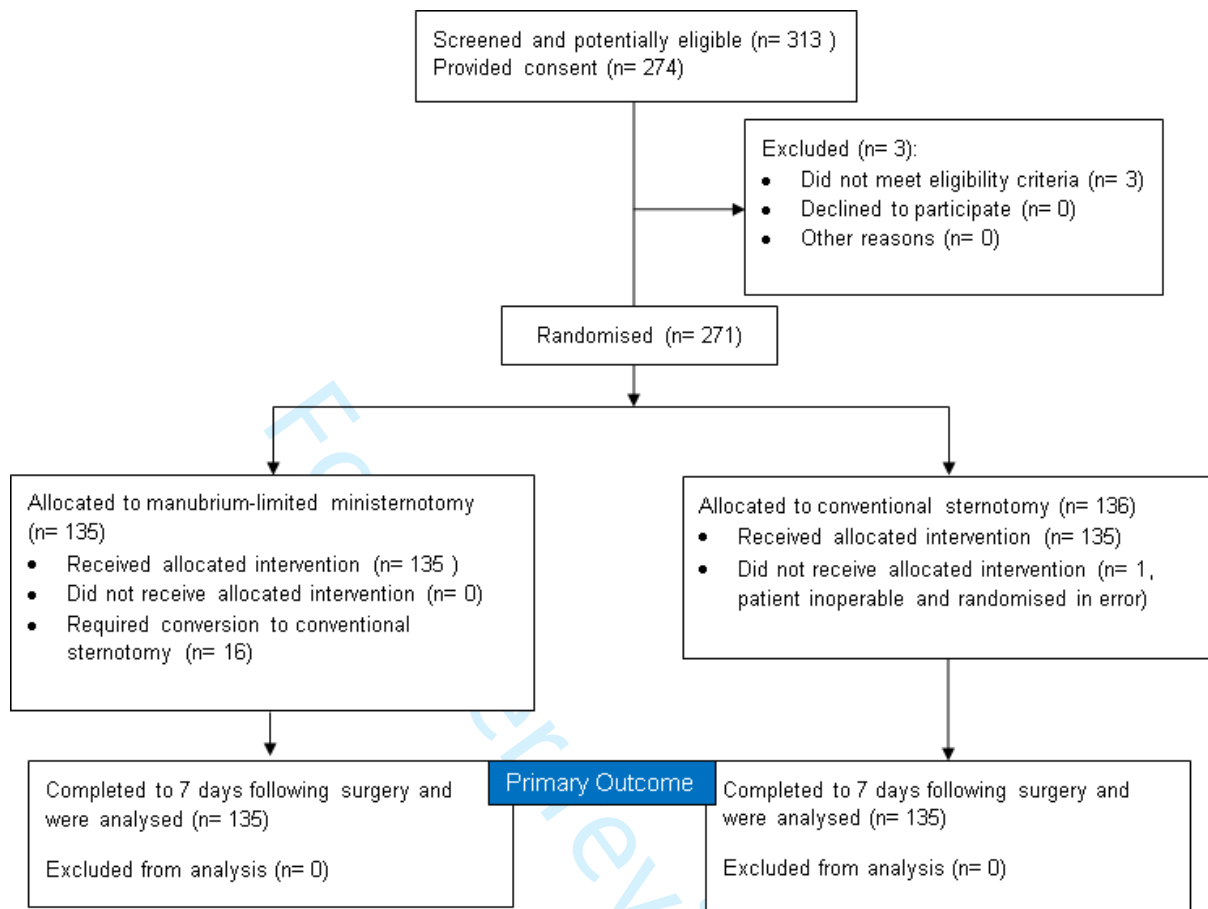
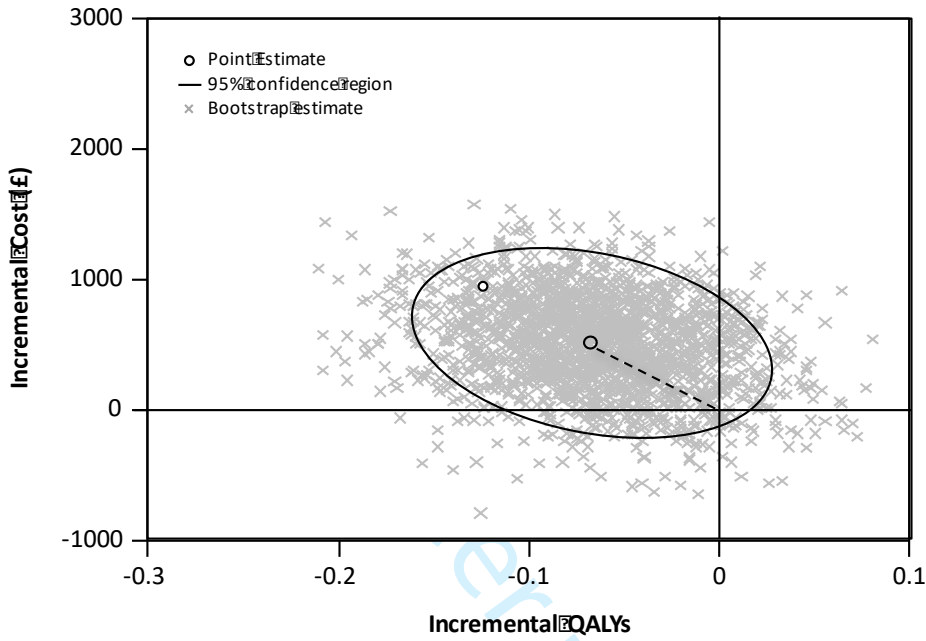


Figure 2 - Cost-effectiveness plane: mini-sternotomy vs. conventional surgery (cost/QALY)



Pre-review only

**Appendix**

Study Investigators: trial site, trial unit. Statistics, health economics, committees	2
Table 1-Eligibility criteria	3
Figure 1- recruitment	4
Table 2- Conversion from mini-sternotomy to conventional sternotomy	5
Table 3- Number of operations by surgeon	6
Figure 2- Haemoglobin profiles	6
Table 4- Analgesic use	7
Table 4- Adverse Events	8
Table 6- Health status, resource use and cost (complete cases)	9



**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

1  
2  
3 **Table 1 - Eligibility criteria**  
4

5 Inclusion Criteria

- 6  
7
  - 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

10  
11

12 Exclusion Criteria

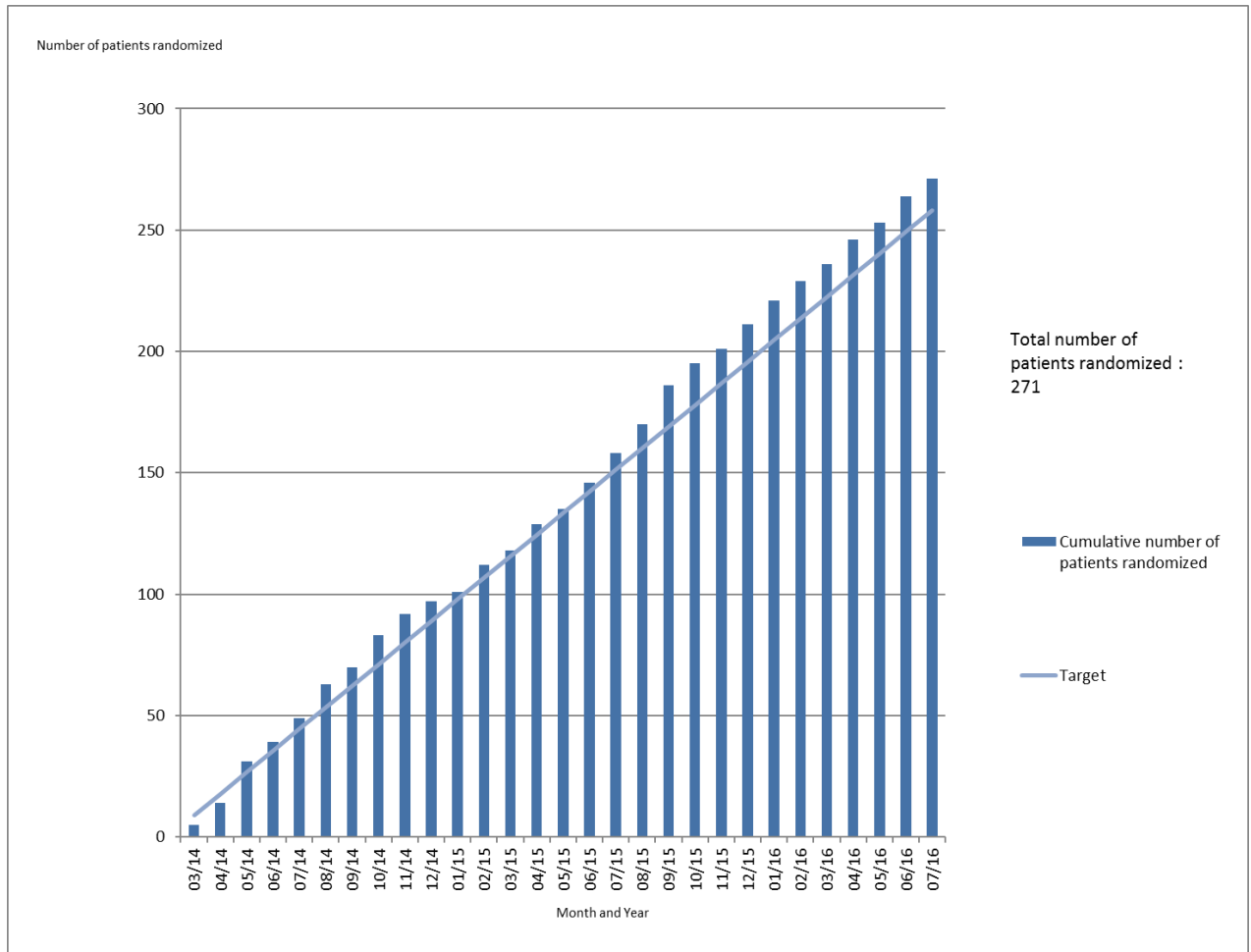
- 13  
14
  - requiring concomitant cardiac procedure(s) including redo surgery, emergency or salvage surgery,
  - only conventional median sternotomy indicated,
  - haemoglobin level < 90g/L,
  - pregnant\*,
  - currently participating in another interventional clinical trial,
  - previous cardiac surgery,
  - 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. -HKRØKΨ:LWQHVVHV
  - having any other medical, psychiatric and or social reason as determined by the consenting surgeon that precludes participation.

29

30 \* in women of child bearing age (18 ± 50) a pregnancy test was be performed within 14 days of surgery prior to  
31 randomisation.  
32

33  
34 \*\*for patients in both trial arms, pre-operative antiplatelet drugs (including clopidogrel and ticagrelor), and anti-  
35 coagulants (including warfarin and heparin) were discontinued 5 days prior to surgery. These drugs were re-  
36 started following surgery at the discretion of the clinical team. The exception to this was aspirin, which was  
37 stopped 5 days prior to surgery where possible, however continuation until the day of surgery did not exclude a  
38 patient from the trial.  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Figure 1 - Recruitment

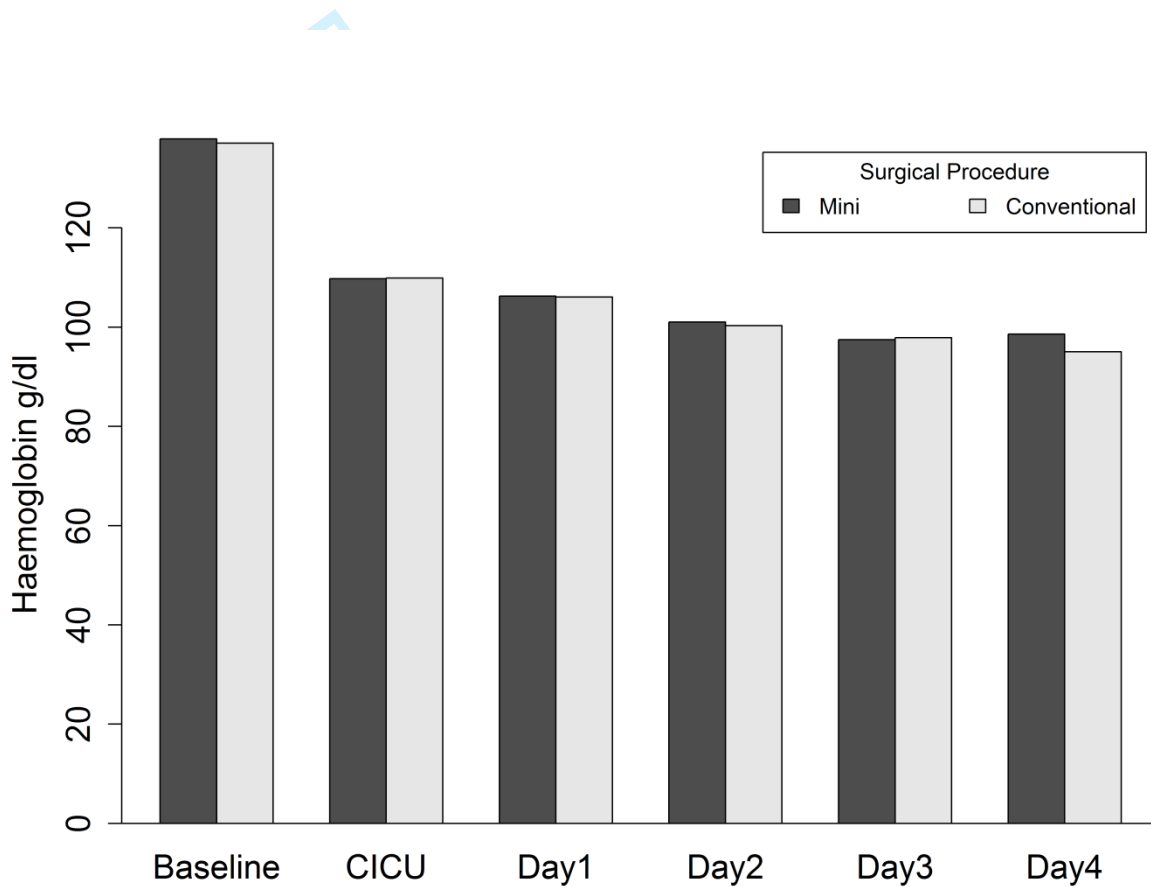


**Table 2 - Conversion from mini-sternotomy to conventional sternotomy**

Reason for conversion	Number of patients	Details
<b>Anesthetic emergency</b>	<b>2</b>	<ul style="list-style-type: none"> <li>• Patient became unstable as they were transferred into theatre and BP dropped ± required conventional to re-stabilise</li> <li>• 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)</li> </ul>
<b>Difficult vascular access (venous or arterial)</b>	<b>9</b>	<p>Venous</p> <ul style="list-style-type: none"> <li>• Femoral vessels unsuitable for cannulation</li> <li>• Poor venous drainage</li> <li>• Unable to pass venous dilators</li> <li>• Unable to insert pipe. Resistance felt, no back flow of blood. Femoral cannulation abandoned</li> <li>• Impossible to dilate femoral vein. Despite re-wiring, guide wire coiling within pelvic venous system</li> </ul> <p>Arterial</p> <ul style="list-style-type: none"> <li>• Difficulties cannulating femoral artery leading to haemodynamic instability</li> <li>• Poor access, unable to clamp aorta</li> <li>• Severe calcification of ascending aorta</li> <li>• Difficult access; aorta displaced to the left. Body habitus limited access</li> </ul>
<b>Intra-operative complications</b>	<b>5</b>	<ul style="list-style-type: none"> <li>• Bleeding from aortotomy site</li> <li>• Bleeding</li> <li>• Intra-operative decision to performed bypass graft to LAD</li> <li>• Post implant TOE showed small paravalvular leak and bleeding from aortotomy incision</li> <li>• Mild/moderate paravalvar leak on TOE. Required valve re-implant</li> </ul>
<b>TOTAL</b>	<b>16</b>	

**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 - Hemoglobin 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 (%)
<b>Analgesic use at baseline</b>			
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)
<b>At least one med at baseline</b>	<b>16 (11.9)</b>	<b>12 (8.9)</b>	<b>28 (10.4)</b>
<b>Analgesic use at day 2</b>			
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)
<b>At least one med at day 2</b>	<b>99 (73.3)</b>	<b>86 (63.7)</b>	<b>185 (68.5)</b>
<b>Analgesic use at day 3</b>			
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)
<b>At least one med at day 3</b>	<b>90 (66.7)</b>	<b>101 (74.8)</b>	<b>191 (70.7)</b>
<b>Analgesic use at Day 4</b>			
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)
<b>At least one med at day 4</b>	<b>88 (65.2)</b>	<b>81 (60.0)</b>	<b>169 (62.6)</b>
<b>Analgesic use at Week 6</b>			
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)
<b>At least one med at week 6</b>	<b>41(30.4)</b>	<b>41(30.4)</b>	<b>82(30.4)</b>
<b>Analgesic use at Week 12</b>			
Buprenorphine Patch	3(2.2)	0(0.0)	3(1.1)
Codeine Phosphate	7(5.2)	4(3.0)	11(4.1)

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Dihydrocodeine 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)
<b>At least one med at week 12</b>	<b>23(17·0)</b>	<b>22(16·3)</b>	<b>45(16·7)</b>

For peer review only

**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] <sup>1</sup>	
	mean	(SD)	N	mean	(SD)	N	mean	(95%CI)
<b>Health status<sup>2</sup></b>								
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)
<b>Resource use</b>								
Index Admission								
Length of stay (d) <sup>3</sup>	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) <sup>4</sup>	0.08	0.34	135	0.03	0.17	135	-0.05	(-0.11 to 0.02)
Time in surgery (h) <sup>4</sup>	2.32	0.63	135	3.01	0.71	135	0.69	(0.53 to 0.85)
RBC (u) <sup>4</sup>	0.59	1.45	135	0.55	1.28	135	-0.04	(-0.37 to 0.28)
FFP (u) <sup>4</sup>	0.57	1.43	135	0.34	1.21	135	-0.23	(-0.55 to 0.09)
Platelets (u) <sup>4</sup>	0.22	0.64	135	0.12	0.46	135	-0.10	(-0.24 to 0.03)
Cryoprecipitate (u) <sup>4</sup>	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)
<b>Cost<sup>5</sup></b>								
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
<b>Title and abstract</b>			
	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
<b>Introduction</b>			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	3,5
<b>Methods</b>			
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
<b>Randomisation:</b>			
Sequence	8a	Method used to generate the random allocation sequence	2,4
generation	8b	Type of randomisation; details of any restriction (such as blocking and block size)	2,4

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

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	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	2,4
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	4
	11b	If relevant, description of the similarity of interventions	2,4,5
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	4
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	7
<b>Results</b>			
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	7
Recruitment	13b	For each group, losses and exclusions after randomisation, together with reasons	9,17
	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
<b>Discussion</b>			
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

1			
2			
3	Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence
4			13,14
5	<b>Other information</b>		
6	Registration	23	Registration number and name of trial registry
7			1,4
8	Protocol	24	Where the full trial protocol can be accessed, if available
9			4
10	Funding	25	Sources of funding and other support (such as supply of drugs), role of funders
11			4, 15

11 \*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If  
 12 relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal  
 13 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](http://www.consort-statement.org).  
 14  
 15  
 16  
 17  
 18  
 19  
 20  
 21  
 22  
 23  
 24  
 25  
 26  
 27  
 28  
 29  
 30  
 31  
 32  
 33  
 34  
 35  
 36  
 37  
 38  
 39  
 40  
 41  
 42  
 43  
 44  
 45  
 46

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

For peer review only

# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-041398.R1
Article Type:	Original research
Date Submitted by the Author:	26-Oct-2020
Complete List of Authors:	Hancock, Helen; Newcastle University, Newcastle Clinical Trials Unit Maier, Rebecca; Newcastle University, Newcastle Clinical Trials Unit Kasim, Adetayo; Durham University, Wolfson Research Institute for Health and Wellbeing Mason, James; University of Warwick, Warwick Medical School Murphy, Gavin; University of Leicester, Department of Cardiovascular Sciences and NIHR Leicester Biomedical Research Unit in Cardiovascular Medicine Goodwin, Andrew; South Tees Hospitals NHS Foundation Trust, James Cook Hospital Owens, W; South Tees Hospitals NHS Foundation Trust, James Cook Hospital Akowuah, Enoch; South Tees Hospitals NHS Foundation Trust, James Cook Hospital
<b>Primary Subject Heading</b>:	Surgery
Secondary Subject Heading:	Evidence based practice, Intensive care, Research methods, Cardiovascular medicine
Keywords:	HEALTH ECONOMICS, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Adult surgery < SURGERY, Cardiac surgery < SURGERY, Clinical trials < THERAPEUTICS

SCHOLARONE™  
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

**Title**

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

**Authors**

Helen C Hancock, PhD<sup>1</sup>, Rebecca H Maier<sup>1</sup>, MSc, Adetayo S Kasim, PhD<sup>2</sup>, James M Mason, DPhil<sup>3</sup>, Gavin J. Murphy, FRCS (C.Th)<sup>4</sup>, Andrew T Goodwin, FRCS (C.Th)<sup>5</sup>, W Andrew Owens, FRCS (C.Th)<sup>5</sup>, Enoch F Akowuah, FRCS (C.Th)<sup>5</sup>.

