Mini-Stern Trial: A randomized trial comparing mini-sternotomy to full median sternotomy for aortic valve replacement

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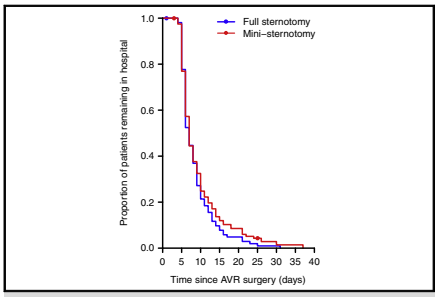
ABSTRACT

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

Methods: This pragmatic, open-label, parallel randomized controlled trial (RCT) compared MS with FS for first-time isolated AVR in 2 United Kingdom National Health Service hospitals. Primary endpoints were duration of postoperative hospital stay and the time to fitness for discharge from hospital after AVR, analyzed in the intent-to-treat population.

Results: In this RCT, 222 patients were recruited and randomized (n = 118 in the MS group; n = 104 in the FS group). Compared with the FS group, the MS group had a longer hospital length of stay (mean, 9.5 days vs 8.6 days) and took longer to achieve fitness for discharge home (mean, 8.5 days vs 7.5 days). Adjusting for valve type, sex, and surgeon, hazard ratios (HRs) from Cox models did not show a statistically significant effect of MS (relative to FS) on either hospital stay (HR, 0.874; 95% confidence interval [CI], 0.668-1.143; P = .3246) or time to fitness for discharge (HR, 0.907; 95% CI, 0.688-1.197; P value = .4914). During a mean follow-up of 760 days (745 days for the MS group and 777 days for the FS group), 12 patients (10%) in the MS group and 7 patients (7%) in the FS group died (HR, 1.871; 95% CI, 0.723-4.844; P = .1966). Average extra cost for MS was £1714 during the first 12 months after AVR.

Conclusions: Compared with FS for AVR, MS did not result in shorter hospital stay, faster recovery, or improved survival and was not cost-effective. The MS approach is not superior to FS for performing AVR. (J Thorac Cardiovasc Surg 2018;156:2124-32)



Duration of hospital stay after aortic valve replacement: full median sternotomy versus mini-sternotomy.

Central Message

In the United Kingdom's National Health Service, compared with a conventional median sternotomy approach for surgical aortic valve replacement, mini-sternotomy did not hasten recovery or hospital discharge and was not cost-effective.

Perspective

Minimal access surgery is appealing for its perceived advantages, including better patient recovery, satisfaction, and cost-effectiveness. This randomized controlled trial conducted within the United Kingdom's National Health Service setting did not demonstrate quicker patient recovery or cost-effectiveness associated with mini-sternotomy compared with a full median sternotomy approach. These findings are relevant to physicians, patients, and health care funders.

See Editorial Commentary page 2133.

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Abbreviations and Acronyms

AVR = aortic valve replacement
CI = confidence interval
CPB = cardiopulmonary bypass
FS = full median sternotomy
HR = hazard ratio
HRQoL = health-related quality of life
mAVR = minimal access aortic valve replacement
MS = mini-sternotomy
NHS = National Health Service
OR = odds ratio
QALY = quality-adjusted life-year
RCT = randomized controlled trial
SAE = serious adverse event
SF-36 = Short Form Health Survey
TOE = transoesophageal echocardiography

Scanning this QR code will take you to the supplemental video, figures, tables, and appendix for the article.

Aortic valve replacement (AVR) is the second most frequent cardiac surgery in the United Kingdom,[1] which has an ever-increasing proportion of older patients.[1,2] Minimal access AVR (mAVR) might shorten the hospital stay and the postoperative recovery period and could be beneficial if offered safely and cost-effectively.

Currently, most AVRs are performed safely through full median sternotomy (FS).[2-6] However, mAVR may be associated with less postoperative pain and blood loss, fewer pulmonary and wound complications, and a shorter hospital stay.[2] The most common mAVR technique involves a mini-sternotomy (MS), which could potentially hasten postoperative recovery, shorten hospital stay and improve patient satisfaction.[2-10]

Most previous studies comparing MS and FS for AVR were nonrandomized. Although systematic reviews with meta-analyses[11,12] have been conducted, inadequate statistical power and heterogeneity of studies calls for prospective, randomized controlled trials (RCTs) to assess the benefits and risks of mAVR. Published evidence on cost-effectiveness comparing MS and FS is sparse and weak. A recent review comparing the cost-effectiveness of FS and MS called for a well-designed RCT to evaluate the cost-effectiveness of mAVR up to at least 1 year after surgery.[13] A recent propensity-matched study from United Kingdom national data concluded that mAVR is safe and associated with shorter postoperative hospital stay.[14] The authors concluded that although general clinical equipoise exists between FS and MS, a well-constructed and adequately powered RCT is essential before widespread adoption of MS. That retrospective study did not analyze the cost-effectiveness of either surgical approach, however.

The Mini-Stern trial assessed whether MS is superior to FS in shortening postoperative recovery time and improving patient outcomes without compromising patient safety. It also assessed the cost-effectiveness of MS from the perspective of the United Kingdom's National Health Service (NHS) as a health care provider.

MATERIALS AND METHODS

Mini-Stern was a 2-center, pragmatic, open-label RCT conducted in the United Kingdom. Patients were randomized (1:1) to AVR by either MS or FS.

Sample Size

In 4 published RCTs[5,6,9,10] and 2 cohort studies,[7,8] a 20% reduction in median length of hospital stay from 11.7 to 9.36 days was considered clinically significant. Based on an internal audit of 252 first-time elective AVRs performed at Papworth Hospital in 2007 to 2008 (mean hospital length of stay, 11.7 [6.2] days), to detect this change with 80% power and 2-sided significance of 5%, 110 patients per group were required. Because randomization was performed on the day of surgery after induction of anesthesia and introduction of the transesophageal echocardiography (TOE) probe, no subjects dropped out between randomization and surgery, thereby achieving the total trial recruitment target of 220 patients.

