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1 **Mini-Stern Trial: A randomised trial comparing mini-sternotomy to full median**  
2 **sternotomy for aortic valve replacement**

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30 to the co-ordination and management of the trial, data collection, data analysis and

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33 revised manuscript on acceptance for publication.

34

35 **Glossary of Abbreviations**

36

37	AVR	aortic valve replacement
38	mAVR	minimal access aortic valve replacement
39	BMI	body mass index
40	CI	95% confidence interval
41	COPD	chronic obstructive pulmonary disease
42	CPB	cardiopulmonary bypass
43	FEV <sub>1</sub>	forced expiratory volume in one second
44	FS	full median sternotomy
45	HR	hazard ratio
46	HRQoL	health-related quality of life
47	ICER	incremental cost-effectiveness ratio
48	LVEF	left ventricular ejection fraction
49	MS	mini-sternotomy
50	NHS	National Health Service
51	OR	odds ratio
52	QALY	quality-adjusted life year
53	RCT	randomised control trial
54	SAE	serious adverse event
55	SD	standard deviation
56	TLCO	transfer factor of the lung for carbon monoxide
57	TOE	transoesophageal echocardiogram
58	UK	United Kingdom

59

60 **Central Message**

61

62 In the UK NHS, compared to conventional median sternotomy approach for surgical AVR,

63 mini-sternotomy did not hasten recovery or hospital discharge, and was not cost-effective.

64 **Perspective Statement**

65 Minimal access surgery is appealing for its perceived advantages including better patient  
66 recovery, satisfaction and cost-effectiveness. This RCT conducted within the UK NHS  
67 setting did not demonstrate quicker patient recovery or cost-effectiveness associated with  
68 mini-sternotomy compared to full median sternotomy approach. These findings are relevant  
69 to physicians, patients and health care funders.

70

71 **Structured Abstract**

72 **Objective:** Aortic valve replacement (AVR) can be performed either through full median  
73 sternotomy (FS) or upper mini-sternotomy (MS). The Mini-Stern trial aimed to establish  
74 whether MS leads to quicker postoperative recovery and shorter hospital stay after first-time  
75 isolated AVR.

76 **Methods:** This pragmatic, open-label, parallel RCT compared MS with FS for first-time  
77 isolated AVR in two UK NHS hospitals. Primary endpoints were duration of postoperative  
78 hospital stay and the time to fitness for discharge from hospital after AVR, analysed in the  
79 intent-to-treat population.

80 **Results:** In this RCT, 222 patients were recruited and randomised (118 MS, 104 FS).  
81 Compared to FS patients, MS patients had longer hospital stay (mean 9.5 vs. 8.6 days) and  
82 took longer to achieve fitness for discharge home (mean 8.5 vs. 7.5 days). Adjusting for valve  
83 type, sex and surgeon, hazard ratios (HR) from Cox models did not show a statistically  
84 significant effect of MS (relative to FS) on either hospital stay (HR 0.874, 95% CI 0.668-  
85 1.143, p-value 0.3246) or time to fitness for discharge (HR 0.907, 95% CI 0.688-1.197, p-  
86 value 0.4914). During mean follow up of 760 days (MS:745 and FS:777 days), 12 (10%) MS  
87 and 7 (7%) FS patients died (HR 1.871, 95% CI 0.723-4.844, p-value 0.1966). Average extra  
88 cost for MS was £1,714, during the first 12 months after AVR.

89 **Conclusions:** Compared to FS for AVR, MS did not result in shorter hospital stay, faster  
90 recovery or improved survival and was not cost-effective. MS approach is not superior to FS  
91 for performing AVR.

92 **Word count for Abstract:** 248

93 **Introduction**

94 Aortic valve replacement (AVR) is the second commonest cardiac surgery in the UK [1] with  
95 an increasing proportion of older patients [1, 2]. Minimal access AVR (mAVR) might  
96 shorten hospital stay and postoperative recovery period and could be beneficial if offered  
97 safely and cost-effectively.