1. Newcastle Clinical Trials Unit, Newcastle University; 2. Durham Research Methods Centre, Durham University; 3. Warwick Medical School, University of Warwick; 4. Department of Cardiovascular Sciences, University of Leicester; 5. Cardiothoracic Services, South Tees Hospitals NHS Foundation Trust, The James Cook University Hospital.

**Word count 3343**

**Corresponding author:** Enoch Akowuah

Cardiothoracic Services, South Tees Hospitals NHS Foundation Trust, The James Cook University Hospital, Marton Road, Middlesbrough. TS3 4BW.  
E mail Enoch.Akowuah@nhs.net



**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

1  
2  
3 138.7) vs conventional, mean 306.9ml (SD 348.6)); this did not reduce red-cell transfusions. Mean  
4  
5 valve size and post-operative valve function were comparable between mini-sternotomy and  
6  
7 conventional groups; 23mm vs 24mm, and 6/134 moderate or severe aortic regurgitation vs 3/130,  
8  
9 respectively. Mini-sternotomy resulted in longer bypass (82.7 minutes (SD 23.5) vs 59.6 minutes (SD  
10  
11 15.1)) and cross clamp times (64.1 minutes (SD 17.1) vs 46.3 minutes (SD 10.7)). Conventional  
12  
13 sternotomy was more cost-effective with only a 5.8% probability of mini-sternotomy being cost-  
14  
15 effective at a willingness to pay of £20,000/QALY.  
16  
17

### 18 **Conclusions**

19  
20  
21  
22 AVR via mini-sternotomy did not reduce red blood cell transfusion within 7 days following surgery  
23  
24 when compared to conventional sternotomy.  
25  
26

27  
28  
29 **Clinical Trials Registry:** ISRCTN29567910  
30  
31

32  
33  
34  
35 Key word: minimally invasive, aortic valve, clinical trial, cardiac surgery, replacement,  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## 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.<sup>1</sup>

In the UK, the National adult cardiac surgery audit published by NICOR (National Institute for Cardiac Outcome Reporting) reported 13,027 procedures for aortic valve disease in the UK from April 2018 to March 2019.<sup>2</sup> Outcomes are generally excellent with in-hospital observed mortality in the UK of 1.5% for first time elective procedures.<sup>3</sup> 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.<sup>2</sup>

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.<sup>4</sup> 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<sup>5,6</sup> may be confounded by multiple sources of bias and are at odds with limited evidence from RCTs that have not shown improved outcomes.<sup>7</sup> This uncertainty is reflected by variations in uptake internationally.<sup>8,9,10</sup>

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

1  
2  
3 transfusion rates, a contemporary marker of surgical trauma and indicator of adverse outcomes;<sup>11</sup>  
4  
5 this has been contested,<sup>12</sup> though the evidence is not conclusive.<sup>13</sup> An embedded cost effectiveness  
6  
7 analysis evaluated whether the intervention was cost effective in a UK National Health Service (NHS)  
8  
9 setting.  
10

## 11 **Patients and Methods**

### 12 **Trial Design**

13  
14 MAVRIC was a single centre, single-blind, RCT comparing AVR via manubrium-limited mini-  
15  
16 sternotomy group (intervention) and AVR via conventional sternotomy group (usual care). A NHS  
17  
18 Research Ethics Committee approved the trial, which was conducted in accordance with the  
19  
20 principles of the International Conference on Harmonisation of Good Clinical Practice.<sup>14</sup> South Tees  
21  
22 Hospitals NHS Foundation Trust was the Sponsor and recruiting centre.  
23  
24  
25  
26  
27

### 28 **Patient Public Involvement**

29  
30 In designing the study, we asked patients their view on what factors may affect whether they took  
31  
32 part in the study. This was done in an outpatient setting and via a postal questionnaire. They felt  
33  
34 expertise was important. Most patients felt that although the cosmetic benefit of the minimally  
35  
36 invasive approach was appealing, they expected some clinical benefit from minimally invasive  
37  
38 surgery as well. Importantly most patients said they would accept being blind to the type of surgery  
39  
40 they had received for 48 hours after the procedure.  
41  
42  
43

### 44 **Participants**

45  
46 Patients were eligible if they were aged 18 years or over; required first-time, non-emergency,  
47  
48 isolated AVR surgery; and were willing to provide written informed consent. Full details of the  
49  
50 eligibility criteria are in the **Supplementary Material**.  
51  
52  
53

### 54 **Randomisation**

55  
56 Eligible patients were randomised by members of the research team using a 24-hour, central,  
57  
58 secure, web-based randomisation system with concealed allocation, managed by the Clinical Trials  
59  
60

1  
2  
3 Unit; randomisation was in a 1:1 ratio between mini and conventional sternotomy and stratified by  
4  
5 baseline logistic EuroSCORE and pre-operative Hemoglobin (Hb).  
6  
7

### 8 **Interventions**

9  
10 Manubrium-limited mini-sternotomy was performed using a 5-7cm midline skin incision dividing the  
11  
12 manubrium from the sternal notch to 1cm below the manubrium-sternal junction. Cardiopulmonary  
13  
14 bypass was established with an ascending aortic cannula and percutaneous femoral venous  
15  
16 cannulation. Conventional median sternotomy was performed using a midline incision from the  
17  
18 sternal notch to the xiphisternum. Key aspects of anaesthesia were standardised, and are detailed in  
19  
20 the protocol.<sup>15</sup>  
21  
22  
23

### 24 **Blinding**

25  
26 All patients were blinded to type of sternotomy received until after their day 2 Quality of Life and  
27  
28 pain assessments. All patients had trial-specific opaque dressings applied to their sternal wound, and  
29  
30 groin before leaving theatre.  
31  
32

### 33 **Transfusion Protocol**

34  
35 The post-operative period, and trial protocol in relation to red cell and non-red cell transfusion,  
36  
37 began on admission to the Cardiothoracic Intensive Care Unit (CICU); it specified that patient's  
38  
39 should receive a red cell transfusion if their Hb dropped below 80 g/L; or were bleeding by 400ml/h  
40  
41 or more, or were bleeding 100ml/h or more for 4 or more hours with a Hb equal to or greater than  
42  
43 80g/L; or had blood loss with haemodynamic instability irrespective of thromboelastography (TEG)  
44  
45 and/or clotting profile results. One unit of red cells was transfused and Hb level checked before  
46  
47 transfusing another unit.  
48  
49

50  
51 Participants received a non-red cell transfusion if both of the following criteria were met: bleeding  
52  
53 defined by 400ml/h or more, or blood loss of 100ml/h or more for 4 hours or more; TEG or  
54  
55 coagulation guided transfusion indicated.  
56  
57  
58  
59  
60

## Outcomes

All outcomes 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 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)

1  
2  
3 undergoing AVR via mini-sternotomy. Using Fisher's Exact test, 90% power, 5% alpha, we estimated  
4 that 260 patients would be required to detect a 17% reduction in the proportion of patients  
5 requiring a red cell transfusion (13% compared with 30%), using a two-sided test. Allowing for loss to  
6 follow up, the sample size was increased to 270.  
7  
8  
9

10  
11  
12 The primary analysis was based on intention-to-treat principles, in accordance with a pre-specified  
13 statistical analysis plan.  
14

15  
16  
17 The primary efficacy analysis was based on a logistic regression model with only group (minimally  
18 invasive and conventional) and stratifying factors (baseline logistic EuroSCORE and Hb) as the  
19 predictors. Odds ratios and their associated 95% confidence interval are reported in the primary  
20 analysis. Sensitivity analysis using alternating logistic regression was performed for the primary  
21 endpoint to sensitise for surgeon effects; the odds of receiving a red cell transfusion for two patients  
22 treated by the same surgeon was compared to two patients treated by different surgeons.  
23  
24  
25  
26  
27  
28  
29

30  
31 All analyses of secondary continuous efficacy endpoints at single time points were based on linear  
32 models where, if appropriate, a log normal model was fitted to sensitise the linearity assumption.  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65  
66  
67  
68  
69  
70  
71  
72  
73  
74  
75  
76  
77  
78  
79  
80  
81  
82  
83  
84  
85  
86  
87  
88  
89  
90  
91  
92  
93  
94  
95  
96  
97  
98  
99  
100  
101  
102  
103  
104  
105  
106  
107  
108  
109  
110  
111  
112  
113  
114  
115  
116  
117  
118  
119  
120  
121  
122  
123  
124  
125  
126  
127  
128  
129  
130  
131  
132  
133  
134  
135  
136  
137  
138  
139  
140  
141  
142  
143  
144  
145  
146  
147  
148  
149  
150  
151  
152  
153  
154  
155  
156  
157  
158  
159  
160  
161  
162  
163  
164  
165  
166  
167  
168  
169  
170  
171  
172  
173  
174  
175  
176  
177  
178  
179  
180  
181  
182  
183  
184  
185  
186  
187  
188  
189  
190  
191  
192  
193  
194  
195  
196  
197  
198  
199  
200  
201  
202  
203  
204  
205  
206  
207  
208  
209  
210  
211  
212  
213  
214  
215  
216  
217  
218  
219  
220  
221  
222  
223  
224  
225  
226  
227  
228  
229  
230  
231  
232  
233  
234  
235  
236  
237  
238  
239  
240  
241  
242  
243  
244  
245  
246  
247  
248  
249  
250  
251  
252  
253  
254  
255  
256  
257  
258  
259  
260  
261  
262  
263  
264  
265  
266  
267  
268  
269  
270  
271  
272  
273  
274  
275  
276  
277  
278  
279  
280  
281  
282  
283  
284  
285  
286  
287  
288  
289  
290  
291  
292  
293  
294  
295  
296  
297  
298  
299  
300  
301  
302  
303  
304  
305  
306  
307  
308  
309  
310  
311  
312  
313  
314  
315  
316  
317  
318  
319  
320  
321  
322  
323  
324  
325  
326  
327  
328  
329  
330  
331  
332  
333  
334  
335  
336  
337  
338  
339  
340  
341  
342  
343  
344  
345  
346  
347  
348  
349  
350  
351  
352  
353  
354  
355  
356  
357  
358  
359  
360  
361  
362  
363  
364  
365  
366  
367  
368  
369  
370  
371  
372  
373  
374  
375  
376  
377  
378  
379  
380  
381  
382  
383  
384  
385  
386  
387  
388  
389  
390  
391  
392  
393  
394  
395  
396  
397  
398  
399  
400  
401  
402  
403  
404  
405  
406  
407  
408  
409  
410  
411  
412  
413  
414  
415  
416  
417  
418  
419  
420  
421  
422  
423  
424  
425  
426  
427  
428  
429  
430  
431  
432  
433  
434  
435  
436  
437  
438  
439  
440  
441  
442  
443  
444  
445  
446  
447  
448  
449  
450  
451  
452  
453  
454  
455  
456  
457  
458  
459  
460  
461  
462  
463  
464  
465  
466  
467  
468  
469  
470  
471  
472  
473  
474  
475  
476  
477  
478  
479  
480  
481  
482  
483  
484  
485  
486  
487  
488  
489  
490  
491  
492  
493  
494  
495  
496  
497  
498  
499  
500  
501  
502  
503  
504  
505  
506  
507  
508  
509  
510  
511  
512  
513  
514  
515  
516  
517  
518  
519  
520  
521  
522  
523  
524  
525  
526  
527  
528  
529  
530  
531  
532  
533  
534  
535  
536  
537  
538  
539  
540  
541  
542  
543  
544  
545  
546  
547  
548  
549  
550  
551  
552  
553  
554  
555  
556  
557  
558  
559  
560  
561  
562  
563  
564  
565  
566  
567  
568  
569  
570  
571  
572  
573  
574  
575  
576  
577  
578  
579  
580  
581  
582  
583  
584  
585  
586  
587  
588  
589  
590  
591  
592  
593  
594  
595  
596  
597  
598  
599  
600  
601  
602  
603  
604  
605  
606  
607  
608  
609  
610  
611  
612  
613  
614  
615  
616  
617  
618  
619  
620  
621  
622  
623  
624  
625  
626  
627  
628  
629  
630  
631  
632  
633  
634  
635  
636  
637  
638  
639  
640  
641  
642  
643  
644  
645  
646  
647  
648  
649  
650  
651  
652  
653  
654  
655  
656  
657  
658  
659  
660  
661  
662  
663  
664  
665  
666  
667  
668  
669  
670  
671  
672  
673  
674  
675  
676  
677  
678  
679  
680  
681  
682  
683  
684  
685  
686  
687  
688  
689  
690  
691  
692  
693  
694  
695  
696  
697  
698  
699  
700  
701  
702  
703  
704  
705  
706  
707  
708  
709  
710  
711  
712  
713  
714  
715  
716  
717  
718  
719  
720  
721  
722  
723  
724  
725  
726  
727  
728  
729  
730  
731  
732  
733  
734  
735  
736  
737  
738  
739  
740  
741  
742  
743  
744  
745  
746  
747  
748  
749  
750  
751  
752  
753  
754  
755  
756  
757  
758  
759  
760  
761  
762  
763  
764  
765  
766  
767  
768  
769  
770  
771  
772  
773  
774  
775  
776  
777  
778  
779  
780  
781  
782  
783  
784  
785  
786  
787  
788  
789  
790  
791  
792  
793  
794  
795  
796  
797  
798  
799  
800  
801  
802  
803  
804  
805  
806  
807  
808  
809  
810  
811  
812  
813  
814  
815  
816  
817  
818  
819  
820  
821  
822  
823  
824  
825  
826  
827  
828  
829  
830  
831  
832  
833  
834  
835  
836  
837  
838  
839  
840  
841  
842  
843  
844  
845  
846  
847  
848  
849  
850  
851  
852  
853  
854  
855  
856  
857  
858  
859  
860  
861  
862  
863  
864  
865  
866  
867  
868  
869  
870  
871  
872  
873  
874  
875  
876  
877  
878  
879  
880  
881  
882  
883  
884  
885  
886  
887  
888  
889  
890  
891  
892  
893  
894  
895  
896  
897  
898  
899  
900  
901  
902  
903  
904  
905  
906  
907  
908  
909  
910  
911  
912  
913  
914  
915  
916  
917  
918  
919  
920  
921  
922  
923  
924  
925  
926  
927  
928  
929  
930  
931  
932  
933  
934  
935  
936  
937  
938  
939  
940  
941  
942  
943  
944  
945  
946  
947  
948  
949  
950  
951  
952  
953  
954  
955  
956  
957  
958  
959  
960  
961  
962  
963  
964  
965  
966  
967  
968  
969  
970  
971  
972  
973  
974  
975  
976  
977  
978  
979  
980  
981  
982  
983  
984  
985  
986  
987  
988  
989  
990  
991  
992  
993  
994  
995  
996  
997  
998  
999  
1000

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,<sup>16</sup> was employed. Health care utilisation



1  
2  
3 was captured up to three months following discharge from index surgery. Resource use was valued  
4  
5 in 2016 pounds sterling using national sources,<sup>17,18</sup> and where necessary, local micro-costing  
6  
7 (£1=\$1.50). Resources included surgery, transfusions, length of hospital stay (by level of care),  
8  
9 complications and further surgery, and community care following discharge.