Recruitment

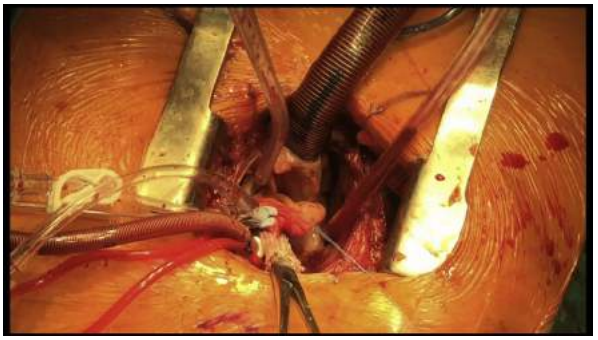
Adult patients undergoing first-time isolated AVR were included. Exclusion criteria included emergency AVR, left ventricular ejection fraction $\leq$30%, chest wall deformities, severe chronic obstructive pulmonary disease (forced expiratory volume in 1 second or transfer factor of the lung for carbon monoxide <40% of predicted), body mass index >35 kg/m^2, concomitant cardiac surgery, redo surgery, and inability to perform TOE. Details of patient enrolment are given in the online protocol.

Randomization

Randomization (1:1) used random permuted blocks of variable lengths (6 or 8), stratified by surgeon and valve prosthesis (bioprosthetic or mechanical). Random allocations were pregenerated, held in secure files by the Papworth Trials Unit. During early days of the trial, TOE probe could not be passed in 4 patients due to technical reasons. These patients underwent the allocated procedure and were included in the trial. Subsequently, the Trial Steering Committee determined that under such circumstances, MS would be unsafe, and patients should be excluded from the trial to FS. Because eligibility for MS required TOE, to avoid postrandomization dropout, group allocation for the study subjects was retrieved via telephone by theatre staff soon after induction of anesthesia and introduction of the TOE probe. Owing to the nature of the interventions, this trial could not be blinded.

Outcomes

Primary endpoints. Two closely related primary endpoints were measured: (1) length of postoperative hospital stay (ie, days between surgery and actual hospital discharge) which is easily measured, a surrogate for early postoperative events and sensitive to outcomes that



VIDEO 1. Mini-sternotomy approach for aortic valve replacement. Video available at: https://www.jtcvs.org/article/S0022-5223(18)31482-X/fulltext.

affect health-related quality of life (HRQoL); and (2) the interval between surgery and the patient being medically fit for discharge (in days). To reduce investigator bias, standard discharge criteria were followed to determine the day of fitness for discharge. This endpoint was chosen to address exogenous effects (eg, social factors, lack of transport, nonavailability of space in nursing homes) that commonly delay hospital discharge in the United Kingdom.

Secondary endpoints. Clinical secondary endpoints included duration of surgery, total theatre time, aortic cross-clamp and cardiopulmonary bypass (CPB) times, blood loss in the first 12 hours after surgery, transfusion of blood and clotting products in the first 48 hours (the blood transfusion trigger was a hemoglobin level <80 g/L), frequency of reintubation, time to initial extubation, mediastinal drain removal and first independent mobilization, daily pain scores at rest and on deep breathing (over the first 10 days or until hospital discharge) on a scale of 0 to 10, left ventricular ejection fraction, severity of paraprosthetic regurgitation at hospital discharge and at 6 months, and time to all-cause death. Definitions of adverse events and details of their reporting are provided in the online protocol. To exclude bias, clinical outcome data were collected by a research team not involved in routine care of the subjects, following standardized protocols.

Nonclinical secondary endpoints included HRQoL and health care resource use.

HRQoL. Patients completed the EQ-5D-3L[15] and Short Form Health Survey (SF-36)[16,17] questionnaires at baseline and at 6 weeks, 6 months, and 12 months postsurgery. The EQ-5D-3L was repeated on the fourth postoperative day and at discharge.

Health care resource use. Patient-specific resource use data collected from hospital records and patient interviews during the primary admission included phases of care (operative surgery, critical care, and post-surgical ward care) and medication administration. Postdischarge resource use included attending wound clinics, community nurse visits, physiotherapy sessions, occupational therapy services, medical tests, cost of analgesics and other drugs, and further hospitalization within the first year after AVR.

Surgical Details

All participating surgeons were consultants experienced in performing AVR by both FS and MS. They followed the operative surgical protocol as described below. Video 1 shows the MS approach and is available in the online version of this article.

MS approach. With the patient anesthetized in accordance with standard protocol, skin was incised from halfway between the suprasternal notch and the sternal angle to the level of the fourth intercostal space, approximately 8 cm. The manubrium was divided in the midline from the suprasternal notch inferiorly and then into the right fourth intercostal space. The thymus was divided and the pericardium was opened, exposing the ascending aorta, aortic root, and right atrial appendage. A 300 U/kg loading dose of unfractionated heparin followed by boluses of 5000 U was administered to achieve activated clotting time >450 seconds. The aorta was cannulated using a wired flexible aortic cannula. The right atrial appendage was cannulated using a flat venous cannula, and CPB was initiated. The ascending aorta was cross-clamped and intermittent, antegrade, cold blood cardioplegia administered. The aorta was then incised open in an oblique or transverse fashion, the diseased valve was excised, and the annulus was decalcified. A suitably sized aortic valve prosthesis was inserted using either horizontal mattress 2-0 Ethibond sutures or semi-continuous 2-0 Prolene sutures. Surgeons adopted either of these suture techniques and adhered to the same technique irrespective of the type of valve prosthesis or the surgical approach. The aortotomy was then closed, the heart was deaired, right atrial and ventricular epicardial pacing wires were inserted, and the patient was weaned off CPB. Once satisfactory functioning of the aortic valve prosthesis was confirmed by TOE, heparin was reversed with protamine (1 mg/100 U of heparin). Chest drains were inserted into the anterior mediastinum, posterior pericardial space, and pleural space as necessary. Sternal wires were inserted, and the incision was closed in layers. Conversion to FS was performed to ensure patient safety if access proved difficult or if intraoperative complications occurred.