98

99 Currently, most AVRs are performed safely through full median sternotomy (FS) [2-6].

100 However, mAVR may be associated with less postoperative pain, blood loss, pulmonary and  
101 wound complications and shorter hospital stay [2]. The most commonly practised mAVR  
102 involves mini-sternotomy (MS), which could potentially hasten postoperative recovery,  
103 shorten hospital stay and improve patient satisfaction [2-10].

104

105 Most studies comparing MS and FS for AVR are non-randomised. Although systematic  
106 reviews with meta-analyses [11, 12] have been conducted, inadequate statistical power and  
107 heterogeneity of studies calls for prospective, randomised control trials (RCTs) to assess  
108 benefits and risks of mAVR. Published evidence on cost-effectiveness comparing MS to FS  
109 is sparse and weak. A recent review comparing cost-effectiveness of FS and MS called for a  
110 well-designed RCT to evaluate cost-effectiveness of mAVR up to at least a year after surgery  
111 [13]. Recently, a propensity-matched study from the UK national data concluded that mAVR  
112 is safe and was associated with shorter postoperative hospital stay [14]. The authors  
113 concluded that although general clinical equipoise exists between FS and MS, it is essential  
114 to have a well-constructed and adequately powered RCT before widespread adoption of MS.  
115 This retrospective study did not analyse cost-effectiveness of either surgical approach.

116



117 The Mini-Stern trial assessed whether MS is superior to FS in shortening postoperative  
118 recovery time and improving patient outcomes without compromising patient safety. It also  
119 assessed cost-effectiveness of MS from the perspective of the UK NHS as a health care  
120 provider.

121

## 122 **Materials and Methods**

123 Mini-Stern was a two-centre, pragmatic, open-label RCT conducted in the UK. Patients were  
124 randomised (1:1) to AVR either by MS or FS.

125

## 126 **Sample Size**

127 Considering four published RCTs [5, 6, 9, 10] and two cohort studies [7, 8], a 20% reduction  
128 in hospital stay from 11.7 to 9.36 days was considered clinically significant. Based on an  
129 internal audit of 252 first-time elective AVRs performed at Papworth Hospital in 2007/08  
130 (mean hospital stay 11.7 days, SD 6.2), to detect this change with 80% power and 2-sided  
131 significance of 5%, 110 patients per group were required. As randomisation was performed  
132 on the day of surgery after induction of anaesthesia and introduction of the transoesophageal  
133 echocardiogram (TOE) probe, no subjects dropped out between randomisation and surgery  
134 thereby making the total trial recruitment target, 220 patients.

135

## 136 **Recruitment**

137 Adult patients undergoing first-time isolated AVR were included. Exclusion criteria included  
138 emergency AVR, LVEF $\leq$  30%, chest wall deformities, severe COPD (FEV<sub>1</sub> or TLCO < 40%  
139 predicted), BMI > 35kg/m<sup>2</sup>, concomitant cardiac surgery, redo-surgery and inability to  
140 perform TOE. Details of patient enrolment are given in the online protocol.

141

142 **Randomisation**

143 Randomisation (1:1) used random permuted blocks of variable lengths (6 or 8), stratified by  
144 surgeon and valve prosthesis (bio-prosthetic or mechanical). Random allocations were pre-  
145 generated, held in secure files by Papworth Trials Unit. During early days of the trial, TOE  
146 probe could not be passed in four patients due to technical reasons. These patients underwent  
147 the allocated procedure and were included in the trial. Later the Trial Steering Committee  
148 decided that under such circumstances, MS would be unsafe and patients should be excluded  
149 from the trial to FS. Since eligibility for MS required TOE, in order to avoid post-  
150 randomisation drop-out, group allocation for the study subjects was retrieved via telephone  
151 by theatre staff soon after anaesthesia and introduction of the TOE probe. Due to the nature  
152 of interventions, this trial could not be blinded.