10  
11  
12 Mechanisms of missingness within the data were explored and multiple imputation methods were  
13  
14 applied to impute missing data and minimise bias, using chained equations and predictive mean  
15  
16 matching. Imputation sets were analysed within a bivariate analysis of costs and QALYS, to generate  
17  
18 incremental within-trial cost per QALY estimates and credible intervals. Findings were presented on  
19  
20 the ICER plane and with Cost-Effectiveness Acceptability Curves, using the net monetary benefit  
21  
22 approach.  
23  
24

25  
26 Imputation was conducted according to good practice guidance.<sup>19,20</sup> Multiple imputation provides  
27  
28 unbiased estimates of treatment effect if data are missing at random (MAR) and the missingness  
29  
30 process is adequately characterised : this assumption was explored in the data, for example by using  
31  
32 logistic regression for missingness of costs and QALYS against baseline variables.<sup>21</sup> A regression  
33  
34 model was used to generate multiple imputed datasets (or 'draws') for individual treatment groups,  
35  
36 where missing values were predicted drawing on predictive covariates. Outcome measures and  
37  
38 costs (at each time point) contributed as predictors and imputed variables. Each draw provided a  
39  
40 complete dataset, reflecting the distributions and correlations between variables. Predictive mean  
41  
42 matching drawn from the five nearest neighbours (knn=5) was used to enhance the plausibility and  
43  
44 robustness of imputed values; normality was not assumed. The imputation model used fully  
45  
46 conditional (MCMC) methods. Draws were analysed using bivariate regression (see below) within  
47  
48 the Stata MI framework, capturing within and between variances for imputed samples.<sup>22</sup> After  
49  
50 examining the fraction of missing information (FMI) from finite imputation sampling, 20 draws was  
51  
52 taken in the final imputation model.  
53  
54  
55  
56  
57  
58  
59  
60

## Results

### Trial Population

MAVRIC recruited to time and target; 313 patients were considered for the trial; 274 patients consented between 20<sup>th</sup> March 2014 and 25<sup>th</sup> 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

1  
2  
3 Mini-sternotomy resulted in longer Cardio Pulmonary Bypass times; mini group 82.7 minutes (SD  
4 23.5), conventional 59.6 minutes (SD 15.1). Aortic cross clamp times were also longer; mini group  
5 64.1 minutes (SD 17.1), conventional 46.3 minutes (SD 10.7) (**Table 4**).

### 10 **Chest drain losses**

11  
12  
13 Mini-sternotomy resulted in a 40.8% reduction in chest drain losses at 12 hours, the mini group  
14 mean was 181.6ml (SD 138.7), conventional group mean was 306.9ml (SD 348.6); the mean  
15 difference was -127.7ml (95% CI -191.7, -63.8, p=0.0001). At drain removal mean difference was -  
16 145.3ml (95% CI -218.1, -72.3; p=0.0001) (**Table 4**).

### 22 **Ventilation time**

23  
24  
25 Ventilation time between the groups was similar; 9.6 hours (SD 5.6) in the mini group and 9.8 hours  
26 (SD 6.9) in the conventional (**Table 4**).

### 30 **Intensive care unit length of stay**

31  
32  
33 There was no difference in intensive care unit length of stay between groups (**Supplementary**  
34 **Material**).

### 38 **Post-operative pain**

39  
40  
41 There was no difference in pain scores between groups; analgesic use is also included to assist  
42 interpretation (**Supplementary Material**).

### 46 **Lung function**

47  
48  
49 There was no difference between groups in lung function at baseline. At 4 days post-surgery, mean  
50 Forced Expiratory Volume 1 (FEV1) 1123mls (SD 433) and Forced Vital Capacity, FVC 1479mls (SD  
51 583) were significantly reduced in the mini group, compared to the conventional; FEV1 1321 (SD  
52 524), FVC 1698 (SD 707). Mean differences for FEV1 and FVC were statistically significant at 4 days  
53 post-surgery; -171mls (95% CI -265, -77; p=0.0004) and -130mls (95% CI -269, 0; p=0.0498)

1  
2  
3 respectively, after adjusting for baseline FEV1, FVC, and randomisation factors (**Supplementary**  
4  
5 **Material**).

### 8 **Hospital length of stay**

9  
10 The mean time to patients being fit for hospital discharge following index surgery was similar  
11  
12 between groups. The mean post-operative hospital length of stay was 7.4 (SD 7.5, range 3-79) in the  
13  
14 mini group, and 6.3 days (SD 3.2, range 3-31) in the conventional (**Supplementary Material**).

### 17 **Post-operative valve function**

18  
19 The distribution of valve types and valve sizes were similar; mean valve size inserted was 23mm in  
20  
21 the mini group and 24mm in the conventional (**Table 4**). Over 70% of patients in each group received  
22  
23 a tissue valve, over 25% received a mechanical valve and 2-3% received a sutureless tissue valve.  
24  
25 Post operative transthoracic echo showed a similar decrease in mean aortic valve gradient in both  
26  
27 groups to 16mmHg; peak gradient decreased to 30mmHg in both groups (**Table 4**). 6/134 patients  
28  
29 had moderate or severe aortic regurgitation in the mini group compared to 3/130 in the  
30  
31 conventional (**Table 4**).

### 35 **Adverse events**

36  
37 There were no in-hospital deaths in either group. At 12 weeks follow up, there were 4 deaths; 2 in  
38  
39 each arm of the study. Adverse events in each group were broadly similar and within acceptable  
40  
41 clinical limits. By 12 weeks, 4/135 patients in the mini-sternotomy group and 1/135 in the  
42  
43 conventional group had suffered a stroke (defined as a persistent neurological deficit). Atrial  
44  
45 arrhythmias were identified in 61/135 patients in the mini group and 51/135 in the conventional. By  
46  
47 12 weeks, 11/135 patients in the mini group and 3/135 patients in the conventional had a sternal  
48  
49 wound infection (**Supplementary Material**).

### 53 **Quality of Life, Costs and Cost-Effectiveness**

54  
55 Costs during the index admission were significantly greater for the mini group (mini-conventional:  
56  
57 mean difference £1140; 95% CI 303, 1977), primarily reflecting the additional cost of theatre time  
58  
59  
60

1  
2  
3 **(Supplementary Material)**. Overall costs were not significantly different (mini-conventional: mean  
4 difference £746; 95% CI -245, 1737). There was no significant difference in quality of life between  
5  
6 groups up to 12 weeks (mini-conventional: mean difference area under curve -0.009 QALYs; 95% CI  
7  
8 0.020, 0.002). Although differences in costs and quality-of-life were not individually significant, the  
9  
10 bivariate cost-QALY distribution (combining these two) suggests conventional surgery might be more  
11  
12 cost-effective (**Figure 2**). In the base-case model, mini was dominated by conventional surgery (due  
13  
14 to greater cost and less benefit), with only a 5.8% probability of being cost-effective at a willingness  
15  
16 to pay of £20,000/QALY (**Table 5**).

### 21 **Sensitivity and Subgroup Analyses**

22  
23 There was no significant surgeon effect; the odds of receiving a red cell transfusion for two patients  
24  
25 treated by the same surgeon compared to two patients treated by different surgeons was 1.2 (95%  
26  
27 CI 0.9, 1.6;  $p=0.1379$ ).

28  
29 Protocol deviations in respect of cell transfusions did not affect the results of the primary analysis;  
30  
31 excluding these patients produced the same results as those from the intention-to-treat analysis.

### 36 **Discussion**

#### 37 **Main findings**

38  
39 Mini-sternotomy was not superior to conventional sternotomy with respect to red cell transfusion  
40  
41 requirements within 7 days of surgery. Analysis of secondary endpoints showed a statistically  
42  
43 significant difference in transfusion volumes of non-red cell blood components. Aortic valve size and  
44  
45 post-operative function were comparable in the 2 groups. Mini-sternotomy resulted in a relative  
46  
47 reduction in chest drain losses however, higher blood loss in the conventional group did not  
48  
49 translate into red cell transfusions. Mini patients had substantially longer bypass and cross clamp  
50  
51 times and worse lung function at 4 days post-surgery. Lung function at twelve weeks, and adverse  
52  
53 event rates were otherwise not different between groups. Conventional sternotomy was found to be  
54  
55 more cost-effective. MAVRIC findings contradict those from other trials that pre-date it.<sup>23,24</sup> Two 100  
56  
57 patient RCTs published since MAVRIC and the systematic review, do not alter the discussion.<sup>25,26</sup>  
58  
59  
60

1  
2  
3 Both found no difference in major clinical outcomes, and findings relating to shorter hospital stay in  
4 mini-sternotomy; a reduction in bleeding through chest drains, and mean difference in EQ-5D scores  
5  
6 at baseline and at 6 weeks<sup>25</sup> are consistent with MAVRIC findings.  
7  
8  
9

### 10 11 12 *Strengths and limitations*

13  
14 This is the largest single trial to have compared minimally invasive sternotomy to conventional  
15 median sternotomy for AVR. A recent Cochrane review identified 511 patients from 7 previous  
16 RCTs.<sup>7</sup> In MAVRIC, the mini-sternotomy technique divided only the manubrium and is therefore less  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

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.<sup>7</sup> 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%.<sup>27</sup> 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.<sup>7</sup> 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.<sup>7</sup> 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.<sup>7</sup> This information should be disseminated to patients, clinicians and commissioners to inform decisions about AVR surgery including commissioning.

**Role of funding source**

This work was supported by the NIHR Research for Patient Benefit Programme (grant number PB-PG-1112-29035). GJM is supported by the British Heart Foundation (CH/12/1/29419) and the NIHR Leicester Biomedical Research Centre.

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

Adetayo S Kasim (ASK): None

James M Mason (JMM): None

Gavin J Murphy (GJM) declares research grant funding from Zimmer Biomet for a trial of blood transfusion.

Andrew T Goodwin (ATG): None

W Andrew Owens (WAO): None

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.

**Acknowledgements**

We are grateful to the patients who agreed to take part in the MAVRIC trial. This trial would not have been possible without the support of all staff in the Cardiothoracic Services in The James Cook University Hospital. We would like to thank Heather Robinson and Jonathan Broughton for their



1  
2  
3 assistance with recruitment, data collection and data entry. We would like to thank the team at the  
4  
5 Clinical Trials Unit, including Jennifer Wilkinson, Andrew Thorpe, Leanne Marsay and Catherine Frost  
6  
7 for their work in managing the trial and its data.  
8  
9

#### 10 **Data Sharing Statement**

11 Anonymised data from this study may be available to the scientific community subject to  
12  
13 appropriate ethical approval. Requests for data should be directed to the senior author.  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

**Table 1.** Baseline characteristics of participants by group

	Mini-sternotomy group (n=135)	Conventional sternotomy group (n=135)
<b>Baseline characteristics</b>		
<b>Age: (years)</b>		
Mean $\pm$ SD	69.3 $\pm$ 9.3	68.7 $\pm$ 8.4
Range	43 - 85	39 - 88
<b>Gender: n (%)</b>		
Male	78 (57.8)	87 (64.4)
Female	57 (42.2)	48 (35.6)
<b>Ethnicity: n (%)</b>		
White British	135 (100)	135 (100)
<b>Body Mass Index (kg.m<sup>-2</sup>)</b>		
Mean $\pm$ SD	30.5 $\pm$ 5.6	30.4 $\pm$ 6.1
Range (Min – Max)	19.0 - 45.4	19.3 - 52.0
<b>EuroSCORE: Mean <math>\pm</math> SD (Min-Max)</b>		
Logistic	5.2 $\pm$ 3.5 (1.5 - 29.5)	5.1 $\pm$ 3.5 (1.5 - 21.0)
II – Mean	1.5 $\pm$ 1.1 (0.5 - 10.2)	1.5 $\pm$ 1.2 (0.5 - 10.0)
<b>Diagnosis echocardiogram: n (%)</b>		
Regurgitation	3 (2.2)	8 (5.9)
Stenosis	132 (97.8)	127 (94.1)
<b>NYHA class: n (%)</b>		
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)
<b>*Haemoglobin prior to randomisation: g/dl</b>		
Mean $\pm$ SD	137.9 $\pm$ 14.3	137.1 $\pm$ 16.1
Range (Min – Max)	97 -173	90 -175
<b>Surgery type: n (%)</b>		
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)
<b>Red Cell Transfusions</b>				
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)	
<b>Red Cell Units – post operatively to 7 days</b>				
Number of patients	23/135	23/135		
Mean $\pm$ SD	1.6 $\pm$ 0.7	2.3 $\pm$ 1.7		
Range (Min – Max)	1 - 3	1 - 9		
<b>Red Cell Units – post operatively to discharge</b>				
Number of patients	34/135	29/135		
Mean $\pm$ SD	2.5 $\pm$ 2.5	2.6 $\pm$ 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<sup>28</sup>, 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)
<b>Non-Red Cell Transfusions</b>			
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)
<b>Non-Red Cell Component Units – Post operatively to 7 days</b>			
Number of patients	6	18	
Mean ± SD	3.2 ± 0.9	4.6 ± 1.6	
Range (Min – Max)	2 - 5	1 - 7	
<b>Non-red Blood Cell Units – post operatively to discharge</b>			
Number of patients	13	21	
Mean ± SD	4.8 ± 2.3	4.9 ± 2.3	
Range (Min – Max)	1 - 8	1 - 12	
<b>Non-red Cell Component Transfusions</b>			
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)
<b>Cardio Pulmonary Bypass time (minutes)</b>			
Mean $\pm$ SD	82.7 $\pm$ 23.5	59.6 $\pm$ 15.1	
Range (Min – Max)	41.0 - 199	37.0 - 170.0	
<b>Aortic cross clamp time (minutes)</b>			
Mean $\pm$ SD	64.1 $\pm$ 17.1	46.3 $\pm$ 10.7	
Range (Min – Max)	32.0 - 132.0	32.0 - 97.0	
<b>Drain losses at 12 hours</b>			
Mean $\pm$ SD	181.6 $\pm$ 138.7	306.9 $\pm$ 348.6	-127.7 (-191.7, -63.8; p=0.0001)
Range (Min – Max)	25 - 925	25 - 3000	
<b>Drain losses at drain removal</b>			
Mean $\pm$ SD	251.7 $\pm$ 198.4	393.7 $\pm$ 378.7	-145.3 (-218.1, -72.3; p=0.0001)
Range (Min – Max)	25 - 1425	50 - 3000	
<b>Valve Characteristics</b>			
<b>Valve size: mm</b>			
Mean $\pm$ SD	23.1 $\pm$ 2.1	23.6 $\pm$ 2.5	
Range (Min – Max)	19.0 - 29.0	19.0 - 31.0	
<b>Valve type: n (%)</b>			
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)	
<b>Valve function</b>			
<b>Mean Gradient</b>			
<b>Baseline</b>			
n	111*	110*	
Mean $\pm$ SD	47.9 $\pm$ 15.7	47.7 $\pm$ 20.2	0.2 (-4.6, 5.0)
Min - Max	10-93	8-110	
<b>6 weeks</b>			
n	120*	126*	
Mean $\pm$ SD	15.7 $\pm$ 5.5	15.7 $\pm$ 5.8	0.5** (-1.0, 2.1)
Min - Max	6-33	4-34	
<b>Peak Gradient</b>			
<b>Baseline</b>			
n	125*	124*	
Mean $\pm$ SD	82.3 $\pm$ 25.9	77.1 $\pm$ 29.1	5.2 (-1.7, 2.3)
Min - Max	16-152	8-173	
<b>6 weeks</b>			
n	130*	130*	
Mean $\pm$ SD	29.9 $\pm$ 10.5	29.7 $\pm$ 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			
<b>Aortic Valve Regurgitation</b>			
<b>Nil/trivial</b>			
n/n (%)	109/134* (81.3)	109/130* (83.8)	218/264 (82.6)
<b>Mild</b>			
n/n (%)	19/134* (14.2)	18/130* (13.9)	37/264 (14.0)
<b>Moderate</b>			
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

For peer review only

**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

	<b>Model</b>	<b>Incremental cost (95%CI)</b>	<b>Incremental QALYs (95%CI)</b>	<b>ICER (95%CI)</b>	<b>p<sup>1</sup></b>	<b>p<sup>2</sup></b>
1	Multiple imputation, covariate adjusted <sup>4</sup>	508 (-202 to 1217)	-0.007 (-0.016 to 0.002)	Dominated <sup>3</sup>	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 <sup>4</sup>	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

## References

1. Matiasz R, Rigolin VH. 2017 Focused Update for Management of Patients With Valvular Heart Disease: Summary of New Recommendations. *Journal of the American Heart Association* 2018: <https://doi.org/10.1161/JAHA.117.007596>
2. NATIONAL ADULT CARDIAC SURGERY AUDIT 2020 Summary Report (2016/17-2018/19 data)
3. Blue Book Online. The Society for Cardiothoracic Surgery in Great Britain & Ireland <http://bluebook.scts.org/#> (accessed 23<sup>rd</sup> July, 2018).
4. Leontyev S, Walther T, Borger MA, et al. Aortic Valve Replacement in Octogenarians: Utility of Risk Stratification With EuroSCORE. *Ann Thorac Surg* 2009; **87**: 1440–5.
5. Phan K, Xie A, Di Eusano M, Yan TD. The Collaborative Research (CORE) Group. Meta-Analysis of Minimally Invasive Versus Conventional Sternotomy for Aortic Valve Replacement. *Ann Thorac Surg* 2014; **98**: 1499–511.
6. Ghanta RK, Lapar DJ, Kern JA, et al. Minimally invasive aortic valve replacement provides equivalent outcomes at reduced cost compared with conventional aortic valve replacement: A real-world multi-institutional analysis. *J Thorac Cardiovasc Surg* 2015; **149**: 1060–5.
7. Kirmani BH, Jones SG, Malaisrie SC, Chung DA, Williams RJ. Limited versus full sternotomy for aortic valve replacement. *Cochrane Database Syst Rev* **2017**; 4: CD011793.
8. Fujita B, Ensminger S, Bauer T, et al; GARY Executive Board. Trends in practice and outcomes from 2011 to 2015 for surgical aortic valve replacement: an update from the German Aortic Valve Registry on 42,776 patients. *Eur J Cardiothorac Surg*. **2018**; 53: 552–559.
9. Lehmann S, Merk DR, Etz CD, et al. Minimally invasive aortic valve replacement: the Leipzig experience. *Ann Cardiothorac Surg* **2015**; 4: 49–56.
10. Johnston DR, Roselli EE. Minimally invasive aortic valve surgery: Cleveland Clinic Experience. *Ann Cardiothorac Surg* 2015; **4**: 140–147.
11. Patel NN, Avlonitis VS, Jones HE, Reevesw BC, Sterne JA, Murphy GJ. Indications for red blood cell transfusion in cardiac surgery: a systematic review and meta-analysis. *Lancet Haem* 2015; **12**: e543–53.
12. Chen QH, Wang HL, Liu L, Shao J, Yu J, Zheng RQ. Effects of restrictive red blood cell transfusion on the prognoses of adult patients undergoing cardiac surgery: a meta-analysis of randomized controlled trials. *Crit Care* 2018; **22**: 142.
13. Pagano D, Milojevic M, Meesters MI, et al. The Task Force on Patient Blood Management for Adult Cardiac Surgery of the European Association for Cardio-Thoracic Surgery (EACTS) and the European Association of Cardiothoracic Anaesthesiology (EACTA). EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery. *Eur J Cardio-Thorac Surg* 2018; **53**: 79–111.
14. Dixon JR. The International Conference on Harmonization Good Clinical Practice guideline. *ICH GCP Qual Assur* 1998; **6**: 65–74.
15. Akowuah E, Goodwin AT, Owens WA, et al. Manubrium-limited ministernotomy versus conventional sternotomy for aortic valve replacement (MAVRIC): study protocol for a randomised controlled trial. <https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-016-1768-4> *Trials* 2017; **18**: 46.
16. NICE. Guide to the methods of Technology Appraisal. London, National Institute for Health and Care Excellence, 2013.
17. NHS Reference Costs 2015-16. London: Department of Health, 2016.
18. Curtis L, Burns A. Unit costs of health and social care 2015. Canterbury: the University of Kent, 2015.