FS approach. Anesthesia and positioning of patients was the same as for the MS approach. The skin incision was made between the suprasternal notch and the xiphoid process and sternum divided in the midline from the suprasternal notch to the xiphoid process. A 2-stage venous cannula was used for atrial cannulation. The remaining steps were similar to those for the MS approach.

Statistical Analysis

Analyses of primary and secondary endpoints used intention-to-treat and included all randomized patients. Unless stated otherwise, statistical models included treatment (MS vs FS), valve (mechanical vs bioprosthetic), and sex as fixed effects and surgeons as random effects. Hypothesis testing was 2-sided at a 5% significance level, with no adjustments for multiple testing. All confidence intervals (CIs) were estimated at the 95% confidence level.

Distributions of time-to-event endpoints were compared between study groups using Kaplan–Meier curves and log-rank tests (stratified by sex, valve, and surgeon). Hazard ratios (HRs) for MS relative to FS were estimated from a Cox model. The null hypothesis of no treatment effect (HR = 1) was tested. Patients who were lost to follow-up, withdrew, or died before the event were censored at the latest time they were known to be event-free. Models were checked by plotting Schoenfeld and deviance residuals. For primary endpoints, Cox models were refitted using the per-protocol population and used in sensitivity analyses (Appendix E1, Table E4).

The need for reintubation and other dichotomous endpoints were compared between groups by estimating an MS/FS odds ratio (OR) via logistic regression. EQ-5D, SF-36, and pain scores were modeled using repeated-measures linear regression. When possible, random intercepts and random time coefficients for patients were included. For EQ-5D and SF-36, fixed effects for baseline scores were included. Models were fitted using complete cases, then refitted with multiple imputation of missing scores via chained equations.

Serious adverse events (SAEs) were analyzed in the safety population according to intervention received. Patients randomized to MS who crossed over to FS before surgery were considered to have received FS; those who crossed over after the initiation of MS were considered to have received MS. Rates of SAEs were explored using Poisson regression with a random patient effect.

CONSORT guidelines (Online Data Supplement and Figure E1)[18] were followed. Analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC). No interim analyses were conducted, but reports were presented annually to the Data Monitoring and Ethics Committee.

TABLE 1. Baseline characteristics

Characteristic	MS (n = 118)	FS (n = 104)
Age, y, mean (SD)	71.3 (12.3)	72.1 (10.9)
Body mass index, kg/m^2, mean (SD)	26.6 (3.2)	27.7 (3.7)
Sex, n (%)		
Female	53 (45)	57 (55)
Male	65 (55)	47 (45)
Valve type, %		
Mechanical	15 (13)	14 (13)
Tissue	103 (87)	90 (87)
EuroSCORE, %, mean (SD)	5.9 (2.1)*	6.1 (2.1)

MS, Mini-sternotomy; *FS*, full median sternotomy; *SD*, standard deviation. *EuroSCORE was missing for 1 patient in the MS group.

Economic Analysis

Unit costs were obtained from nationally published sources in the United Kingdom[19-22] or from the Finance Department of Papworth Hospital when the former did not provide the required information. The total cost per patient was calculated by summing resource use items multiplied by unit costs across the in-patient stay and the 12-month postoperative follow-up period (Appendix E1, Table E22). Health state utilities from the EQ-5D-3L and SF-36, based on United Kingdom value sets,[15,23] were used to generate quality-adjusted life years (QALYs) using the area under the curve method and assigning a value of 0 from the date of death. Missing values were imputed using chained predictive mean matching, stratified by treatment and conditional on age, sex, and baseline EQ-5D-3L data.

Differences in mean costs and QALYs were estimated using seemingly unrelated regression, controlling for age, sex, valve type, baseline EQ-5D-3L, and treatment to accommodate skewness.[24] Uncertainty in cost-effectiveness was estimated by drawing 1000 bootstrapped samples and conducting a probabilistic sensitivity analysis. Results are presented as incremental net monetary benefit at various thresholds of willingness to pay per QALY, cost-effectiveness planes, and cost-effectiveness acceptability curves. Deterministic sensitivity analyses explored the effects of using complete cases only, SF6D-based QALY estimates, and the procedure inpatient admission only and excluding patients who died and additional equipment costs (Appendix E1, Table E26).

RESULTS

A total of 1024 patients were screened between January 28, 2010, and April 13, 2015, of whom 222 were recruited and randomized to the MS (n = 118) or FS (n = 104) group. The 1-year follow-up was completed on May 23, 2016.

Study groups were similar at baseline except for a nonsignificant sex imbalance (Table 1). In this trial, MS was not completed in 14 of 118 patients randomized to MS (12%). Of these patients, 6 (5%) had a conversion from MS to FS owing to reasons listed in Figure 1. The remaining 8 patients underwent FS after randomization to MS but without an initial MS incision, because MS was considered unsafe or impractical. Thus, the true rate of intraoperative conversion of MS to FS was 5%. Four patients (2%) were censored before discharge, 1 patient who withdrew before surgery (FS group) and 3 patients who died (all randomized to and received MS) (Table 2). Another 13 patients (6%) were censored before fitness for discharge, including 6 discharged to an acute hospital (3 in each group) and 7 discharged to long-term care or rehabilitation (3 in the FS group and 4 in the MS group).