153

154 **Outcomes**

155 **Primary endpoints:** Two closely related primary endpoints were measured. Firstly, length  
156 of postoperative hospital stay (days between surgery and actual hospital discharge) which is  
157 easily measured, a surrogate for early postoperative events and sensitive to outcomes that  
158 affect health-related quality of life (HRQoL). Secondly, the interval in days between surgery  
159 and the patient being medically fit for discharge. To reduce investigator bias, standard  
160 discharge criteria were followed to decide the day of fitness for discharge. This endpoint was  
161 chosen to address exogenous effects (social factors, lack of transport, non-availability of  
162 space in nursing homes etc.) that commonly delay hospital discharge in the UK.

163

164 **Clinical secondary endpoints:** duration of surgery, total theatre time, aortic cross-clamp  
165 and cardiopulmonary bypass (CPB) times, blood loss in the first 12 hours after surgery,  
166 transfusion of blood and clotting products in the first 48 hours (blood transfusion trigger was

167 haemoglobin level < 80g/L), frequency of re-intubation, time to initial extubation,  
168 mediastinal drain removal and first independent mobilisation, daily pain scores at rest and on  
169 deep breath (over the first ten days or until hospital discharge) on a scale of 0 to 10, LVEF  
170 and severity of para-prosthetic regurgitation at hospital discharge and at 6 months, and time  
171 to all-cause death. Definitions of adverse events and details of their reporting are in the online  
172 protocol. To exclude bias, clinical outcome data were collected by research team who were  
173 not involved in routine care of subjects, following standardised protocols.

174

175 **Non-clinical secondary endpoints:** Health-related Quality of Life and Healthcare resource  
176 use.

177 **HRQoL:** Patients completed EQ-5D-3L [15] and SF-36 [16, 17] questionnaires at baseline,  
178 6 weeks, 6 months and 12 months following surgery. EQ-5D-3L was repeated on fourth  
179 postoperative day and at discharge.

180 **Healthcare resource use:** Patient-specific resource use collected from hospital records and  
181 patient interviews during the primary admission included phases of care including operative  
182 surgery, critical care, post-surgical ward care and medications. Post-discharge resource use  
183 included attending wound clinics, community nurse visits, physiotherapy sessions,  
184 occupational therapy services, medical tests, cost of analgesics and other drugs and further  
185 hospitalisation within the first year after AVR.

186

### 187 **Surgical details**

188 All participating surgeons were consultants experienced in performing AVR by both FS and  
189 MS. They followed the operative surgical protocol as described below.

190 **MS approach:** With the patient anaesthetised as per standard protocol, skin was incised from  
191 half-way between the suprasternal notch and the sternal angle to the level of the fourth

192 intercostal space, measuring approximately 8cm. The manubrium was divided in the midline  
193 from the suprasternal notch inferiorly and then into the right 4th intercostal space. Thymus  
194 was divided and pericardium opened exposing the ascending aorta, aortic root and right atrial  
195 appendage. A loading dose of unfractionated heparin 300U/kg followed by boluses of 5000U  
196 was administered to achieve activated clotting time above 450 seconds. Aorta was  
197 cannulated using a wired flexible aortic cannula. Right atrial appendage was cannulated using  
198 a flat venous cannula and CPB commenced. The ascending aorta was cross-clamped and  
199 intermittent, antegrade, cold blood cardioplegia administered. The aorta was then incised  
200 open in an oblique or transverse fashion, the diseased valve excised and annulus decalcified.  
201 A suitably sized aortic valve prosthesis was inserted using either horizontal mattress, 2-0  
202 Ethibond sutures or semi-continuous, 2-0 Prolene sutures. Surgeons adopted either of these  
203 suture techniques and adhered to the same technique irrespective of the type of valve  
204 prosthesis or the surgical approach. Aortotomy was then closed, heart de-aired, right atrial  
205 and ventricular epicardial pacing wires inserted and patient weaned off CPB. After  
206 confirming satisfactory functioning of the aortic valve prosthesis by TOE, heparin was  
207 reversed with protamine (1mg/100U of heparin). Chest drains were inserted into the anterior  
208 mediastinum, posterior pericardial space and pleural space if necessary. Sternal wires were  
209 inserted and incision closed in layers. Conversion to FS was performed to ensure patient  
210 safety if access was difficult or if intraoperative complications occurred.