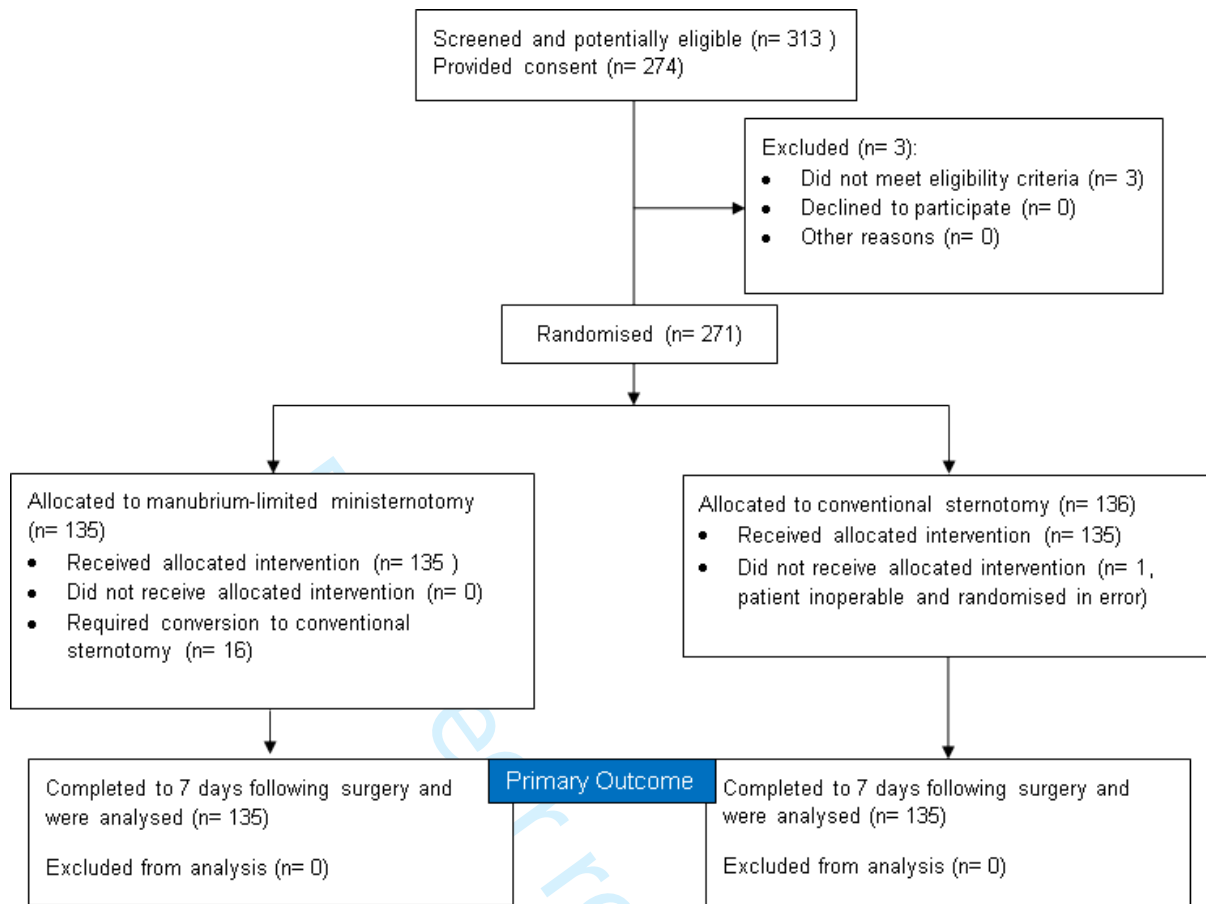


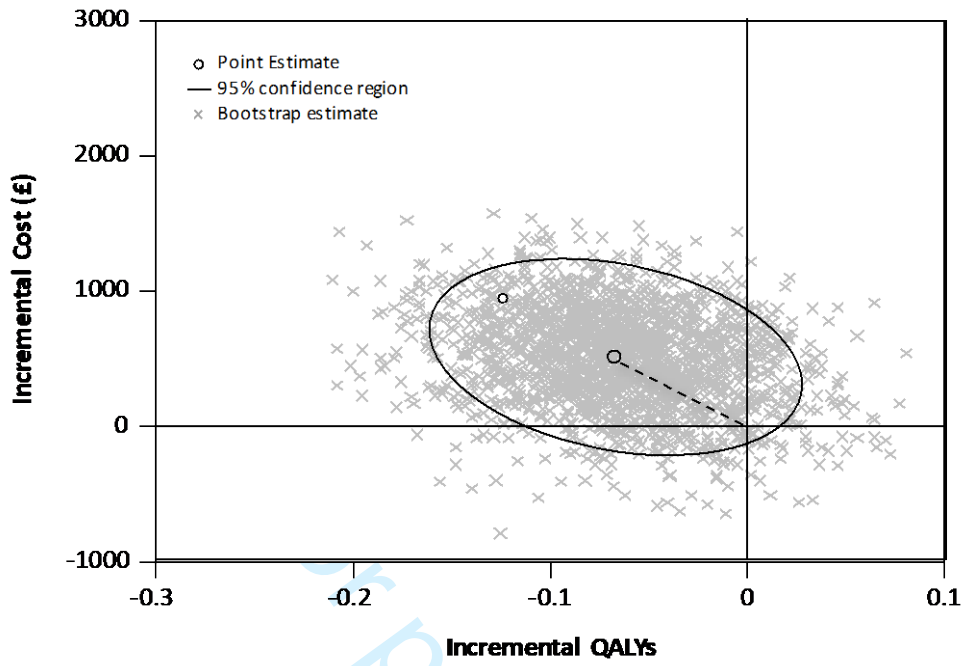
19. Sterne Jonathan A C, White Ian R, Carlin John B, Spratt Michael, Royston Patrick, Kenward Michael G et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls BMJ 2009; 338 :b2393
20. White Ian R, Horton Nicholas J, Carpenter James, Pocock Stuart J. Strategy for intention to treat analysis in randomised trials with missing outcome data BMJ 2011; 342 :d40
21. Faria R, Gomes M, Epstein D, White IR. A Guide to Handling Missing Data in Cost-Effectiveness Analysis Conducted Within Randomised Controlled Trials. *PharmacoEconomics* (2014) 32:1157–1170
22. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med*. 2011 Feb 20;30(4):377-99
23. Aris A, Camara ML, Montiel J Delgado LJ, Galan J, Litvan H. Ministernotomy versus median sternotomy for aortic valve replacement: a prospective, randomized study. *Ann Thor Surg* 1999; **67**: 1583–7.
24. Moustafa MA, Abdelsamad AA, Zakaria G, Omarah MM. Minimal vs median sternotomy for aortic valve replacement. *Asian Cardiovasc Thorac Annals* 2007; **15**: 472–5.
25. Rodríguez-Caulo EA, ArantzaGuzón A, Otero-Forero J, José Mataró M, Sánchez-Espín G, Porras C, Villaescusa J.M, Melero-Tejedor JM, Jiménez-Navarro M. Quality of life after ministernotomy versus full sternotomy aortic valve replacement doi.org/10.1053/j.semtcvs.2020.07.013
26. Vukovic P.M, Milojevic P, Stojanovic I, Micovic S, Zivkovic I, Miodrag P, Milicic M, Milacic P, Milojevic M, Bojic M. The role of ministernotomy in aortic valve surgery-A prospective randomized study doi: 10.1111/jocs.14053. Epub 2019 Apr 24.
27. National Comparative Audit of Blood Transfusion [http://hospital.blood.co.uk/media/26859/nca-2011\\_use\\_of\\_blood\\_in\\_adult\\_cardiac\\_surgery\\_report.pdf](http://hospital.blood.co.uk/media/26859/nca-2011_use_of_blood_in_adult_cardiac_surgery_report.pdf) (accessed 23<sup>rd</sup> July, 2018).
28. 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. *Journal of the American College of Cardiology* 2019 Vol 73; 2491-2492

1  
2  
3 **Figure 1.** CONSORT Diagram. Flow of participants through trial.  
4  
5

6 **Figure 2.** Cost-effectiveness plane, cost/QALY (£): mini-sternotomy versus conventional surgery.  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only





peer review only

**Supplementary Material**

1		
2		
3		
4		
5		
6		
7		
8		
9		
10	Study Investigators: trial site, clinical trials unit, statistics, health economics, committees	2
11		
12	Table 1. Eligibility criteria	3
13		
14	Figure 1. Trial recruitment by month	4
15		
16	Table 2. Conversion from mini-sternotomy to conventional sternotomy	5
17		
18	Table 3. Number of operations by Consultant Surgeon	6
19		
20	Figure 2. Haemoglobin profiles	7
21		
22	Table 4. Analgesic use and Pain scores	8-9
23		
24	Table 5. Adverse Events	10
25		
26	Table 6. Health status, resource use and cost (complete cases)	11
27		
28	Table 7. ICU Length of Stay, Fitness for Discharge and Hospital Length of Stay	12
29		
30	Table 8. Pulmonary function tests	13
31		
32		
33		
34		
35		
36		
37		
38		
39		
40		
41		
42		
43		
44		
45		
46		
47		
48		
49		
50		
51		
52		
53		
54		
55		
56		
57		
58		
59		
60		

**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. 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 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.

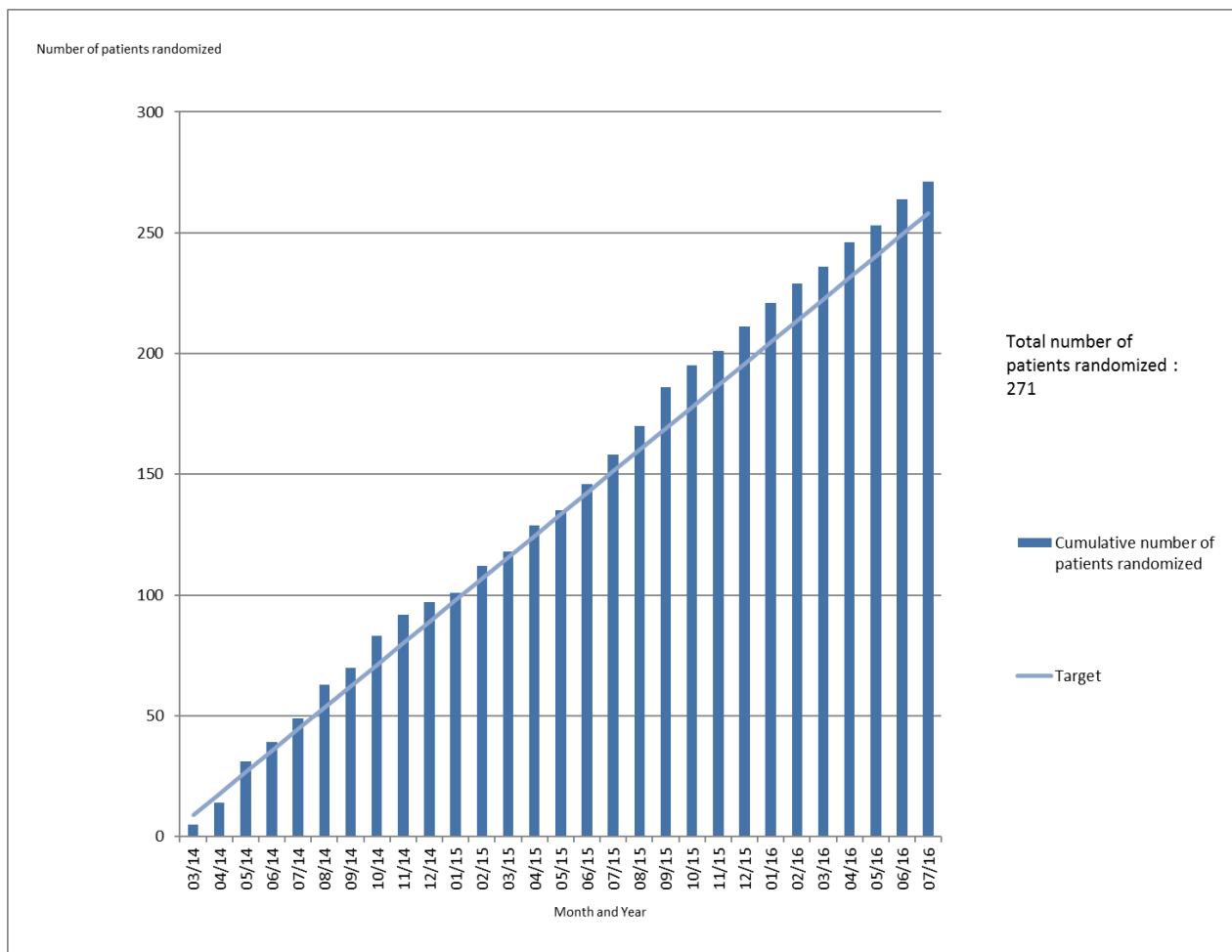


Figure 1. Trial recruitment by month.



**Table 2. Conversion from mini-sternotomy to conventional sternotomy**

Reason for conversion	Number of patients	Details
<b>Anaesthetic emergency</b>	2	<ul style="list-style-type: none"> <li>• Patient became unstable as they were transferred into theatre and BP dropped – required conventional to re-stabilise</li> <li>• 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)</li> </ul>
<b>Difficult vascular access (venous or arterial)</b>	9	<p>Venous</p> <ul style="list-style-type: none"> <li>• Femoral vessels unsuitable for cannulation</li> <li>• Poor venous drainage</li> <li>• Unable to pass venous dilators</li> <li>• Unable to insert pipe. Resistance felt, no back flow of blood. Femoral cannulation abandoned</li> <li>• Impossible to dilate femoral vein. Despite re-wiring, guide wire coiling within pelvic venous system</li> </ul> <p>Arterial</p> <ul style="list-style-type: none"> <li>• Difficulties cannulating femoral artery leading to haemodynamic instability</li> <li>• Poor access, unable to clamp aorta</li> <li>• Severe calcification of ascending aorta</li> <li>• Difficult access; aorta displaced to the left. Body habitus limited access</li> </ul>
<b>Intra-operative complications</b>	5	<ul style="list-style-type: none"> <li>• Bleeding from aortotomy site</li> <li>• Bleeding</li> <li>• Intra-operative decision to performed bypass graft to LAD</li> <li>• Post implant TOE showed small paravalvular leak and bleeding from aortotomy incision</li> <li>• Mild/moderate paravalvar leak on TOE. Required valve re-implant</li> </ul>
<b>TOTAL</b>	<b>16</b>	

**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)

For peer review only

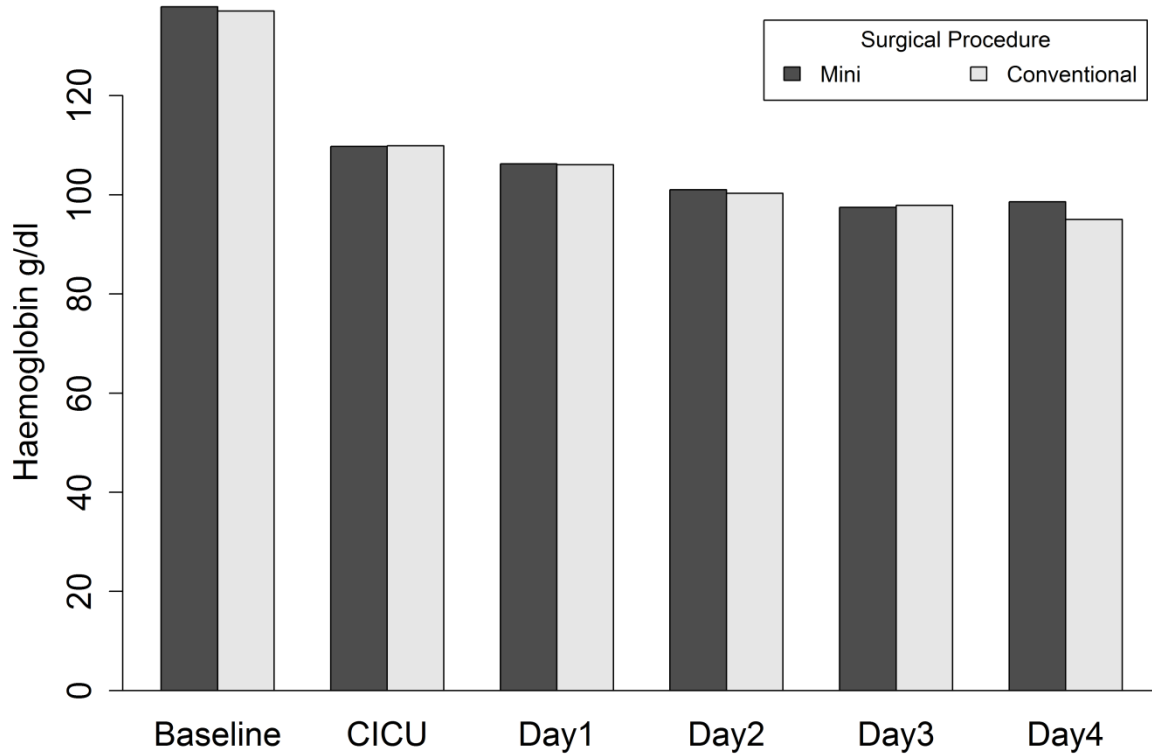


Figure 2. Haemoglobin profiles at Baseline, during CICU stay, and day 1 to day 4 post index surgery, by group