The mean time to hospital discharge was longer in the MS group than in the FS group (9.5 days vs 8.6 days), as was mean time to fitness for discharge (8.5 days vs 7.5 days). The distributions of these endpoints were similar in the 2 groups, however (Figure 2 and Table 2). The difference was not statistically significant in primary analyses using Cox models (Figure 3), log-rank tests (Table 2), or sensitivity analyses (Table E4). The gamma-distributed frailty term in the Cox models was estimated to have a variance of 0.006675 for time to fitness and of 0.000100 for time to discharge, suggesting that surgeon heterogeneity was negligible.

The time to drain removal (including drains inserted/retained to treat complications) was longer for the MS group, but times to extubation and independent mobilization did not differ significantly between the groups (Table 2 and Figure 3), nor did the number of patients reintubated (6 in the MS group vs 5 in the FS group; OR, 1.039; 95% CI, 0.306-3.531; $P = .9512$). Statistically significant HRs indicated longer duration of operative, CPB, cross-clamp, and theatre times for the MS group (Figure 3). No significant between-group differences were seen in blood loss (Table E3) or in the number of patients requiring transfusion of blood (50 in the MS group vs 51 in the FS group; OR, 0.797; 95% CI, 0.453-1.402; $P = .4310$) or clotting products (11 in the MS group vs 4 in the FS group; OR, 2.616; 95% CI, 0.801-8.541; $P = .1112$).

Regression models for pain at rest, EQ-5D utilities, and SF-36 domain scores (Tables E6-E8) estimated greater rates of improvement over time in MS patients for 3 SF-36 domains (social functioning, vitality, and role physical). After multiple imputation, the difference was only significant for the role physical domain (Table E9). Pain on deep breathing was not analyzed, because only less than one-half of the data were collected owing to poor patient compliance.

Nine patients (4%) died within 1 year of surgery, including 7 (6%) in the MS group and 2 (2%) in the FS group. Five deaths were possibly related to treatment (4 in the MS group and 1 in the FS group), and none was likely or definitely related (Table E15). Overall, 12 patients (10%) in the MS group and 7 patients (7%) in the FS group died during follow-up (mean follow-up, 760 days; 745 days in the MS group and 777 days in the FS group). Time to all-cause death, adjusted for age, showed a moderately large but statistically nonsignificant HR (MS/FS) of 1.871 (95% CI, 0.723-4.844; $P = .1966$).

Safety analyses excluded 1 patient who was withdrawn before surgery. There were significantly more SAEs in the MS recipients (rate ratio, 1.615; 95% CI, 1.070-2.437;