211

212 **FS approach:** Anaesthesia and positioning of patients was the same as for MS approach.  
213 The skin incision was made between the suprasternal notch and the xiphoid process and  
214 sternum divided in the midline from the suprasternal notch to the xiphoid process. A two-  
215 stage venous cannula was used for atrial cannulation. Remaining steps were similar to MS  
216 approach.

217 **Statistical analysis**

218 Analyses of primary and secondary endpoints used intention-to-treat and included all  
219 randomised patients. Unless stated otherwise, statistical models included treatment (MS vs.  
220 FS), valve (mechanical vs. bio-prosthetic) and sex as fixed effects, and surgeons as random  
221 effects. Hypothesis testing was two-sided at the 5% significance level, with no adjustments  
222 for multiple testing. All confidence intervals (CI) were estimated at the 95% confidence level.

223 Distributions of time-to-event endpoints were compared between study groups using Kaplan-  
224 Meier curves and log-rank tests (stratified by sex, valve and surgeon). Hazard ratios (HR) for  
225 MS relative to FS were estimated from a Cox model. The null hypothesis of no treatment  
226 effect (HR = 1) was tested. Patients who were lost to follow-up, withdrew or died before the  
227 event were censored at the latest time they were known to be event-free. Models were  
228 checked by plotting Schoenfeld and deviance residuals. For primary endpoints, Cox models  
229 were re-fitted using the per-protocol population and in sensitivity analyses (Appendix A.  
230 Table A4).

231 Need for reintubation and other dichotomous endpoints were compared between groups by  
232 estimating a MS/FS odds ratio (OR) via logistic regression. EQ-5D, SF-36 and pain scores  
233 were modelled using repeated measures linear regression. Where possible, random intercepts  
234 and random time coefficients for patients were included. For EQ-5D and SF-36, fixed effects  
235 for baseline scores were included. Models were fitted using complete cases, then re-fitted  
236 with multiple imputation of missing scores via chained equations.

237 Serious adverse events (SAEs) were analysed in the safety population according to  
238 intervention received. Patients randomised to MS who crossed over to FS prior to surgery  
239 were considered to have received FS; those who crossed over after MS had commenced were

240 considered to have received MS. Rates of SAEs were explored using Poisson regression with  
241 a random patient effect.

242 CONSORT guidelines [18] were followed. Analyses were performed in SAS version 9.4  
243 (SAS Institute Inc., Cary, NC, USA). No interim analyses were undertaken but reports were  
244 presented annually to the Data Monitoring and Ethics Committee.

### 245 **Economic analysis**

246 Unit costs were obtained from nationally published sources in the UK [19, 20, 21, 22] or  
247 from the Finance department, Papworth Hospital when the former did not provide the  
248 required information. Total cost per patient was calculated by summing resource use items  
249 multiplied by unit costs across the in-patient stay and the 12-month postoperative follow-up  
250 period (Appendix B. Table B7). Health state utilities from the EQ-5D-3L and SF-36, based  
251 on UK value sets [15, 23] were used to generate quality-adjusted life years (QALYs) using  
252 the area under the curve method and assigning a value of zero from date of death. Missing  
253 values were imputed using chained predictive mean matching, stratified by treatment and  
254 conditional on age, sex and baseline EQ-5D-3L.