**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 (%)
<b>Analgesic use at baseline</b>			
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)
<b>At least one med at baseline</b>	<b>16 (11.9)</b>	<b>12 (8.9)</b>	<b>28 (10.4)</b>
<b>Analgesic use at day 2</b>			
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)
<b>At least one med at day 2</b>	<b>99 (73.3)</b>	<b>86 (63.7)</b>	<b>185 (68.5)</b>
<b>Analgesic use at day 3</b>			
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)
<b>At least one med at day 3</b>	<b>90 (66.7)</b>	<b>101 (74.8)</b>	<b>191 (70.7)</b>
<b>Analgesic use at Day 4</b>			
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)
<b>At least one med at day 4</b>	<b>88 (65.2)</b>	<b>81 (60.0)</b>	<b>169 (62.6)</b>
<b>Analgesic use at Week 6</b>			
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)
<b>At least one med at week 6</b>	<b>41(30.4)</b>	<b>41(30.4)</b>	<b>82(30.4)</b>
<b>Analgesic use at Week 12</b>			
Buprenorphine Patch	3(2.2)	0(0.0)	3(1.1)
Codeine Phosphate	7(5.2)	4(3.0)	11(4.1)

1				
2				
3	Dihydrocodeine Tartrate	0(0-0)	1(0-7)	1(0-4)
4	Gabapentin	2(1-5)	0(0-0)	2(0-7)
5	Ibuprofen	1(0-7)	0(0-0)	1(0-4)
6	Morphine Sulfate	1(0-7)	1(0-7)	2(0-7)
7	Naproxen	1(0-7)	0(0-0)	1(0-4)
8	Paracetamol	19(14-1)	20(14-8)	39(14-4)
9	Tramadol Hydrochloride	1(0-7)	1(0-7)	2(0-7)
10	<b>At least one med at week 12</b>	<b>23(17-0)</b>	<b>22(16-3)</b>	<b>45(16-7)</b>

	Mini-sternotomy Group (n=135 patients)	Conventional sternotomy group (n=135)
11		
12		
13		
14	<b>Baseline pain score</b>	
15	n	128*
16	Mean± SD	1.3 ± 2.1
17	(min-max)	0 - 10
18	<b>Day 2 pain score**</b>	
19	n	123*
20	Mean± SD	3.4 ± 2.4
21	(min-max)	0 - 10
22	<b>Day 3 pain score</b>	
23	n	120*
24	Mean± SD	2.8 ± 2.5
25	(min-max)	0 - 9
26	<b>Day 4 pain score</b>	
27	n	116*
28	Mean± SD	2.5 ± 2.2
29	(min-max)	0 - 8
30	<b>6 week pain score</b>	
31	n	112*
32	Mean± SD	1.5 ± 1.9
33	(min-max)	0 - 8
34	<b>12 week pain score</b>	
35	n	128*
36	Mean± SD	1.1 ± 1.9
37	(min-max)	0 - 8

\*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] <sup>1</sup>	
	mean	(SD)	N	mean	(SD)	N	mean	(95%CI)
<b>Health status<sup>2</sup></b>								
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)
<b>Resource use</b>								
Index Admission								
Length of stay (d) <sup>3</sup>	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) <sup>4</sup>	0.08	0.34	135	0.03	0.17	135	-0.05	(-0.11 to 0.02)
Time in surgery (h) <sup>4</sup>	2.32	0.63	135	3.01	0.71	135	0.69	(0.53 to 0.85)
RBC (u) <sup>4</sup>	0.59	1.45	135	0.55	1.28	135	-0.04	(-0.37 to 0.28)
FFP (u) <sup>4</sup>	0.57	1.43	135	0.34	1.21	135	-0.23	(-0.55 to 0.09)
Platelets (u) <sup>4</sup>	0.22	0.64	135	0.12	0.46	135	-0.10	(-0.24 to 0.03)
Cryoprecipitate (u) <sup>4</sup>	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)
<b>Cost<sup>5</sup></b>								
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)
<b>ICU stay (days)</b>		
n	135	135
Mean $\pm$ SD	1.9 $\pm$ 5.8	1.3 $\pm$ 1.1
Min-Max	0 - 64*	0 - 7
<b>Fitness for discharge (days)</b>		
n	129**	133**
Mean $\pm$ SD	6.5 $\pm$ 3.7	6.3 $\pm$ 3.2
Min - Max	3 - 36	3 - 31
<b>Post-operative length of stay (days)</b>		
n	135	135
Mean $\pm$ SD	7.4 $\pm$ 7.5	6.3 $\pm$ 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)
<b>FEV1</b>			
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	
<b>FVC</b>			
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
<b>Title and abstract</b>			
	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
<b>Introduction</b>			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	3,5
<b>Methods</b>			
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
<b>Randomisation:</b>			
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

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

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	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	2,4
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	4
	11b	If relevant, description of the similarity of interventions	2,4,5
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	4
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	7
<b>Results</b>			
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	7
Recruitment	13b	For each group, losses and exclusions after randomisation, together with reasons	9,17
	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
<b>Discussion</b>			
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

1			
2			
3	Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence
4			13,14
5	<b>Other information</b>		
6	Registration	23	Registration number and name of trial registry
7			1,4
8	Protocol	24	Where the full trial protocol can be accessed, if available
9			4
10	Funding	25	Sources of funding and other support (such as supply of drugs), role of funders
11			4, 15

11 \*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If  
 12 relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal  
 13 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](http://www.consort-statement.org).  
 14  
 15  
 16  
 17  
 18  
 19  
 20  
 21  
 22  
 23  
 24  
 25  
 26  
 27  
 28  
 29  
 30  
 31  
 32  
 33  
 34  
 35  
 36  
 37  
 38  
 39  
 40  
 41  
 42  
 43  
 44  
 45  
 46

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

For peer review only

# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-041398.R2
Article Type:	Original research
Date Submitted by the Author:	04-Dec-2020
Complete List of Authors:	Hancock, Helen; Newcastle University, Newcastle Clinical Trials Unit Maier, Rebecca; Newcastle University, Newcastle Clinical Trials Unit Kasim, Adetayo; Durham University, Wolfson Research Institute for Health and Wellbeing Mason, James; University of Warwick, Warwick Medical School Murphy, Gavin; University of Leicester, Department of Cardiovascular Sciences and NIHR Leicester Biomedical Research Unit in Cardiovascular Medicine Goodwin, Andrew; South Tees Hospitals NHS Foundation Trust, James Cook Hospital Owens, W; South Tees Hospitals NHS Foundation Trust, James Cook Hospital Akowuah, Enoch; South Tees Hospitals NHS Foundation Trust, James Cook Hospital
<b>Primary Subject Heading</b>:	Surgery
Secondary Subject Heading:	Evidence based practice, Intensive care, Research methods, Cardiovascular medicine
Keywords:	HEALTH ECONOMICS, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Adult surgery < SURGERY, Cardiac surgery < SURGERY, Clinical trials < THERAPEUTICS

SCHOLARONE™  
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

**Title**

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

**Authors**

Helen C Hancock, PhD<sup>1</sup>, Rebecca H Maier<sup>1</sup>, MSc, Adetayo Kasim, PhD<sup>2</sup>, James Mason, DPhil<sup>3</sup>, Gavin Murphy, FRCS (C.Th)<sup>4</sup>, Andrew Goodwin, FRCS (C.Th)<sup>5</sup>, W Andrew Owens, FRCS (C.Th)<sup>5</sup>, Enoch Akowuah, FRCS (C.Th)<sup>5</sup>.

1. Newcastle Clinical Trials Unit, Newcastle University; 2. Durham Research Methods Centre, Durham University; 3. Warwick Medical School, University of Warwick; 4. Department of Cardiovascular Sciences, University of Leicester; 5. Cardiothoracic Services, South Tees Hospitals NHS Foundation Trust, The James Cook University Hospital.

**Word count 3703**

**Corresponding author:** Enoch Akowuah

Cardiothoracic Services, South Tees Hospitals NHS Foundation Trust, The James Cook University Hospital. Marton Road, Middlesbrough. TS3 4BW.  
E mail Enoch.Akowuah@nhs.net



**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

1  
2  
3 138·7) vs conventional, mean 306·9ml (SD 348·6)); this did not reduce red-cell transfusions. Mean  
4  
5 valve size and post-operative valve function were comparable between mini-sternotomy and  
6  
7 conventional groups; 23mm vs 24mm, and 6/134 moderate or severe aortic regurgitation vs 3/130,  
8  
9 respectively. Mini-sternotomy resulted in longer bypass (82·7 minutes (SD 23·5) vs 59·6 minutes (SD  
10  
11 15·1)) and cross clamp times (64·1 minutes (SD 17·1) vs 46·3 minutes (SD 10·7)). Conventional  
12  
13 sternotomy was more cost-effective with only a 5·8% probability of mini-sternotomy being cost-  
14  
15 effective at a willingness to pay of £20,000/QALY.  
16  
17

### 18 **Conclusions**

19  
20  
21  
22 AVR via mini-sternotomy did not reduce red blood cell transfusion within 7 days following surgery  
23  
24 when compared to conventional sternotomy.  
25  
26

27  
28  
29 **Clinical Trials Registry:** ISRCTN29567910  
30  
31

32  
33  
34  
35 Key word: minimally invasive, aortic valve, clinical trial, cardiac surgery, replacement,  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## 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.<sup>1</sup>

In the UK, the National adult cardiac surgery audit published by NICOR (National Institute for Cardiac Outcome Reporting) reported 13,027 procedures for aortic valve disease in the UK from April 2018 to March 2019.<sup>2</sup> Outcomes are generally excellent with in-hospital observed mortality in the UK of 1.5% for first time elective procedures.<sup>3</sup> 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.<sup>2</sup>

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.<sup>4</sup> 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<sup>5,6</sup> may be confounded by multiple sources of bias and are at odds with limited evidence from RCTs that have not shown improved outcomes.<sup>7</sup> This uncertainty is reflected by variations in uptake internationally.<sup>8,9,10</sup>

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

1  
2  
3 transfusion rates, a contemporary marker of surgical trauma and indicator of adverse outcomes;<sup>11</sup>  
4  
5 this has been contested,<sup>12</sup> though the evidence is not conclusive.<sup>13</sup> An embedded cost effectiveness  
6  
7 analysis evaluated whether the intervention was cost effective in a UK National Health Service (NHS)  
8  
9 setting.  
10

## 11 **Patients and Methods**

### 12 **Trial Design**

13  
14 MAVRIC was a single centre, single-blind, RCT comparing AVR via manubrium-limited mini-  
15  
16 sternotomy group (intervention) and AVR via conventional sternotomy group (usual care). A NHS  
17  
18 Research Ethics Committee approved the trial, which was conducted in accordance with the  
19  
20 principles of the International Conference on Harmonisation of Good Clinical Practice.<sup>14</sup> South Tees  
21  
22 Hospitals NHS Foundation Trust was the Sponsor and recruiting centre.  
23  
24  
25  
26  
27

### 28 **Patient Public Involvement**

29  
30 In designing the study, we asked patients their view on what factors may affect whether they took  
31  
32 part in the study. This was done in an outpatient setting and via a postal questionnaire. They felt  
33  
34 expertise was important. Most patients felt that although the cosmetic benefit of the minimally  
35  
36 invasive approach was appealing, they expected some clinical benefit from minimally invasive  
37  
38 surgery as well. Importantly most patients said they would accept being blind to the type of surgery  
39  
40 they had received for 48 hours after the procedure.  
41  
42  
43

### 44 **Participants**

45  
46 Patients were eligible if they were aged 18 years or over; required first-time, non-emergency,  
47  
48 isolated AVR surgery; and were willing to provide written informed consent. Full details of the  
49  
50 eligibility criteria are in the **Supplementary Material**.  
51  
52  
53

### 54 **Randomisation**

55  
56 Eligible patients were randomised by members of the research team using a 24-hour, central,  
57  
58 secure, web-based randomisation system with concealed allocation, managed by the Clinical Trials  
59  
60

1  
2  
3 Unit; randomisation was in a 1:1 ratio between mini and conventional sternotomy and stratified by  
4  
5 baseline logistic EuroSCORE and pre-operative Hemoglobin (Hb).  
6  
7

### 8 **Interventions**

9  
10 Manubrium-limited mini-sternotomy was performed using a 5-7cm midline skin incision dividing the  
11  
12 manubrium from the sternal notch to 1cm below the manubrium-sternal junction. Cardiopulmonary  
13  
14 bypass was established with an ascending aortic cannula and percutaneous femoral venous  
15  
16 cannulation. Conventional median sternotomy was performed using a midline incision from the  
17  
18 sternal notch to the xiphisternum. Key aspects of anaesthesia were standardised, and are detailed in  
19  
20 the protocol.<sup>15</sup>  
21  
22  
23

### 24 **Blinding**

25  
26 All patients were blinded to type of sternotomy received until after their day 2 Quality of Life and  
27  
28 pain assessments. All patients had trial-specific opaque dressings applied to their sternal wound, and  
29  
30 groin before leaving theatre.  
31  
32

### 33 **Transfusion Protocol**

34  
35 The post-operative period, and trial protocol in relation to red cell and non-red cell transfusion,  
36  
37 began on admission to the Cardiothoracic Intensive Care Unit (CICU); it specified that patient's  
38  
39 should receive a red cell transfusion if their Hb dropped below 80 g/L; or were bleeding by 400ml/h  
40  
41 or more, or were bleeding 100ml/h or more for 4 or more hours with a Hb equal to or greater than  
42  
43 80g/L; or had blood loss with haemodynamic instability irrespective of thromboelastography (TEG)  
44  
45 and/or clotting profile results. One unit of red cells was transfused and Hb level checked before  
46  
47 transfusing another unit.  
48  
49

50  
51 Participants received a non-red cell transfusion if both of the following criteria were met: bleeding  
52  
53 defined by 400ml/h or more, or blood loss of 100ml/h or more for 4 hours or more; TEG or  
54  
55 coagulation guided transfusion indicated.  
56  
57  
58  
59  
60

## Outcomes

All outcomes 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 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)

1  
2  
3 undergoing AVR via mini-sternotomy. Using Fisher's Exact test, 90% power, 5% alpha, we estimated  
4 that 260 patients would be required to detect a 17% reduction in the proportion of patients  
5 requiring a red cell transfusion (13% compared with 30%), using a two-sided test. Allowing for loss to  
6 follow up, the sample size was increased to 270.  
7  
8  
9

10  
11  
12 The primary analysis was based on intention-to-treat principles, in accordance with a pre-specified  
13 statistical analysis plan.  
14

15  
16  
17 The primary efficacy analysis was based on a logistic regression model with only group (minimally  
18 invasive and conventional) and stratifying factors (baseline logistic EuroSCORE and Hb) as the  
19 predictors. Odds ratios and their associated 95% confidence interval are reported in the primary  
20 analysis. Sensitivity analysis using alternating logistic regression was performed for the primary  
21 endpoint to sensitise for surgeon effects; the odds of receiving a red cell transfusion for two patients  
22 treated by the same surgeon was compared to two patients treated by different surgeons.  
23  
24  
25  
26  
27  
28  
29

30  
31 All analyses of secondary continuous efficacy endpoints at single time points were based on linear  
32 models where, if appropriate, a log normal model was fitted to sensitise the linearity assumption.  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65  
66  
67  
68  
69  
70  
71  
72  
73  
74  
75  
76  
77  
78  
79  
80  
81  
82  
83  
84  
85  
86  
87  
88  
89  
90  
91  
92  
93  
94  
95  
96  
97  
98  
99  
100  
101  
102  
103  
104  
105  
106  
107  
108  
109  
110  
111  
112  
113  
114  
115  
116  
117  
118  
119  
120  
121  
122  
123  
124  
125  
126  
127  
128  
129  
130  
131  
132  
133  
134  
135  
136  
137  
138  
139  
140  
141  
142  
143  
144  
145  
146  
147  
148  
149  
150  
151  
152  
153  
154  
155  
156  
157  
158  
159  
160  
161  
162  
163  
164  
165  
166  
167  
168  
169  
170  
171  
172  
173  
174  
175  
176  
177  
178  
179  
180  
181  
182  
183  
184  
185  
186  
187  
188  
189  
190  
191  
192  
193  
194  
195  
196  
197  
198  
199  
200  
201  
202  
203  
204  
205  
206  
207  
208  
209  
210  
211  
212  
213  
214  
215  
216  
217  
218  
219  
220  
221  
222  
223  
224  
225  
226  
227  
228  
229  
230  
231  
232  
233  
234  
235  
236  
237  
238  
239  
240  
241  
242  
243  
244  
245  
246  
247  
248  
249  
250  
251  
252  
253  
254  
255  
256  
257  
258  
259  
260  
261  
262  
263  
264  
265  
266  
267  
268  
269  
270  
271  
272  
273  
274  
275  
276  
277  
278  
279  
280  
281  
282  
283  
284  
285  
286  
287  
288  
289  
290  
291  
292  
293  
294  
295  
296  
297  
298  
299  
300  
301  
302  
303  
304  
305  
306  
307  
308  
309  
310  
311  
312  
313  
314  
315  
316  
317  
318  
319  
320  
321  
322  
323  
324  
325  
326  
327  
328  
329  
330  
331  
332  
333  
334  
335  
336  
337  
338  
339  
340  
341  
342  
343  
344  
345  
346  
347  
348  
349  
350  
351  
352  
353  
354  
355  
356  
357  
358  
359  
360  
361  
362  
363  
364  
365  
366  
367  
368  
369  
370  
371  
372  
373  
374  
375  
376  
377  
378  
379  
380  
381  
382  
383  
384  
385  
386  
387  
388  
389  
390  
391  
392  
393  
394  
395  
396  
397  
398  
399  
400  
401  
402  
403  
404  
405  
406  
407  
408  
409  
410  
411  
412  
413  
414  
415  
416  
417  
418  
419  
420  
421  
422  
423  
424  
425  
426  
427  
428  
429  
430  
431  
432  
433  
434  
435  
436  
437  
438  
439  
440  
441  
442  
443  
444  
445  
446  
447  
448  
449  
450  
451  
452  
453  
454  
455  
456  
457  
458  
459  
460  
461  
462  
463  
464  
465  
466  
467  
468  
469  
470  
471  
472  
473  
474  
475  
476  
477  
478  
479  
480  
481  
482  
483  
484  
485  
486  
487  
488  
489  
490  
491  
492  
493  
494  
495  
496  
497  
498  
499  
500  
501  
502  
503  
504  
505  
506  
507  
508  
509  
510  
511  
512  
513  
514  
515  
516  
517  
518  
519  
520  
521  
522  
523  
524  
525  
526  
527  
528  
529  
530  
531  
532  
533  
534  
535  
536  
537  
538  
539  
540  
541  
542  
543  
544  
545  
546  
547  
548  
549  
550  
551  
552  
553  
554  
555  
556  
557  
558  
559  
560  
561  
562  
563  
564  
565  
566  
567  
568  
569  
570  
571  
572  
573  
574  
575  
576  
577  
578  
579  
580  
581  
582  
583  
584  
585  
586  
587  
588  
589  
590  
591  
592  
593  
594  
595  
596  
597  
598  
599  
600  
601  
602  
603  
604  
605  
606  
607  
608  
609  
610  
611  
612  
613  
614  
615  
616  
617  
618  
619  
620  
621  
622  
623  
624  
625  
626  
627  
628  
629  
630  
631  
632  
633  
634  
635  
636  
637  
638  
639  
640  
641  
642  
643  
644  
645  
646  
647  
648  
649  
650  
651  
652  
653  
654  
655  
656  
657  
658  
659  
660  
661  
662  
663  
664  
665  
666  
667  
668  
669  
670  
671  
672  
673  
674  
675  
676  
677  
678  
679  
680  
681  
682  
683  
684  
685  
686  
687  
688  
689  
690  
691  
692  
693  
694  
695  
696  
697  
698  
699  
700  
701  
702  
703  
704  
705  
706  
707  
708  
709  
710  
711  
712  
713  
714  
715  
716  
717  
718  
719  
720  
721  
722  
723  
724  
725  
726  
727  
728  
729  
730  
731  
732  
733  
734  
735  
736  
737  
738  
739  
740  
741  
742  
743  
744  
745  
746  
747  
748  
749  
750  
751  
752  
753  
754  
755  
756  
757  
758  
759  
760  
761  
762  
763  
764  
765  
766  
767  
768  
769  
770  
771  
772  
773  
774  
775  
776  
777  
778  
779  
780  
781  
782  
783  
784  
785  
786  
787  
788  
789  
790  
791  
792  
793  
794  
795  
796  
797  
798  
799  
800  
801  
802  
803  
804  
805  
806  
807  
808  
809  
810  
811  
812  
813  
814  
815  
816  
817  
818  
819  
820  
821  
822  
823  
824  
825  
826  
827  
828  
829  
830  
831  
832  
833  
834  
835  
836  
837  
838  
839  
840  
841  
842  
843  
844  
845  
846  
847  
848  
849  
850  
851  
852  
853  
854  
855  
856  
857  
858  
859  
860  
861  
862  
863  
864  
865  
866  
867  
868  
869  
870  
871  
872  
873  
874  
875  
876  
877  
878  
879  
880  
881  
882  
883  
884  
885  
886  
887  
888  
889  
890  
891  
892  
893  
894  
895  
896  
897  
898  
899  
900  
901  
902  
903  
904  
905  
906  
907  
908  
909  
910  
911  
912  
913  
914  
915  
916  
917  
918  
919  
920  
921  
922  
923  
924  
925  
926  
927  
928  
929  
930  
931  
932  
933  
934  
935  
936  
937  
938  
939  
940  
941  
942  
943  
944  
945  
946  
947  
948  
949  
950  
951  
952  
953  
954  
955  
956  
957  
958  
959  
960  
961  
962  
963  
964  
965  
966  
967  
968  
969  
970  
971  
972  
973  
974  
975  
976  
977  
978  
979  
980  
981  
982  
983  
984  
985  
986  
987  
988  
989  
990  
991  
992  
993  
994  
995  
996  
997  
998  
999  
1000