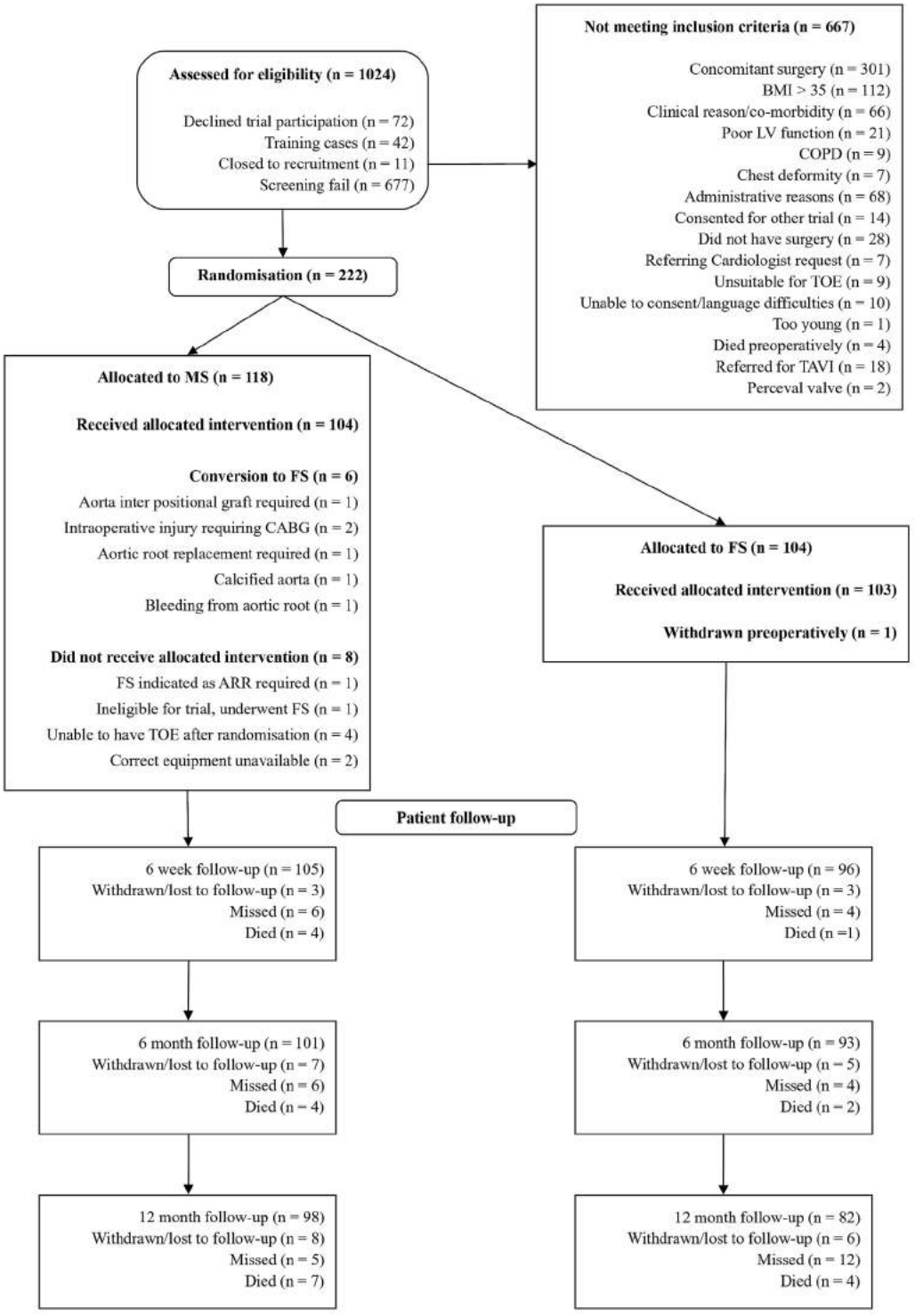


FIGURE 1. Trial flow diagram. *BMI*, Body mass index; *LV*, left ventricular; *COPD*, chronic obstructive pulmonary/airway disease; *TOE*, transesophageal echocardiography; *TAVI*, transcutaneous aortic valve implantation; *MS*, mini-sternotomy; *FS*, full median sternotomy; *CABG*, coronary artery bypass grafting; *ARR*, aortic root replacement.

$P = .0225$) (Table E11). The number of patients experiencing SAEs did not differ significantly between the 2 groups (OR, 1.559; 95% CI, 0.895-2.715; $P = .1161$). The incidence of paraprosthetic regurgitation did not differ significantly between the 2 groups (Table E13). Seven patients developed pericardial collection (3 in the MS group and 4 in the FS group; OR, 0.680; 95% CI, 0.146-3.178; $P = .6229$). Wound infections

TABLE 2. Kaplan–Meier medians (quartiles) for time-to-event endpoints

Endpoint	MS (n = 118)	FS (n = 104)	*P* value*
Time to discharge (d)	7 (6-10)	7 (6-10)	.6924
Censored	3	1	
Time until fit for discharge (d)	6 (5-10)	6 (5-9)	.5597
Censored	10	7	
Time to independent mobilization (d)	4 (3-7)	4 (3-6)	.5819
Censored	8	7	
Time to mediastinal drain removal (h)	26.1 (20.6-53.3)	22.5 (19.4-37.8)	.0157
Censored	2	2	
Time to extubation (h)	9.2 (7.8-12.1)	8.3 (6.8-11.7)	.5488
Censored	1	1	
Theatre time (min)	191 (172-225)	176 (152-203)	<.0001
Censored	0	0	
CPB time (min)	80 (70-95)	66 (52-85)	<.0001
Censored	0	0	
Cross-clamp time (min)	65 (53-76)	49 (39-64)	<.0001
Censored	0	0	
Surgery duration (min)	163 (139-190)	149 (114-167)	<.0001
Censored	3	4	

MS, Mini-sternotomy; *FS*, full median sternotomy; *CPB*, cardiopulmonary bypass. *Log-rank test. Seven surgery durations were not recorded and censored at 1 minute.

(including superficial and deep infections) were more common in the FS group (13 vs 4 in the MS group; OR, 0.312; 95% CI, 0.097-1.005; $P = .0511$). Deep sternal wound infection developed in 1 MS recipient and 1 FS recipient, neither of whom required plastic surgical repair.

Economic analyses are summarized in Table 3 and the cost-effectiveness planes depicting cost-effectiveness between MS and FS are shown in Figure 4. There was additional cost for MS relative to FS (£1714 per patient; $P = .0765$) in the first year following surgery. Patients in

TABLE 3. Costs, QALYs, and cost-effectiveness

Cost and QALYs (with imputation)	Cost per patient, £, mean (SD)	
	FS (n = 118)	MS (n = 104)
Primary admission costs		
Theatre use	3824 (1243)	4422 (2053)
Additional surgical items	16.52 (0.0)	52.0 (0.0)
Critical care (ITU)	1834 (3023)	2934 (5030)
Cardiac ward	2744 (1664)	2676 (1500)
Physical and occupational therapy	77 (55)	78 (68)
Rehabilitation	384 (1878)	263 (1621)
Acute hospital	347 (1919)	298 (1971)
Subtotal cost	9226 (6511)	10,724 (8850)
Post primary admission costs to 12 mo		
Hospital readmission	418 (1475)	575 (1863)
Follow-up tests	224 (258)	282 (279)
Follow-up health care visits	373 (359)	311 (263)
Subtotal cost	1015 (1778)	1168 (2079)
Drugs	379 (548)	441 (977)
Total cost over 12 mo	10,620 (7624)	12,333 (9864)
Incremental cost-effectiveness (probabilistic analysis with baseline adjustment)*		
Incremental cost at 12 mo (MS-FS)		2154.0 (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)		−£2397
NMB (at WTP £30,000/QALY)		−£2519

QALY, Quality-adjusted life-year; *SD*, standard deviation; *FS*, full median sternotomy; *MS*, mini-sternotomy; *ITU*, intensive therapy unit; *SE*, standard error; *ICER*, incremental cost-effectiveness ratio; *NMB*, net monetary benefit; *WTP*, willingness to pay. *Incremental costs and effects estimated using SUR, adjusting for baseline differences.