255

256 Differences in mean costs and QALYs were estimated using seemingly unrelated regression,  
257 controlling for age, sex, valve, baseline EQ-5D-3L and treatment, to accommodate skewness  
258 [24]. Uncertainty in cost-effectiveness was estimated by drawing 1000 bootstrapped samples  
259 and conducting probabilistic sensitivity analysis. Results are presented as incremental net  
260 monetary benefit at various thresholds of willingness to pay per QALY, cost-effectiveness  
261 planes and cost-effectiveness acceptability curves. Deterministic sensitivity analyses explored  
262 effects of using complete cases only, SF6D-based QALY estimates, the procedure inpatient

263 admission only, excluding patients who died and excluding additional equipment costs  
264 (Appendix B. Table B11).

265

## 266 **Results**

267 Overall 1024 patients were screened between 28 January 2010 and 13 April 2015, of whom  
268 222 were recruited and randomised to MS (118) or FS (104). One-year follow-up was  
269 completed on 23 May 2016.

270 Study groups were similar at baseline except for a non-significant sex imbalance (Table 1). In  
271 this trial, MS was not completed in 14 (12%) of 118 patients randomised to MS. Of these  
272 patients, 6 (5%) had conversion from MS to FS due to reasons listed in Figure 1. The  
273 remaining 8 patients underwent FS after randomisation to MS but without initial MS incision  
274 as MS was considered unsafe/impractical. The true rate of intraoperative conversion of MS  
275 to FS was therefore 5%. Four patients (2%, Table 2) were censored before discharge: one  
276 withdrawal before surgery (FS) and three deaths (all randomised to and received MS). A  
277 further thirteen (6%) were censored before fitness for discharge: six discharged to acute  
278 hospital (three MS, three FS), seven to long-term care or rehabilitation (three FS, four MS).

279 Mean time to hospital discharge was longer for MS than FS (9.5 vs. 8.6 days), as was mean  
280 time to fitness to discharge (8.5 vs. 7.5 days). However, distributions of these endpoints were  
281 similar in both groups (Figure 2, Table 2). The difference was not statistically significant in  
282 either primary analyses using Cox models (Figure 3), log-rank tests (Table 2) or sensitivity  
283 analyses (Appendix A. Table A4). The gamma-distributed frailty term in the Cox models was  
284 estimated to have variance 0.006675 for time to fitness and 0.000100 for time to discharge,  
285 suggesting that surgeon heterogeneity was negligible.

286 Time to drain removal (including drains inserted/retained to treat complications) was longer  
287 for MS, but times to extubation and independent mobilisation did not differ significantly  
288 between groups (Table 2, Figure 3), nor did numbers of patients re-intubated (six MS vs. five  
289 FS, OR 1.039, CI 0.306-3.531,  $p=0.9512$ ). Statistically significant HRs indicated longer  
290 surgery, CPB, cross-clamp and theatre times for MS (Figure 3). No significant differences  
291 were seen in blood loss (Appendix A. Table A3), or in numbers of patients requiring  
292 transfusion of blood (50 MS vs. 51 FS, OR 0.797, CI 0.453-1.402,  $p=0.4310$ ) or clotting  
293 products (11 MS vs 4 FS, OR 2.616, CI 0.801-8.541,  $p=0.1112$ ).

294 Regression models for pain at rest, EQ-5D utilities and SF-36 domain scores (Appendix A.  
295 Tables A6, A7, A8) estimated greater rate of improvement over time in MS patients for three  
296 SF-36 domains (social functioning, vitality and role physical). After multiple imputation, the  
297 difference was only significant for the role physical domain (Appendix A. Table A9). Pain on  
298 deep breath was not analysed as only less than half the data were collected due to poor patient  
299 compliance.

300 Nine (4%) patients died within a year of surgery: seven (6%) MS, two (2%) FS. Five deaths  
301 were possibly related to treatment (four MS, one FS), none were probably or definitely  
302 related (Appendix A. Table A15). Overall, twelve (10%) MS and seven (7%) FS patients died  
303 during follow-up (mean follow-up 760 days: 745 MS, 777 FS). Time to all-cause death,  
304 adjusted for age, showed a moderately large but statistically non-significant HR (MS/FS) of  
305 1.871 (CI 0.723-4.844,  $p=0.1966$ ).