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,<sup>16</sup> was employed. Health care utilisation



1  
2  
3 was captured up to three months following discharge from index surgery. Resource use was valued  
4  
5 in 2016 pounds sterling using national sources,<sup>17,18</sup> and where necessary, local micro-costing  
6  
7 (£1=\$1.50). Resources included surgery, transfusions, length of hospital stay (by level of care),  
8  
9 complications and further surgery, and community care following discharge.

10  
11  
12 Mechanisms of missingness within the data were explored and multiple imputation methods were  
13  
14 applied to impute missing data and minimise bias, using chained equations and predictive mean  
15  
16 matching. Imputation sets were analysed within a bivariate analysis of costs and QALYs, to generate  
17  
18 incremental within-trial cost per QALY estimates and credible intervals. Findings were presented on  
19  
20 the ICER plane and with Cost-Effectiveness Acceptability Curves, using the net monetary benefit  
21  
22 approach.  
23  
24

25  
26 Imputation was conducted according to good practice guidance.<sup>19,20</sup> Multiple imputation provides  
27  
28 unbiased estimates of treatment effect if data are missing at random (MAR) and the missingness  
29  
30 process is adequately characterised : this assumption was explored in the data, for example by using  
31  
32 logistic regression for missingness of costs and QALYs against baseline variables.<sup>21</sup> A regression  
33  
34 model was used to generate multiple imputed datasets (or 'draws') for individual treatment groups,  
35  
36 where missing values were predicted drawing on predictive covariates. Outcome measures and  
37  
38 costs (at each time point) contributed as predictors and imputed variables. Each draw provided a  
39  
40 complete dataset, reflecting the distributions and correlations between variables. Predictive mean  
41  
42 matching drawn from the five nearest neighbours (knn=5) was used to enhance the plausibility and  
43  
44 robustness of imputed values; normality was not assumed. The imputation model used fully  
45  
46 conditional (MCMC) methods. Draws were analysed using bivariate regression (see below) within  
47  
48 the Stata MI framework, capturing within and between variances for imputed samples.<sup>22</sup> After  
49  
50 examining the fraction of missing information (FMI) from finite imputation sampling, 20 draws was  
51  
52 taken in the final imputation model.  
53  
54  
55  
56  
57  
58  
59  
60

## Results

### Trial Population

MAVRIC recruited to time and target; 313 patients were considered for the trial; 274 patients consented between 20<sup>th</sup> March 2014 and 25<sup>th</sup> 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

1  
2  
3 Mini-sternotomy resulted in longer Cardio Pulmonary Bypass times; mini group 82.7 minutes (SD  
4 23.5), conventional 59.6 minutes (SD 15.1). Aortic cross clamp times were also longer; mini group  
5 64.1 minutes (SD 17.1), conventional 46.3 minutes (SD 10.7) (**Table 4**).

### 10 **Chest drain losses**

11  
12  
13 Mini-sternotomy resulted in a 40.8% reduction in chest drain losses at 12 hours, the mini group  
14 mean was 181.6ml (SD 138.7), conventional group mean was 306.9ml (SD 348.6); the mean  
15 difference was -127.7ml (95% CI -191.7, -63.8, p=0.0001). At drain removal mean difference was -  
16 145.3ml (95% CI -218.1, -72.3; p=0.0001) (**Table 4**).

### 22 **Ventilation time**

23  
24  
25 Ventilation time between the groups was similar; 9.6 hours (SD 5.6) in the mini group and 9.8 hours  
26 (SD 6.9) in the conventional (**Table 4**).

### 30 **Intensive care unit length of stay**

31  
32  
33 There was no difference in intensive care unit length of stay between groups (**Supplementary**  
34 **Material**).

### 38 **Post-operative pain**

39  
40  
41 There was no difference in pain scores between groups; analgesic use is also included to assist  
42 interpretation (**Supplementary Material**).

### 46 **Lung function**

47  
48  
49 There was no difference between groups in lung function at baseline. At 4 days post-surgery, mean  
50 Forced Expiratory Volume 1 (FEV1) 1123mls (SD 433) and Forced Vital Capacity, FVC 1479mls (SD  
51 583) were significantly reduced in the mini group, compared to the conventional; FEV1 1321 (SD  
52 524), FVC 1698 (SD 707). Mean differences for FEV1 and FVC were statistically significant at 4 days  
53 post-surgery; -171mls (95% CI -265, -77; p=0.0004) and -130mls (95% CI -269, 0; p=0.0498)

1  
2  
3 respectively, after adjusting for baseline FEV1, FVC, and randomisation factors (**Supplementary**  
4  
5 **Material**).

### 8 **Hospital length of stay**

9  
10  
11 The mean time to patients being fit for hospital discharge following index surgery was similar  
12  
13 between groups. The mean post-operative hospital length of stay was 7.4 (SD 7.5, range 3-79) in the  
14  
15 mini group, and 6.3 days (SD 3.2, range 3-31) in the conventional (**Supplementary Material**).

### 17 **Post-operative valve function**

18  
19  
20 The distribution of valve types and valve sizes by group were similar; mean valve size inserted was  
21  
22 23mm in the mini group and 24mm in the conventional (**Table 5, Figure 2,3**). Over 70% of patients in  
23  
24 each group received a tissue valve, over 25% received a mechanical valve and 2-3% received a  
25  
26 sutureless tissue valve.

27  
28  
29 Post operative transthoracic echo showed a similar decrease in mean aortic valve gradient in both  
30  
31 groups to 16mmHg; peak gradient decreased to 30mmHg in both groups (**Table 5**). 6/134 patients  
32  
33 had moderate or severe aortic regurgitation in the mini group compared to 3/130 in the  
34  
35 conventional (**Table 5**). Only 2 patients in the trial, 1 in each arm, suffered a paravalvular leak; both  
36  
37 were severe. One of these patients, in the mini sternotomy arm had a sutureless valve prosthesis. 7  
38  
39 further patients had moderate regurgitation; these were all intravalvular leaks. Transoesophageal  
40  
41 echo was performed in all patients prior to leaving the operating theatre.

### 44 **Adverse events**

45  
46  
47 There were no in-hospital deaths in either group. At 12 weeks follow up, there were 4 deaths; 2 in  
48  
49 each arm of the study. Adverse events in each group were broadly similar and within acceptable  
50  
51 clinical limits. By 12 weeks, 4/135 patients in the mini-sternotomy group and 1/135 in the  
52  
53 conventional group had suffered a stroke (defined as a persistent neurological deficit). Atrial  
54  
55 arrhythmias were identified in 61/135 patients in the mini group and 51/135 in the conventional. By  
56  
57  
58  
59  
60

1  
2  
3 12 weeks, 11/135 patients in the mini group and 3/135 patients in the conventional had a sternal  
4 wound infection (**Supplementary Material**).

### 8 **Quality of Life, Costs and Cost-Effectiveness**

9  
10 Costs during the index admission were significantly greater for the mini group (mini-conventional:  
11 mean difference £1140; 95% CI 303, 1977), primarily reflecting the additional cost of theatre time  
12 (**Supplementary Material**). Overall costs were not significantly different (mini-conventional: mean  
13 difference £746; 95% CI -245, 1737). There was no significant difference in quality of life between  
14 groups up to 12 weeks (mini-conventional: mean difference area under curve -0.009 QALYs; 95% CI  
15 0.020, 0.002). Although differences in costs and quality-of-life were not individually significant, the  
16 bivariate cost-QALY distribution (combining these two) suggests conventional surgery might be more  
17 cost-effective (**Figure 4**). In the base-case model, mini was dominated by conventional surgery (due  
18 to greater cost and less benefit), with only a 5.8% probability of being cost-effective at a willingness  
19 to pay of £20,000/QALY (**Table 6**).

### 33 **Sensitivity and Subgroup Analyses**

34  
35 There was no significant surgeon effect; the odds of receiving a red cell transfusion for two patients  
36 treated by the same surgeon compared to two patients treated by different surgeons was 1.2 (95%  
37 CI 0.9, 1.6;  $p=0.1379$ ).

38  
39 Protocol deviations in respect of cell transfusions did not affect the results of the primary analysis;  
40 excluding these patients produced the same results as those from the intention-to-treat analysis.

## 47 **Discussion**

### 49 **Main findings**

50  
51 Mini-sternotomy was not superior to conventional sternotomy with respect to red cell transfusion  
52 requirements within 7 days of surgery. Analysis of secondary endpoints showed a statistically  
53 significant difference in transfusion volumes of non-red cell blood components. Aortic valve size and  
54 post-operative function were comparable in the 2 groups. Mini-sternotomy resulted in a relative  
55  
56  
57  
58  
59  
60

1  
2  
3 reduction in chest drain losses however, higher blood loss in the conventional group did not  
4  
5 translate into red cell transfusions. Mini patients had substantially longer bypass and cross clamp  
6  
7 times and worse lung function at 4 days post-surgery. Lung function at twelve weeks, and adverse  
8  
9 event rates were otherwise not different between groups. Conventional sternotomy was found to be  
10  
11 more cost-effective. MAVRIC findings contradict those from other trials that pre-date it.<sup>23,24</sup> Two 100  
12  
13 patient RCTs published since MAVRIC and the systematic review, do not alter the discussion.<sup>25,26</sup>  
14  
15 Both found no difference in major clinical outcomes, and findings relating to shorter hospital stay in  
16  
17 mini-sternotomy; a reduction in bleeding through chest drains, and mean difference in EQ-5D scores  
18  
19 at baseline and at 6 weeks<sup>25</sup> are consistent with MAVRIC findings.  
20  
21  
22  
23  
24  
25

### 26 *Strengths and limitations*

27  
28 This is the largest single trial to have compared minimally invasive sternotomy to conventional  
29  
30 median sternotomy for AVR. A recent Cochrane review identified 511 patients from 7 previous  
31  
32 RCTs.<sup>7</sup> In MAVRIC, the mini-sternotomy technique divided only the manubrium and is therefore less  
33  
34 invasive than other minimally invasive techniques. The trial was undertaken by three experienced  
35  
36 minimally invasive surgeons who were expert at both techniques. Patients were blinded to group  
37  
38 allocation until two days following index surgery, reducing the likelihood of bias. The trial recruited a  
39  
40 significant proportion of eligible patients; 274/313 (86%), with few requiring conversion to  
41  
42 conventional sternotomy, increasing the likelihood that the trial findings are generalisable. A further  
43  
44 strength was the detailed health economic evaluation; this has not been performed previously.  
45  
46  
47

48  
49 The trial had some limitations, including the single centre design. This will tend to have biased  
50  
51 treatment effect estimates away from the null, which is at odds with our observed effect. There  
52  
53 were no significant levels of protocol non-adherence, with no effect on the main trial finding. The  
54  
55 event rate for the primary outcome, was much lower than expected at 17%; nationally red cell  
56  
57 transfusion rates following valve surgery are 46.4%.<sup>27</sup> In our pre-trial audit conducted over 5 years ,  
58  
59 ending 2009, 30% of mini-sternotomy patients received a red cell transfusion. We attribute the  
60

1  
2  
3 observed transfusion rate in MAVRIC to the restrictive red cell transfusion threshold applied; this  
4 followed evidence at the time of trial design. The consultant (expert) led nature of the trial  
5  
6 interventions is also likely to have reduced the need for transfusions post-operatively and to have  
7  
8 biased trial results towards the null.  
9

### 11 12 *Clinical importance*

13  
14 MAVRIC contributes important evidence to the minimally invasive AVR evidence base, summarised  
15  
16 in a Cochrane review.<sup>7</sup> MAVRIC demonstrated longer cross-clamp and bypass times with the  
17  
18 manubrium-limited mini-sternotomy, attributed to known differences between the interventions.  
19  
20 Minimally-invasive techniques in MAVRIC required a number of surgical steps to be performed with  
21  
22 the aortic clamp in place (drain insertion and pacing wire insertion for example), meaning cross-  
23  
24 clamp and bypass were longer. This is not an absolute requirement in other minimally invasive  
25  
26 approaches; for example, where the incision is extended into the body of the sternum, or where  
27  
28 rapid deployment valves are used, there are no differences in cross clamp and bypass times.<sup>7</sup>  
29  
30 The size of MAVRIC and event rate prevents formal comparison of adverse events between the  
31  
32 groups, of note is the difference in stroke rate; this would benefit from exploration in a future trial.  
33  
34 The cost-effectiveness plane indicates that conventional surgery is less costly and more beneficial  
35  
36 than minimally-invasive surgery; contact with healthcare professionals was greater in the mini  
37  
38 group, although there was no clear pattern of use. Wide confidence intervals mean that differences  
39  
40 are imprecise. MAVRIC does not support the use of funds to expand AVR via manubrium-limited  
41  
42 mini-sternotomy practice.  
43  
44  
45  
46  
47

48  
49 MAVRIC, the world's largest RCT at low risk of bias, found no additional clinical benefit, in terms of  
50  
51 red blood cell transfusion rates of minimally invasive AVR. Results are in agreement with the findings  
52  
53 of a Cochrane review of trials that have evaluated mini-sternotomy AVR.<sup>7</sup> This information should be  
54  
55 disseminated to patients, clinicians and commissioners to inform decisions about AVR surgery  
56  
57 including commissioning.  
58  
59  
60

### Role of funding source

This work was supported by the NIHR Research for Patient Benefit Programme (grant number PB-PG-1112-29035).

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

Adetayo Kasim (AK): None

James Mason (JM): None

Gavin Murphy (GM): Declares research grant funding from Zimmer Biomet for a trial of blood transfusion. He is supported by the British Heart Foundation (CH/12/1/29419) and the NIHR Leicester Biomedical Research Centre.