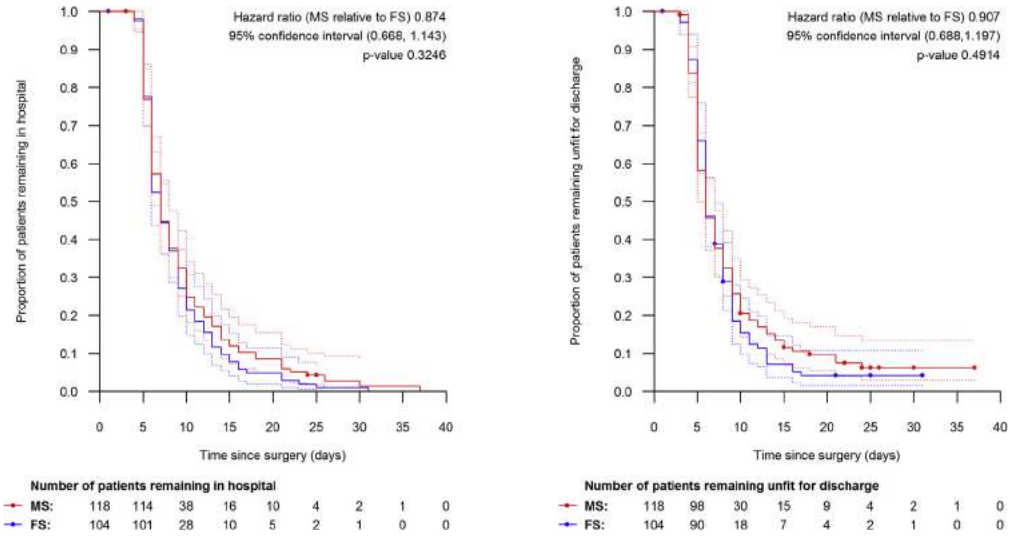


FIGURE 2. Kaplan–Meier curves for primary endpoints. Points indicate censoring, and *dashed lines* represent 95% confidence intervals. *MS*, Mini-sternotomy; *FS*, full median sternotomy.

the MS group had (nonsignificant) better EQ-5D–based QALYs (0.03 per patient; $P = .1509$). The incremental cost per QALY gained was £61,379, but after adjusting for baseline characteristics, MS had higher costs and lower QALYs (ie, was dominated). In deterministic and probabilistic sensitivity analyses, MS was either dominated or had a very large cost per QALY, except for the complete case analysis (Tables E11 and E12).

DISCUSSION

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

In this prospective, pragmatic, open-label RCT, MS did not reduce the total duration of hospital stay after AVR. Because hospital discharge is sometimes delayed due to social factors, we included the time to fitness for discharge as a second primary endpoint. This was also not reduced by MS. These endpoints were recorded by physiotherapists based on a common discharge protocol with specific clinical milestones to achieve, thereby excluding physician-induced bias.

In this study, operation, total theatre, aortic cross-clamp, and CPB times were significantly prolonged with MS. This

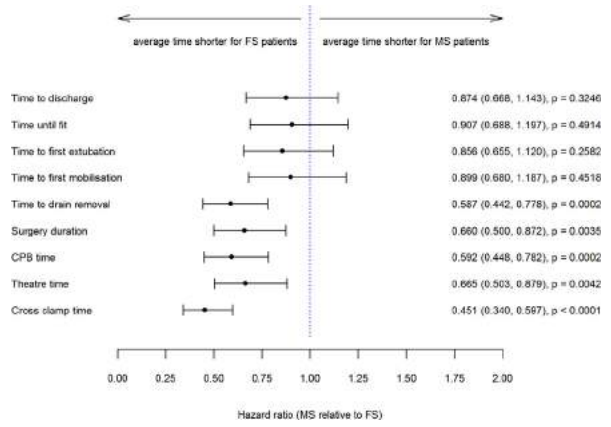


FIGURE 3. Forest plot of hazard ratios and 95% confidence intervals from Cox models. *FS*, Full median sternotomy; *MS*, mini-sternotomy; *CPB*, cardiopulmonary bypass.

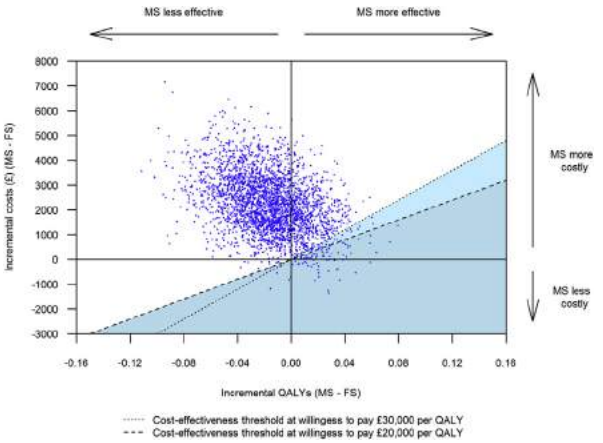


FIGURE 4. Cost-effectiveness planes. The proportion of points below each threshold gives the probability that MS is more cost-effective than FS. This probability is 3.7% for willingness to pay £20,000 per QALY and 5.1% for willingness to pay £30,000 per QALY. *MS*, Mini-sternotomy; *FS*, full median sternotomy; *QALY*, quality-adjusted life-year.

was expected, because in general, minimal access valve operations take longer.[5,9] This would be justifiable if MS was associated with faster recovery, shorter postoperative stay, reduced cost of treatment, or, most importantly, a significant reduction in adverse events and hence superior patient safety. In this RCT, MS did not achieve these benefits, and thus we feel that the prolonged operation, total theatre, cross-clamp, and CPB times do not justify performing AVR through MS.

Two previous meta-analyses[11,12] concluded that mAVR approaches are superior in certain aspects of postoperative recovery. However, both included studies on a mini-thoracotomy approach for AVR, and thus any inferences drawn cannot be extrapolated to MS. A retrospective propensity-matched analysis of data from a United Kingdom national database concluded that MS is safe and comparable to conventional AVR.[14] The authors found that MS resulted in a shorter postoperative hospital stay, in disagreement with our findings. However, a propensity-matched study can suffer from selection bias if its matching algorithm produces treatment groups that are unbalanced in some unobserved characteristics. A recent retrospective study demonstrated the safety of right thoracotomy minimally invasive isolated and concomitant AVR in patients of all age groups.[25] Because randomization balances study groups in known and unknown characteristics, results of the Mini-Stern trial should be more reliable than the findings of nonrandomized studies.