306 Safety analyses excluded one patient who was withdrawn before surgery. There were  
307 significantly more SAEs in MS recipients (rate ratio 1.615, CI 1.070-2.437,  $p=0.0225$ )  
308 (Appendix A. Table A11). The numbers of patients experiencing SAEs were not  
309 significantly different (OR 1.559, CI 0.895-2.715,  $p=0.1161$ ). Incidence of para-prosthetic



310 regurgitation did not differ significantly between groups (Appendix A. Table A13). Seven  
311 patients developed pericardial collection (three MS vs four FS, OR 0.680, CI 0.146-3.178,  
312  $p=0.6229$ ). Wound infections (including superficial and deep infections) were more common  
313 in FS recipients (thirteen FS vs four MS, OR 0.312, CI 0.097-1.005,  $p=0.0511$ ). Deep sternal  
314 wound infection developed in one MS and one FS recipient, neither of whom required plastic  
315 surgical repair.

316 Economic analyses are summarised in Table 4. There was additional cost for MS relative to  
317 FS (£1,714 per patient,  $p=0.0765$ ) in the first year following surgery. MS patients had (non-  
318 significant) better EQ-5D-based QALYs (0.03 per patient,  $p=0.1509$ ). The incremental cost  
319 per QALY gained was £61,379, but after adjusting for baseline characteristics, MS had  
320 higher costs and lower QALYs (i.e. was dominated). In deterministic and probabilistic  
321 sensitivity analyses, MS was either dominated or had a very large cost per QALY, except for  
322 the complete case analysis (Appendix B. Tables B11, B12).

## 323 **Discussion**

324 The UK NHS is a free for patient at point-of-delivery healthcare system. Apart from good  
325 recovery, hospital discharge of a significant proportion of elderly patients depends on the  
326 timely availability of social care services in the community. The Mini-Stern trial is the first  
327 RCT comparing FS and MS for isolated AVR when performed for UK NHS patients.

328

329 In this prospective, pragmatic, open-label RCT, MS did not reduce the total duration of  
330 hospital stay after AVR. As hospital discharge is sometimes delayed due to social factors, we  
331 included time until fit for discharge as a second primary endpoint. This was also not reduced  
332 by MS. These endpoints were recorded by physiotherapists based on a common discharge

333 protocol with specific clinical milestones to achieve, thereby excluding physician-induced  
334 bias.

335

336 In this study operation, total theatre, aortic cross-clamp and CPB times were significantly  
337 prolonged with MS. This was expected as in general, minimal access valve operations take  
338 longer [5, 9]. This is justifiable if MS resulted in either faster recovery, shorter postoperative  
339 stay, reduced cost of treatment or more importantly a significant reduction in adverse events  
340 and therefore superior patient safety. In this RCT, MS did not achieve these benefits and  
341 hence we feel that the prolonged operation time, total theatre, cross-clamp and CPB times are  
342 not justifiable for performing AVR through MS.

343

344 Previously, two meta-analyses [11, 12] concluded that mAVR approaches are superior in  
345 certain aspects of postoperative recovery. However, both included studies on mini-  
346 thoracotomy approach for AVR, and therefore inferences drawn cannot be extrapolated to  
347 MS. A retrospective propensity-matched analysis of data from a UK national database  
348 concluded that MS is safe and comparable to conventional AVR [14]. The authors found  
349 that MS resulted in a shorter postoperative hospital stay, which disagrees with our findings.  
350 However, a propensity-matched study can suffer from selection bias if its matching algorithm  
351 produces treatment groups that are unbalanced in some unobserved characteristics. Recently,  
352 a retrospective study demonstrated safety of right thoracotomy minimally invasive isolated  
353 and concomitant AVR in patients of all age groups [25]. As randomisation balances study  
354 groups in known and unknown characteristics, results of the Mini-Stern trial should be more  
355 reliable than non-randomised studies.