Andrew Goodwin (AG): None

W Andrew Owens (WAO): None

Enoch Akowuah (EA): None

### 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.

### Acknowledgements

We are grateful to the patients who agreed to take part in the MAVRIC trial. This trial would not have been possible without the support of all staff in the Cardiothoracic Services in The James Cook University Hospital. We would like to thank Heather Robinson and Jonathan Broughton for their



1  
2  
3 assistance with recruitment, data collection and data entry. We would like to thank the team at the  
4  
5 Clinical Trials Unit, including Jennifer Wilkinson, Andrew Thorpe, Leanne Marsay and Catherine Frost  
6  
7 for their work in managing the trial and its data.  
8  
9

#### 10 **Data Sharing Statement**

11 Anonymised data from this study may be available to the scientific community subject to  
12  
13 appropriate ethical approval. Requests for data should be directed to the senior author.  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

**Table 1. Baseline characteristics of participants by group**

	Mini-sternotomy group (n=135)	Conventional sternotomy group (n=135)
<b>Baseline characteristics</b>		
<b>Age: (years)</b>		
Mean $\pm$ SD	69.3 $\pm$ 9.3	68.7 $\pm$ 8.4
Range	43 - 85	39 - 88
<b>Gender: n (%)</b>		
Male	78 (57.8)	87 (64.4)
Female	57 (42.2)	48 (35.6)
<b>Ethnicity: n (%)</b>		
White British	135 (100)	135 (100)
<b>Body Mass Index (kg.m<sup>-2</sup>)</b>		
Mean $\pm$ SD	30.5 $\pm$ 5.6	30.4 $\pm$ 6.1
Range (Min – Max)	19.0 - 45.4	19.3 - 52.0
<b>EuroSCORE: Mean <math>\pm</math> SD (Min-Max)</b>		
Logistic	5.2 $\pm$ 3.5 (1.5 - 29.5)	5.1 $\pm$ 3.5 (1.5 - 21.0)
II – Mean	1.5 $\pm$ 1.1 (0.5 - 10.2)	1.5 $\pm$ 1.2 (0.5 - 10.0)
<b>Diagnosis echocardiogram: n (%)</b>		
Regurgitation	3 (2.2)	8 (5.9)
Stenosis	132 (97.8)	127 (94.1)
<b>NYHA class: n (%)</b>		
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)
<b>*Haemoglobin prior to randomisation: g/dl</b>		
Mean $\pm$ SD	137.9 $\pm$ 14.3	137.1 $\pm$ 16.1
Range (Min – Max)	97 -173	90 -175
<b>Surgery type: n (%)</b>		
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)
<b>Red Cell Transfusions</b>				
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)	
<b>Red Cell Units – post operatively to 7 days</b>				
Number of patients	23/135	23/135		
Mean $\pm$ SD	1.6 $\pm$ 0.7	2.3 $\pm$ 1.7		
Range (Min – Max)	1 - 3	1 - 9		
<b>Red Cell Units – post operatively to discharge</b>				
Number of patients	34/135	29/135		
Mean $\pm$ SD	2.5 $\pm$ 2.5	2.6 $\pm$ 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<sup>28</sup>, 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)
<b>Non-Red Cell Transfusions</b>			
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)
<b>Non-Red Cell Component Units – Post operatively to 7 days</b>			
Number of patients	6	18	
Mean ± SD	3.2 ± 0.9	4.6 ± 1.6	
Range (Min – Max)	2 - 5	1 - 7	
<b>Non-red Blood Cell Units – post operatively to discharge</b>			
Number of patients	13	21	
Mean ± SD	4.8 ± 2.3	4.9 ± 2.3	
Range (Min – Max)	1 - 8	1 - 12	
<b>Non-red Cell Component Transfusions</b>			
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)
<b>Cardio Pulmonary Bypass time (minutes)</b>			
<b>Mean ± SD</b>	82.7 ± 23.5	59.6 ± 15.1	
<b>Range (Min – Max)</b>	41.0 - 199	37.0 - 170.0	
<b>Aortic cross clamp time (minutes)</b>			
<b>Mean ± SD</b>	64.1 ± 17.1	46.3 ± 10.7	
<b>Range (Min – Max)</b>	32.0 - 132.0	32.0 - 97.0	
<b>Drain losses at 12 hours</b>			
<b>Mean ± SD</b>	181.6 ± 138.7	306.9 ± 348.6	-127.7 (-191.7,-63.8; p=0.0001)
<b>Range (Min – Max)</b>	25 - 925	25 - 3000	
<b>Drain losses at drain removal</b>			
<b>Mean ± SD</b>	251.7 ± 198.4	393.7 ± 378.7	-145.3 (-218.1,-72.3; p=0.0001)
<b>Range (Min – Max)</b>	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)
<b>Valve size: mm</b>			
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 $\pm$ SD	23.1 $\pm$ 2.1	23.6 $\pm$ 2.5	
Range (Min – Max)	19.0 - 29.0	19.0 - 31.0	
<b>Valve type: n (%)</b>			
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)	
<b>Valve function</b>			
<b>Mean Gradient</b>			
<b>Baseline</b>			
n	111*	110*	
Mean $\pm$ SD	47.9 $\pm$ 15.7	47.7 $\pm$ 20.2	0.2 (-4.6,5.0)
Min - Max	10-93	8-110	
<b>6 weeks</b>			
n	120*	126*	
Mean $\pm$ SD	15.7 $\pm$ 5.5	15.7 $\pm$ 5.8	0.5**(-1.0,2.1)
Min - Max	6-33	4-34	
<b>Peak Gradient</b>			
<b>Baseline</b>			
n	125*	124*	
Mean $\pm$ SD	82.3 $\pm$ 25.9	77.1 $\pm$ 29.1	5.2 (-1.7,2.3)
Min - Max	16-152	8-173	
<b>6 weeks</b>			
n	130*	130*	
Mean $\pm$ SD	29.9 $\pm$ 10.5	29.7 $\pm$ 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			
<b>Aortic Valve Regurgitation</b>			
<b>Nil/trivial</b>			
n/n (%)	109/134* (81.3)	109/130* (83.8)	218/264 (82.6)
<b>Mild</b>			
n/n (%)	19/134* (14.2)	18/130* (13.9)	37/264 (14.0)
<b>Moderate</b>			
n/n (%)	5/134* (3.7)	2/130* (1.5)	7/264 (2.7)
<b>Severe</b>			
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

	<b>Model</b>	<b>Incremental cost (95%CI)</b>	<b>Incremental QALYs (95%CI)</b>	<b>ICER (95%CI)</b>	<b>p<sup>1</sup></b>	<b>p<sup>2</sup></b>
1	Multiple imputation, covariate adjusted <sup>4</sup>	508 (-202 to 1217)	-0.007 (-0.016 to 0.002)	Dominated <sup>3</sup>	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 <sup>4</sup>	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

## References

1. Matiasz R, Rigolin VH. 2017 Focused Update for Management of Patients With Valvular Heart Disease: Summary of New Recommendations. *Journal of the American Heart Association* 2018: <https://doi.org/10.1161/JAHA.117.007596>
2. NATIONAL ADULT CARDIAC SURGERY AUDIT 2020 Summary Report (2016/17-2018/19 data)
3. Blue Book Online. The Society for Cardiothoracic Surgery in Great Britain & Ireland <http://bluebook.scts.org/#> (accessed 23<sup>rd</sup> July, 2018).
4. Leontyev S, Walther T, Borger MA, et al. Aortic Valve Replacement in Octogenarians: Utility of Risk Stratification With EuroSCORE. *Ann Thorac Surg* 2009; **87**: 1440–5.
5. Phan K, Xie A, Di Eusano M, Yan TD. The Collaborative Research (CORE) Group. Meta-Analysis of Minimally Invasive Versus Conventional Sternotomy for Aortic Valve Replacement. *Ann Thorac Surg* 2014; **98**: 1499–511.
6. Ghanta RK, Lapar DJ, Kern JA, et al. Minimally invasive aortic valve replacement provides equivalent outcomes at reduced cost compared with conventional aortic valve replacement: A real-world multi-institutional analysis. *J Thorac Cardiovasc Surg* 2015; **149**: 1060–5.
7. Kirmani BH, Jones SG, Malaisrie SC, Chung DA, Williams RJ. Limited versus full sternotomy for aortic valve replacement. *Cochrane Database Syst Rev* **2017**; 4: CD011793.
8. Fujita B, Ensminger S, Bauer T, et al; GARY Executive Board. Trends in practice and outcomes from 2011 to 2015 for surgical aortic valve replacement: an update from the German Aortic Valve Registry on 42,776 patients. *Eur J Cardiothorac Surg*. **2018**; 53: 552–559.
9. Lehmann S, Merk DR, Etz CD, et al. Minimally invasive aortic valve replacement: the Leipzig experience. *Ann Cardiothorac Surg* **2015**; 4: 49–56.
10. Johnston DR, Roselli EE. Minimally invasive aortic valve surgery: Cleveland Clinic Experience. *Ann Cardiothorac Surg* 2015; **4**: 140–147.
11. Patel NN, Avlonitis VS, Jones HE, Reevesw BC, Sterne JA, Murphy GJ. Indications for red blood cell transfusion in cardiac surgery: a systematic review and meta-analysis. *Lancet Haem* 2015; **12**: e543–53.
12. Chen QH, Wang HL, Liu L, Shao J, Yu J, Zheng RQ. Effects of restrictive red blood cell transfusion on the prognoses of adult patients undergoing cardiac surgery: a meta-analysis of randomized controlled trials. *Crit Care* 2018; **22**: 142.
13. Pagano D, Milojevic M, Meestersa MI, et al. The Task Force on Patient Blood Management for Adult Cardiac Surgery of the European Association for Cardio-Thoracic Surgery (EACTS) and the European Association of Cardiothoracic Anaesthesiology (EACTA). EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery. *Eur J Cardio-Thorac Surg* 2018; **53**: 79–111.
14. Dixon JR. The International Conference on Harmonization Good Clinical Practice guideline. *ICH GCP Qual Assur* 1998; **6**: 65–74.
15. Akowuah E, Goodwin AT, Owens WA, et al. Manubrium-limited ministernotomy versus conventional sternotomy for aortic valve replacement (MAVRIC): study protocol for a randomised controlled trial. <https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-016-1768-4> *Trials* 2017; **18**: 46.
16. NICE. Guide to the methods of Technology Appraisal. London, National Institute for Health and Care Excellence, 2013.
17. NHS Reference Costs 2015-16. London: Department of Health, 2016.
18. Curtis L, Burns A. Unit costs of health and social care 2015. Canterbury: the University of Kent, 2015.



19. Sterne Jonathan A C, White Ian R, Carlin John B, Spratt Michael, Royston Patrick, Kenward Michael G et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls BMJ 2009; 338 :b2393
20. White Ian R, Horton Nicholas J, Carpenter James, Pocock Stuart J. Strategy for intention to treat analysis in randomised trials with missing outcome data BMJ 2011; 342 :d40
21. Faria R, Gomes M, Epstein D, White IR. A Guide to Handling Missing Data in Cost-Effectiveness Analysis Conducted Within Randomised Controlled Trials. *PharmacoEconomics* (2014) 32:1157–1170
22. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med.* 2011 Feb 20;30(4):377-99
23. Aris A, Camara ML, Montiel J Delgado LJ, Galan J, Litvan H. Ministernotomy versus median sternotomy for aortic valve replacement: a prospective, randomized study. *Ann Thor Surg* 1999; **67**: 1583–7.
24. Moustafa MA, Abdelsamad AA, Zakaria G, Omarah MM. Minimal vs median sternotomy for aortic valve replacement. *Asian Cardiovasc Thorac Annals* 2007; **15**: 472–5.
25. Rodríguez-Caulo EA, ArantzaGuzón A, Otero-Forero J, José Mataró M, Sánchez-Espín G, Porras C, Villaescusa J.M, Melero-Tejedor JM, Jiménez-Navarro M. Quality of life after ministernotomy versus full sternotomy aortic valve replacement doi.org/10.1053/j.semtcvs.2020.07.013
26. Vukovic P.M, Milojevic P, Stojanovic I, Micovic S, Zivkovic I, Miodrag P, Milicic M, Milacic P, Milojevic M, Bojic M. The role of ministernotomy in aortic valve surgery-A prospective randomized study doi: 10.1111/jocs.14053. Epub 2019 Apr 24.
27. National Comparative Audit of Blood Transfusion [http://hospital.blood.co.uk/media/26859/nca-2011\\_use\\_of\\_blood\\_in\\_adult\\_cardiac\\_surgery\\_report.pdf](http://hospital.blood.co.uk/media/26859/nca-2011_use_of_blood_in_adult_cardiac_surgery_report.pdf) (accessed 23<sup>rd</sup> July, 2018).
28. 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. *Journal of the American College of Cardiology* 2019 Vol 73; 2491-2492

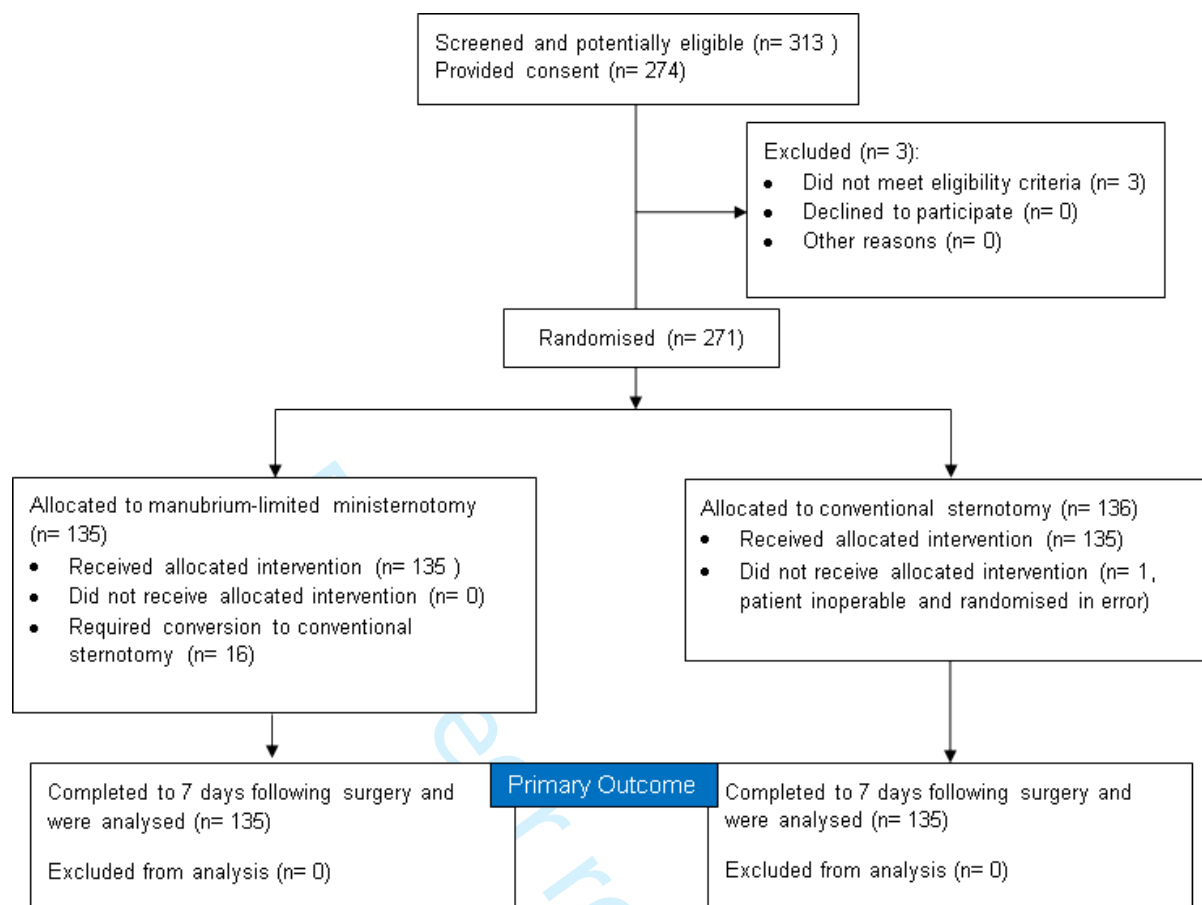
1  
2  
3 **Figure 1. CONSORT Diagram. Flow of participants through trial.**  
4

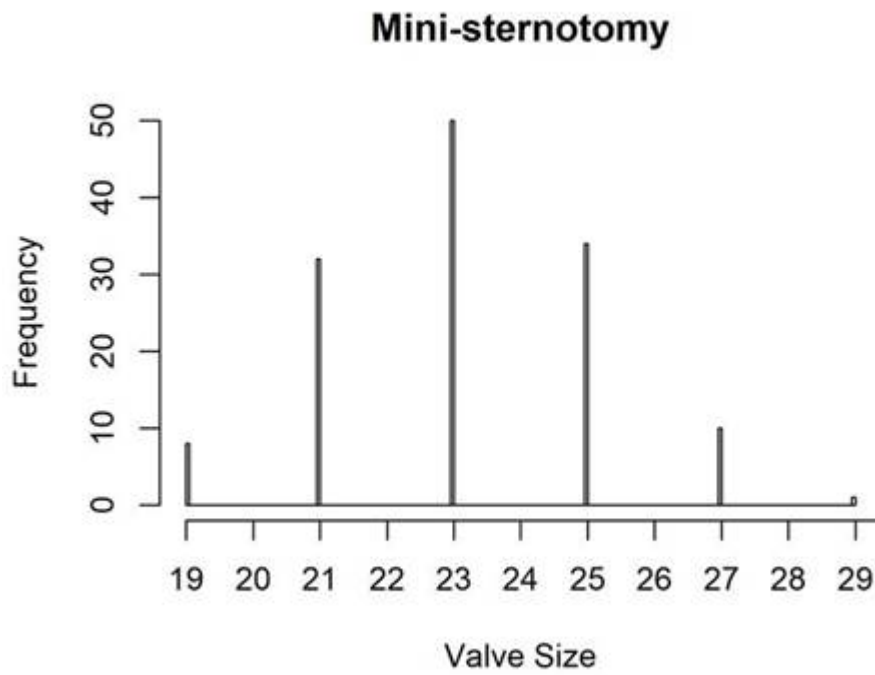
5 **Figure 2. Valve size distribution: mini-sternotomy group**  
6

7 **Figure 3. Valve size distribution: conventional sternotomy group**  
8

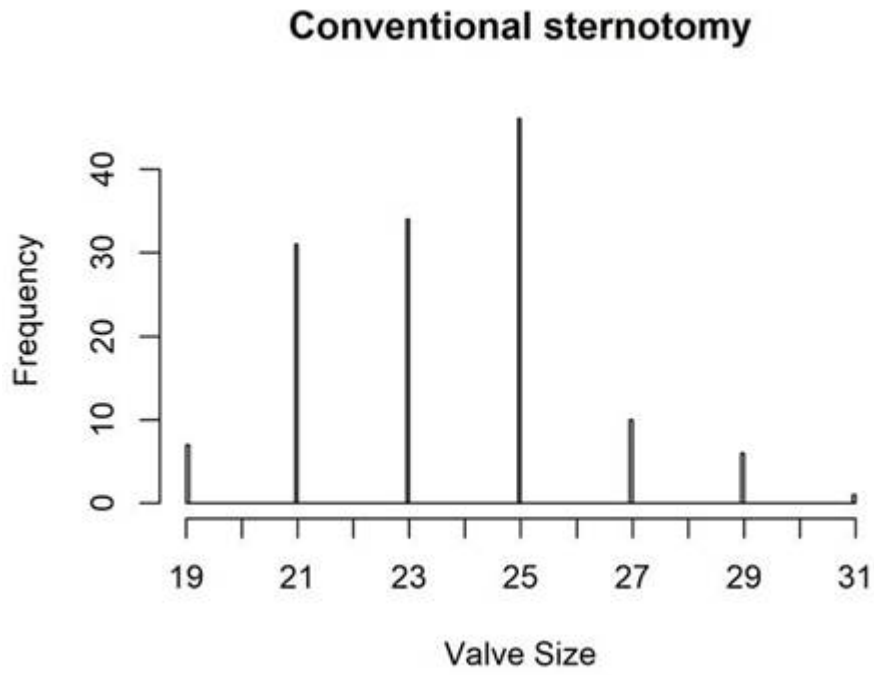
9 **Figure 4. Cost-effectiveness plane, cost/QALY (£): mini-sternotomy versus conventional surgery.**  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