Previous studies investigating cost-effectiveness provided unclear conclusions. A report analyzing registry data from patients who underwent isolated primary AVR[26] reported lower hospital costs with AVR performed through a right anterior thoracotomy compared with sternotomy-based approaches, with no significant differences in outcomes. The main reasons for the lower costs were earlier hospital discharge and reduced use of blood products. Ghanta et al[27] noted that exclusion of rehabilitation costs could alter this finding. A review by Glauber et al,[13] based on uncontrolled studies, noted that the higher cost of instruments and devices in mAVR could be offset by economic advantage gained by shorter hospital stays and lower complication rates. The Mini-Stern trial assessed cost-effectiveness using a range of sensitivity analyses, but only the complete case analysis showed MS to be cost-effective, suggesting lower costs but slightly worse outcomes with MS. However, this analysis used a potentially unrepresentative sample of just 90 patients, and was restricted to the first year following operation, with no long-term analysis beyond 1 year.

This RCT is robust with many merits, including on-table randomization, comprehensive and independent outcome assessment without physician bias, longer-term clinical assessment, HRQoL analysis, and economic analysis. There are some limitations, however. Although we report on secondary endpoints, this trial was powered to address only the primary endpoint. A total of 14 patients (12%) allocated to MS received FS, another possible limitation. However, only 6 patients (5%) had true conversion after an attempted MS, whereas 8 patients (6.7%) went on to FS for safety reasons. Although this RCT was conducted in only 2 centers, thereby limiting generalizability, recruitment by 8 surgeons improved the generalizability. A total of 1024 patients were screened to recruit 222 patients (21.7%). Although this suggests potential selection bias, only 125 eligible patients (12.2%) failed recruitment, whereas the remaining 667 (65.1%) did not meet the inclusion criteria. Blinding was not practical, because sternotomy dressings were usually changed at 48 hours after surgery and patients became aware of the approach, which might have caused bias in self-reported outcomes. Missing "pain at rest" data were unlikely to be missing at random, and thus imputation might not have addressed all potential biases. Despite having 2 primary outcomes, we did not adjust for multiple testing; however, because neither showed a significant between-group difference, this would not have affected our conclusions.

CONCLUSIONS

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

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

We thank Dr Matt Glover, Jacinta Nalpon, and Chelliah Paramasivam for their contributions to this study.

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Key Words: aortic valve replacement, minimal access, health economics

APPENDIX E1. ECONOMIC EVALUATION

This trial collected data on resource and health service use for each patient during their in-patient stay through to the end of follow-up at 1 year. The economic analysis compared the costs and quality of life impacts of full median sternotomy (FS) and mini-sternotomy (MS) and assessed the cost-effectiveness of MS as an alternative to FS.

The Methods section first presents the unit costs, resource use data and the methods used to aggregate resource use and utility data at a patient level.[E1] The methods used to document and impute missing data follow.[E2] The last part describes the construction of incremental cost-effectiveness ratios and representation of uncertainty.

Results are presented first for raw data (with and without imputation) for costs and quality-adjusted life-years (QALYs) separately, followed by estimations of costs and QALYs that account for baseline differences. The final section provides results of probabilistic and deterministic sensitivity analyses.

METHODS

Unit Costs

All resource use data collected formed part of the patient-specific case-report form. Trained research nurses extracted data for inpatient stays from individual patient records. Face-to-face interviews with patients by research nurses provided data for quality of life as well as health service use during follow-up.

Multiplying the unit costs by each unit of resource use and summing these resource costs across each patient's 12-month follow-up from the date of operation enabled aggregation of total cost per patient. Table E16 provides the unit costs used, with source of data. Where possible, national estimates of unit prices were used (eg, Personal Social Services Research Unit,[E3] National Health Service[E4]), to increase generalizability.

All resources were used once by patients (eg, a general practitioner visit or specific test), with the exception of 2 capital items used during surgery; the horizontal saw and defibrillator handles, both acquired for MS. These costs were apportioned, using clinical opinion, to each patient assuming a lifespan of 20 years and that surgeons perform a total of 255 MSs over 5 years.

Patient-Level Aggregation of Cost

This section describes the aggregation of costs, by patient, for the inpatient stay, postdischarge follow-up to 12 months, and drug use.

Hospital stay. The time in the hospital from randomization to discharge was disaggregated into theatre time, critical care unit (CCU), stay and cardiac ward stay (Table E17). The total length of stay comprised the time spent in surgery (measured in minutes), in the CCU (measured in hours), and in the cardiac ward (measured in days). Theatre time included the duration of reoperations where applicable (several patients had up to 2 returns to the theatre), and corresponding CCU stays were added to the CCU hours. The total stay in the hospital, calculated using theatre time, critical care, and ward stay, was compared with a direct calculation of duration using date of operation and date of discharge, to validate the breakdown of patient stay. After discharge from hospital, the majority of patients were discharged to home, but some were referred to an acute hospital or rehabilitation center (short or long term) for more care, and the costs of this additional stay were included.

Postdischarge. Data on resource use after discharge and for up to 12 months postrandomization were collected at 6-week, 6-month, and 12-month follow-up visits, with resource use divided into 3 categories: hospital admissions, tests and health care visits. A total of 28 different health care resources were used and aggregated over the follow-up period. For example, if a patient reported 1 blood test from discharge to the 6-week follow-up, 2 blood tests between the 6-week and 6-month follow-ups, and none after that, resource use was costed as £10.38 (3 × £3.46) postdischarge.