356

357 Previous studies investigating cost-effectiveness provided unclear answers. A report  
358 analysing registry data from patients who underwent isolated primary AVR [26] reported  
359 lower hospital cost when AVR was performed through right anterior thoracotomy compared  
360 to sternotomy-based approaches with no significant differences in outcome. The main reasons  
361 attributed to lower costs were earlier hospital discharge and reduced use of blood products.  
362 Ghanta et al [27] noted that exclusion of rehabilitation costs could alter this finding. A review  
363 by Glauber et al [13], based on uncontrolled studies, noted that higher cost of instruments and  
364 devices in mAVR could be offset by economic advantage gained by shorter hospital stay and  
365 lower complication rates. The Mini-Stern trial assessed cost-effectiveness using a range of  
366 sensitivity analyses, but only the complete case analysis showed MS to be cost-effective,  
367 suggesting lower costs but slightly worse outcomes with MS. However, this analysis used a  
368 potentially unrepresentative sample of just 90 patients. Our analysis was restricted to the  
369 first year following operation without long-term analysis beyond 1 year.

370

371 This RCT is robust with many merits including on-table randomisation, comprehensive and  
372 independent outcome assessment without physician-bias, longer-term clinical assessment,  
373 HRQoL analysis and economic analysis. However there were some limitations. Although we  
374 report on secondary endpoints, this trial was powered only to address the primary endpoint.  
375 A total of 14 patients (12%) allocated to MS received FS, which could be another limitation.  
376 However, only 6 patients (5%) had true conversion after an attempted MS, while 8 patients  
377 (6.7%) went on to FS for safety reasons. Although this RCT took place in only two centres,  
378 thereby limiting generalisability, recruitment by eight surgeons improves generalisability. A  
379 total of 1024 patients were screened to recruit 222 (21.7%) patients. Although this  
380 potentially suggests selection bias, only 125 eligible patients (12.2%) failed recruitment while  
381 the remaining 667 patients (65.1%) did not meet inclusion criteria. Blinding was not

382 practical as sternotomy dressings were usually changed 48 hours after surgery and patients  
383 became aware of the approach. This could have caused bias in self-reported outcomes.  
384 Missing ‘pain at rest’ data were unlikely to be missing at random, and therefore imputation  
385 might not have addressed all potential biases. Despite having two primary outcomes, we did  
386 not adjust for multiple testing. However, as neither showed a significant difference between  
387 groups, this would not have affected our conclusions.

388

389 In conclusion, MS for AVR did not result in quicker recovery or earlier hospital discharge.  
390 MS resulted in longer operations, increased costs, and resulted in more SAEs than FS.  
391 Overall, this pragmatic RCT did not provide evidence that MS results in better clinical or  
392 quality of life outcomes, or that MS is cost-effective compared to FS in the first year after  
393 AVR.

394

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398

399

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407 **Legends**

408 **Central Picture Legend:** Duration of hospital stay after AVR: FS versus MS.

409 **Video Legend:** MS approach for AVR.

410 **Figure 1.** Trial flow diagram.

411 **Figure 2.** Kaplan-Meier curves for primary endpoints. Points indicate censoring and dashed  
412 lines represent 95% confidence intervals.

413 **Figure 3.** Forest plot of HRs and 95% confidence intervals from Cox models.

414 **Figure 4.** Cost-effectiveness planes. Proportion of points below each threshold gives the  
415 probability that MS is more cost-effective than FS. This probability is 3.7% for willingness to  
416 pay £20,000/QALY and 5.1% for willingness to pay £30,000/QALY.

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418 **Table 1. Baseline characteristics**

	<b>MS (n = 118)</b>	<b>FS (n = 104)</b>
<b>Age (years) - Mean (SD)</b>	71.3 (12.3)	72.1 (10.9)
<b>BMI (kg/m<sup>2</sup>) – Mean (SD)</b>	26.6 (3.2)	27.7 (3.7)
<b>Sex - frequency (%)</b>		
Female	53 (45%)	57 (55%)
Male	65 (55%)	47 (45%)
<b>Valve type - frequency (%)</b>		
Mechanical	15 (13%)	14 (13%)
Tissue	103 (87%)	90 (87%)
<b>EuroSCORE (%) - Mean (SD)</b>	5.9 (2.1) *	6.1 (2.1)

419 \* EuroSCORE was missing for one MS patient.