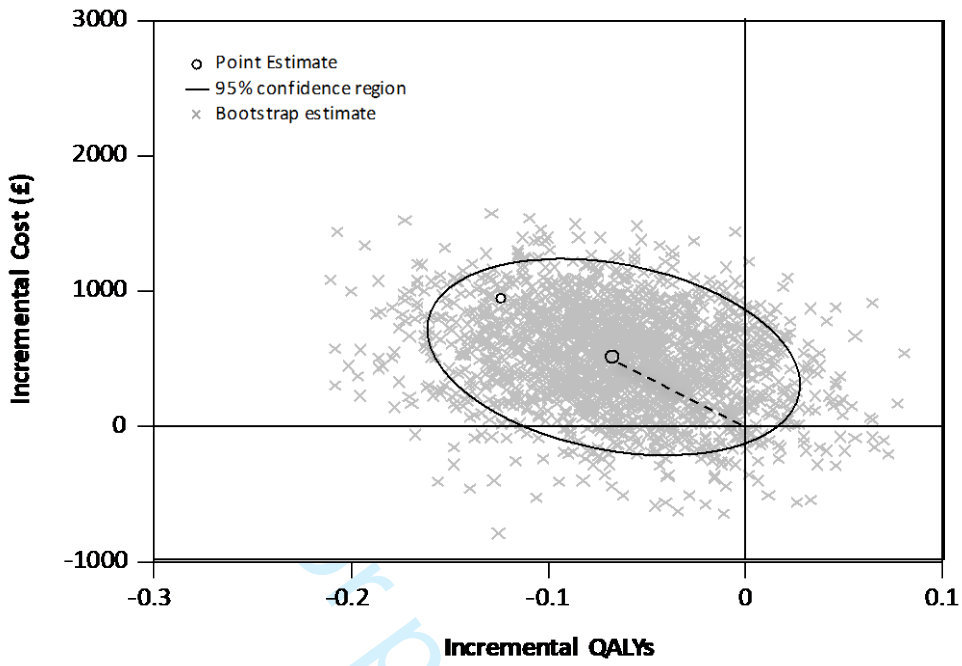




1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



er review only



peer review only

**Supplementary Material**

Study Investigators: trial site, clinical trials unit, statistics, health economics, committees	2
Table 1. Eligibility criteria	3
Figure 1. Trial recruitment by month	4
Table 2. Conversion from mini-sternotomy to conventional sternotomy	5
Table 3. Number of operations by Consultant Surgeon	6
Figure 2. Haemoglobin profiles	7
Table 4. Analgesic use and Pain scores	8-9
Table 5. Adverse Events	10
Table 6. Health status, resource use and cost (complete cases)	11
Table 7. ICU Length of Stay, Fitness for Discharge and Hospital Length of Stay	12
Table 8. Pulmonary function tests	13

**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



1  
2  
3 **Table 1. Eligibility criteria**  
4

5 Inclusion Criteria

- 6
- 7 • Aged 18 years or older at the time of consent
  - 8 • Requiring first-time, non-emergency, isolated Aortic Valve Replacement surgery
  - 9 • Able and willing to provide written informed consent
- 10

11

12 Exclusion Criteria

- 13
- 14 • requiring concomitant cardiac procedure(s) including redo surgery, emergency or salvage surgery,
  - 15 • only conventional median sternotomy indicated\*,
  - 16 • haemoglobin level < 90g/L,
  - 17 • pregnant\*\*,
  - 18 • currently participating in another interventional clinical trial,
  - 19 • previous cardiac surgery,
  - 20 • are unable to stop currently prescribed treatment affecting clotting (e.g., heparin, warfarin), \*\*\*
  - 21 • a history of thrombophilia, thrombocytopenia or other haematological conditions that would affect
  - 22 participation in the trial as determined by one of the three operating surgeons,
  - 23 • infective endocarditis,
  - 24 • prevented from having red blood cells and blood products according to a system of beliefs (e.g.
  - 25 Jehovah's Witnesses),
  - 26 • having any other medical, psychiatric and or social reason as determined by the consenting surgeon
  - 27 that precludes participation.
- 28  
29  
30  
31

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

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

38 \*\*\*for patients in both trial arms, pre-operative antiplatelet drugs (including clopidogrel and ticagrelor), and  
39 anti-coagulants (including warfarin and heparin) were discontinued 5 days prior to surgery. These drugs were  
40 re-started following surgery at the discretion of the clinical team. The exception to this was aspirin, which was  
41 stopped 5 days prior to surgery where possible, however continuation until the day of surgery did not exclude a  
42 patient from the trial.  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

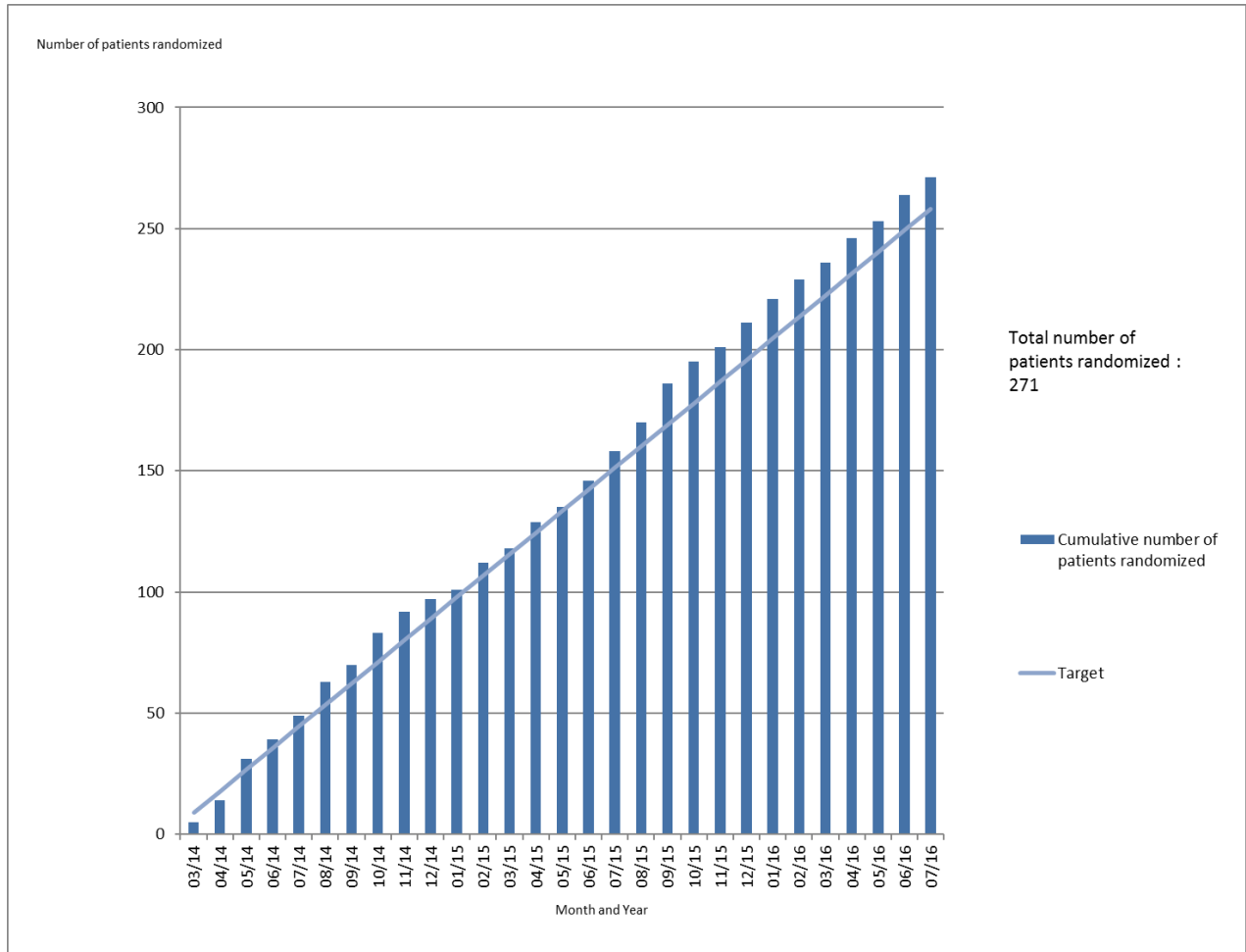


Figure 1. Trial recruitment by month.

**Table 2. Conversion from mini-sternotomy to conventional sternotomy**

Reason for conversion	Number of patients	Details
<b>Anaesthetic emergency</b>	2	<ul style="list-style-type: none"> <li>• Patient became unstable as they were transferred into theatre and BP dropped – required conventional to re-stabilise</li> <li>• 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)</li> </ul>
<b>Difficult vascular access (venous or arterial)</b>	9	<p>Venous</p> <ul style="list-style-type: none"> <li>• Femoral vessels unsuitable for cannulation</li> <li>• Poor venous drainage</li> <li>• Unable to pass venous dilators</li> <li>• Unable to insert pipe. Resistance felt, no back flow of blood. Femoral cannulation abandoned</li> <li>• Impossible to dilate femoral vein. Despite re-wiring, guide wire coiling within pelvic venous system</li> </ul> <p>Arterial</p> <ul style="list-style-type: none"> <li>• Difficulties cannulating femoral artery leading to haemodynamic instability</li> <li>• Poor access, unable to clamp aorta</li> <li>• Severe calcification of ascending aorta</li> <li>• Difficult access; aorta displaced to the left. Body habitus limited access</li> </ul>
<b>Intra-operative complications</b>	5	<ul style="list-style-type: none"> <li>• Bleeding from aortotomy site</li> <li>• Bleeding</li> <li>• Intra-operative decision to performed bypass graft to LAD</li> <li>• Post implant TOE showed small paravalvular leak and bleeding from aortotomy incision</li> <li>• Mild/moderate paravalvar leak on TOE. Required valve re-implant</li> </ul>
<b>TOTAL</b>	<b>16</b>	

**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)

For peer review only

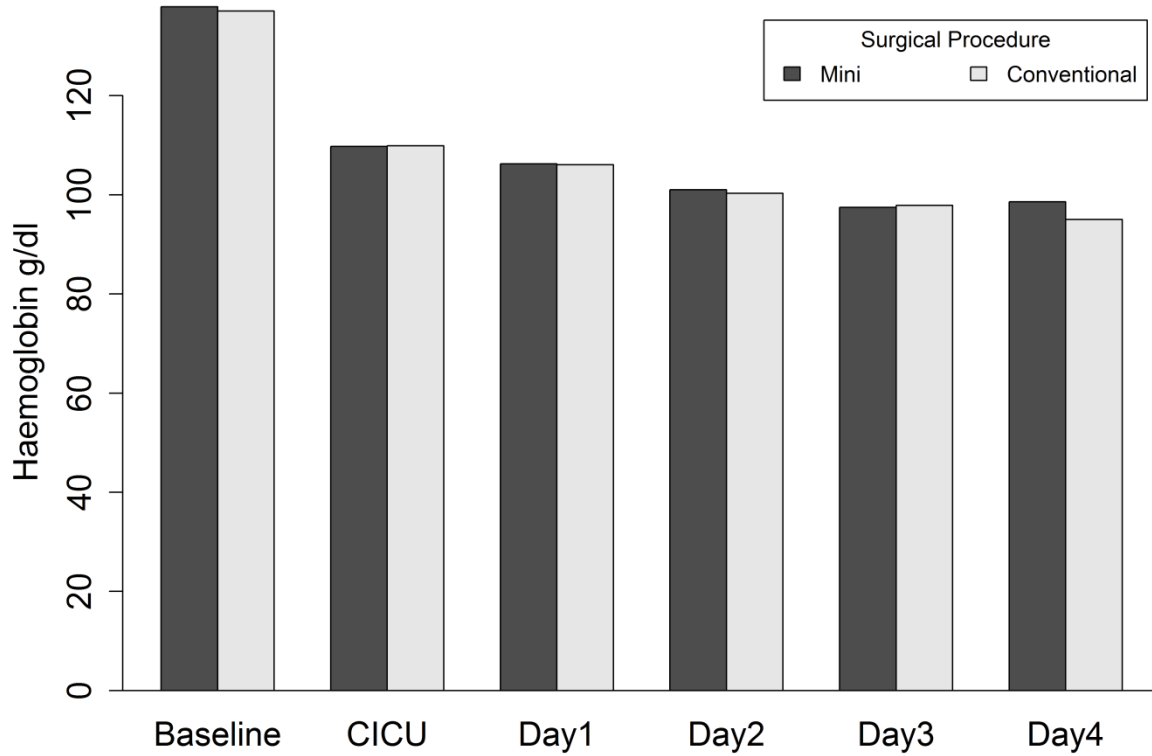


Figure 2. Haemoglobin profiles at Baseline, during CICU stay, and day 1 to day 4 post index surgery, by group

**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 (%)
<b>Analgesic use at baseline</b>			
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)
Naxoprofen	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)
<b>At least one med at baseline</b>	<b>16 (11.9)</b>	<b>12 (8.9)</b>	<b>28 (10.4)</b>
<b>Analgesic use at day 2</b>			
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 (0.4)
Tramadol Hydrochloride	7 (5.2)	5 (3.7)	12 (4.4)
<b>At least one med at day 2</b>	<b>99 (73.3)</b>	<b>86 (63.7)</b>	<b>185 (68.5)</b>
<b>Analgesic use at day 3</b>			
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)
<b>At least one med at day 3</b>	<b>90 (66.7)</b>	<b>101 (74.8)</b>	<b>191 (70.7)</b>
<b>Analgesic use at Day 4</b>			
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)
<b>At least one med at day 4</b>	<b>88 (65.2)</b>	<b>81 (60.0)</b>	<b>169 (62.6)</b>
<b>Analgesic use at Week 6</b>			
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)
<b>At least one med at week 6</b>	<b>41(30.4)</b>	<b>41(30.4)</b>	<b>82(30.4)</b>
<b>Analgesic use at Week 12</b>			
Buprenorphine Patch	3(2.2)	0(0.0)	3(1.1)
Codeine Phosphate	7(5.2)	4(3.0)	11(4.1)

1				
2				
3	Dihydrocodeine Tartrate	0(0-0)	1(0-7)	1(0-4)
4	Gabapentin	2(1-5)	0(0-0)	2(0-7)
5	Ibuprofen	1(0-7)	0(0-0)	1(0-4)
6	Morphine Sulfate	1(0-7)	1(0-7)	2(0-7)
7	Naproxen	1(0-7)	0(0-0)	1(0-4)
8	Paracetamol	19(14-1)	20(14-8)	39(14-4)
9	Tramadol Hydrochloride	1(0-7)	1(0-7)	2(0-7)
10	<b>At least one med at week 12</b>	<b>23(17-0)</b>	<b>22(16-3)</b>	<b>45(16-7)</b>

	Mini-sternotomy Group (n=135 patients)	Conventional sternotomy group (n=135)
11		
12		
13		
14	<b>Baseline pain score</b>	
15	n	128*
16	Mean± SD	1.3 ± 2.1
17	(min-max)	0 - 10
18	<b>Day 2 pain score**</b>	
19	n	123*
20	Mean± SD	3.4 ± 2.4
21	(min-max)	0 - 10
22	<b>Day 3 pain score</b>	
23	n	120*
24	Mean± SD	2.8 ± 2.5
25	(min-max)	0 - 9
26	<b>Day 4 pain score</b>	
27	n	116*
28	Mean± SD	2.5 ± 2.2
29	(min-max)	0 - 8
30	<b>6 week pain score</b>	
31	n	112*
32	Mean± SD	1.5 ± 1.9
33	(min-max)	0 - 8
34	<b>12 week pain score</b>	
35	n	128*
36	Mean± SD	1.1 ± 1.9
37	(min-max)	0 - 8

\*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] <sup>1</sup>	
	mean	(SD)	N	mean	(SD)	N	mean	(95%CI)
<b>Health status<sup>2</sup></b>								
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)
<b>Resource use</b>								
Index Admission								
Length of stay (d) <sup>3</sup>	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) <sup>4</sup>	0.08	0.34	135	0.03	0.17	135	-0.05	(-0.11 to 0.02)
Time in surgery (h) <sup>4</sup>	2.32	0.63	135	3.01	0.71	135	0.69	(0.53 to 0.85)
RBC (u) <sup>4</sup>	0.59	1.45	135	0.55	1.28	135	-0.04	(-0.37 to 0.28)
FFP (u) <sup>4</sup>	0.57	1.43	135	0.34	1.21	135	-0.23	(-0.55 to 0.09)
Platelets (u) <sup>4</sup>	0.22	0.64	135	0.12	0.46	135	-0.10	(-0.24 to 0.03)
Cryoprecipitate (u) <sup>4</sup>	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)
<b>Cost<sup>5</sup></b>								
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)
<b>ICU stay (days)</b>		
n	135	135
Mean $\pm$ SD	1.9 $\pm$ 5.8	1.3 $\pm$ 1.1
Min-Max	0 - 64*	0 - 7
<b>Fitness for discharge (days)</b>		
n	129**	133**
Mean $\pm$ SD	6.5 $\pm$ 3.7	6.3 $\pm$ 3.2
Min - Max	3 - 36	3 - 31
<b>Post-operative length of stay (days)</b>		
n	135	135
Mean $\pm$ SD	7.4 $\pm$ 7.5	6.3 $\pm$ 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)
<b>FEV1</b>			
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	
<b>FVC</b>			
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
<b>Title and abstract</b>			
	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
<b>Introduction</b>			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	3,5
<b>Methods</b>			
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
<b>Randomisation:</b>			
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

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

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	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	2,4
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	4
	11b	If relevant, description of the similarity of interventions	2,4,5
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	4
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	7
<b>Results</b>			
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	7
Recruitment	13b	For each group, losses and exclusions after randomisation, together with reasons	9,17
	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
<b>Discussion</b>			
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

1			
2			
3	Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence
4			13,14
5	<b>Other information</b>		
6	Registration	23	Registration number and name of trial registry
7			1,4
8	Protocol	24	Where the full trial protocol can be accessed, if available
9			4
10	Funding	25	Sources of funding and other support (such as supply of drugs), role of funders
11			4, 15

11 \*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If  
 12 relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal  
 13 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](http://www.consort-statement.org).  
 14  
 15  
 16  
 17  
 18  
 19  
 20  
 21  
 22  
 23  
 24  
 25  
 26  
 27  
 28  
 29  
 30  
 31  
 32  
 33  
 34  
 35  
 36  
 37  
 38  
 39  
 40  
 41  
 42  
 43  
 44  
 45  
 46

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

For peer review only