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423 **Table 2. Kaplan-Meier medians (quartiles) for time-to-event endpoints**

	<b>MS (n = 118)</b>	<b>FS (n = 104)</b>	<b>p-value*</b>
<b>Time to discharge (days)</b>	7 (6, 10)	7 (6, 10)	0.6924
Censored	3	1	
<b>Time until fit for discharge (days)</b>	6 (5, 10)	6 (5, 9)	0.5597
Censored	10	7	
<b>Time to independent mobilisation (days)</b>	4 (3, 7)	4 (3, 6)	0.5819
Censored	8	7	
<b>Time to mediastinal drain removal (hours)</b>	26.1 (20.6, 53.3)	22.5 (19.4, 37.8)	0.0157
Censored	2	2	
<b>Time to extubation (hours)</b>	9.2 (7.8, 12.1)	8.3 (6.8, 11.7)	0.5488
Censored	1	1	
<b>Theatre time (minutes)</b>	191 (172, 225)	176 (152, 203)	< 0.0001
Censored	0	0	
<b>CPB time (minutes)</b>	80 (70, 95)	66 (52, 85)	< 0.0001
Censored	0	0	
<b>Cross-clamp time (minutes)</b>	65 (53, 76)	49 (39, 64)	< 0.0001
Censored	0	0	
<b>Surgery duration (minutes)</b>	163 (139, 190)	149 (114, 167)	< 0.0001
Censored	3	4	

424 \*Log-rank test. Seven surgery durations were not recorded and censored at 1 minute.

426 **Table 3. Costs, QALYs and Cost-effectiveness**

Cost and QALYs (with imputation)		FS (n = 118)		MS (n = 104)	
		Mean Cost per patient	SD	Mean Cost per patient	SD
Primary Admission	Theatre use	£3,824	£1,243	£4,422	£2,053
Costs	Additional surgical items	£16.52	£0.0	£52.0	£0.0
	Critical care (ITU)	£1,834	£3,023	£2,934	£5,030
	Cardiac ward	£2,744	£1,664	£2,676	£1,500
	Physio- and Occupational Therapy	£77	£55	£78	£68
	Rehabilitation	£384	£1,878	£263	£1,621
	Acute hospital	£347	£1,919	£298	£1,971
	<i>Sub-total cost</i>		<i>£9,226</i>	<i>£6,511</i>	<i>£10,724</i>
Post primary admission costs to 12 months	Hospital Re-admission	£418	£1,475	£575	£1,863
	Follow up tests	£224	£258	£282	£279
	Follow up healthcare visits	£373	£359	£311	£263
<i>Sub-total cost</i>		<i>£1,015</i>	<i>£1,778</i>	<i>£1,168</i>	<i>£2,079</i>
	Drugs	£379	£548	£441	£977
<i>Total cost over 12 months</i>		<i>£10,620</i>	<i>£7,624</i>	<i>£12,333</i>	<i>£9,864</i>
Incremental cost-effectiveness* (probabilistic analysis with baseline)	Incremental cost at 12 months (MS-FS)		£2,154.0 (SE £36)		
	Incremental EQ-5D-3L QALYs (MS-FS)		-0.0122 (SE 0.0008)		
	ICER		MS dominated by FS		
	NMB (at WTP £20,000/QALY)		-£2,397		
NMB (at WTP £30,000/QALY)		-£2,519			



adjustment)

SD: standard deviation, SE: standard error, WTP: willingness to pay, NMB: net monetary benefit, ICER: incremental cost-effectiveness ratio. \* Incremental costs and effects estimated using SUR, adjusting for baseline differences.

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