Drugs. Drug use was matched to a corresponding unit cost using the NHS Electronic Drug tariff[E5] and British National Formulary[E6] to sum costs across drug type for each patient. Information on drugs administered during the primary admission was complete, with the total amount of each drug per patient checked against patient prescriptions. However, drug use postdischarge was self-reported, and it was not possible to verify or retrieve any further data on this over the follow-up period.

Health state utilities. These data were collected using EQ-5D-3L and SF-36 questionnaires. EQ-5D-3L responses were converted to utility values using the methods described by Dolan et al.[E7] and to QALYs for the trial period using the area under the curve method. SF-36 data were mapped to SF-6D utility values based on the ScHARR (School of Health and Related Research, University of Sheffield) algorithm and were converted to QALY scores as described by Brazier et al.[E8] A value of 0 was assigned from date of death.

Missing Data

The patterns of missing data for resource use and utilities were tested using Pearson χ^2 goodness-of-fit and Wilcoxon rank-sum tests for being missing at random and completely at random using the following variables: age, sex, treatment, and health status at baseline (EQ-5D). The baseline characteristics assessed were not statistically significantly different between the 2 groups, and multiple imputations were used for economic analysis. Patients were assigned zero cost and zero utility value from point of death.

Hospital stay. For primary admission, there were a few item nonresponses for resource use data but no censored data. Complete information was available on all respondents except for 1 participant who withdrew from the trial after operation.

Postdischarge. The frequency of missing data for resource use after discharge in the 2 groups is provided in Table E18. Imputation models did not converge at month 12, and resource use was aggregated over time; that is, imputation was carried out for the aggregate value for each item rather than at each time period. The proportion of missing values in the aggregated utility data ranged from 11% to 25% in resource use postdischarge (Table E18).

Drugs. Only drugs used from the time of randomization to the 12-month follow-up were accounted for (covering 3078 uses of 118 different drugs). Various assumptions (about quantity/dose and duration of administration) were used to minimize the degree of missing information on the drugs used. For example, when dosage or frequency of dose per day was missing, the mode of use among trial participants or, if not available, the British National Formulary dosage was used. Duration of medicinal use was calculated using start and stop dates for drugs used in primary admission and follow-up. However, when start/stop dates were missing, replies to a ''yes/no'' question on use of drugs at follow-up time points informed duration. For example, if a drug was taken during the inpatient stay and at 6-week, 6-month, and 12-month follow-ups, then the drug was said to be used for the entire 12-month trial period. However, further assumptions about duration of medication were used when data were less forthcoming; for example, drugs taken only at the 12-month follow-up, without a start date or stop date specified, were assumed to have been taken according to

prescription every day for an average of 3 months (based on expert consultation). Fifty-eight records had insufficient information on usage for such personalized manual imputation, necessitating predictive mean matching (conditioned on patient ID and name of drug).

Health state utilities. EQ-5D-3L and SF-6D utility data were imputed at each follow-up as presented in Table E19, and the percentage of missing values ranged from 9% to 23%. Further breakdown of missing data for resource use and health-related quality of life questionnaires, and imputation required for each variable, is provided in Table E19.

Imputation

Missing values were imputed conditional on sex, age, type of replacement valve used, risk classification measured using New York Heart Association functional classification and Canadian Cardiovascular Society grading of angina. To avoid loss in efficiency, missing values for resource use and utility values at different time points were replaced using multiple imputations by chained equations.

Chained predictive mean matching was used to replace missing data for resource use and quality of life variables, and a total of 20 imputed datasets were created, stratified by treatment group. The imputed resource use is summarized in Table E20. However, although probabilistic analysis was conducted using the bootstrap method, multiple imputation was carried out only once for each iteration, with a total of 1000 iterations to adequately retain between-imputation variance. The distribution of imputed values was visually checked for comparability with the observed data.

Adjustment Method

To account for differences in baseline utility values, as well as skewness, censoring, and confounding in cost data, linear regression models were used to provide adjusted estimates of mean values. Control variables used were age, sex, valve, EQ-5D-3L baseline value, and treatment arm. The type of valve used for replacement was also controlled for, because it was used as a stratification factor in the randomization.

Incremental Cost-Effectiveness Analysis and Sensitivity Analyses

Differences in estimated costs and EQ-5D QALYs between trial arms, using raw data with imputation, were tested using a 2-sample *t* test with equal variances. Incremental cost-effectiveness ratios were also constructed using adjusted mean estimates of costs and QALYs using "seemingly unrelated regression," to account for correlation between costs and effects at the patient level. This regression technique relies on the multivariate normality of the group-specific mean costs and QALYs and is valid where the individual costs and QALYs are skewed.[E9]

Probabilistic sensitivity analysis was used to characterize the uncertainty of input parameters, and a bootstrap approach (with 1000 bootstrapped samples) was applied to estimate the precision of results. The probability that MS is cost-effective compared with FS is presented at varying willingness to pay (WTP) threshold values, using a cost-effectiveness acceptability curve and incremental net monetary benefit.

Deterministic sensitivity analyses and scenario analysis were used to explore the robustness of cost-effectiveness results that adopted different methodological approaches or assumptions (Table E21). Baseline characteristics were assessed using the χ^2 and rank-sum tests, to assess whether patients included in the complete-case analysis were different from those outside the complete-case analysis.

RESULTS

The comparison of mean costs per patient up to 1 year, using raw data with imputation, shows that MS cost £1714 more than FS, although this was not statistically significant (Table E22). The higher costs resulted from longer surgery time, additional equipment, and longer time in critical care. EQ-5D QALYs were very slightly higher in the MS arm compared with the FS arm (difference, 0.0279), but this was not statistically significant (Table E23), and there was no statistically significant difference in SF-6D QALYs either. Figures E2 and E3 illustrate the distribution of total costs and QALYs across the patients in the trial.

Table E24 summarizes the comparison of costs and QALYs. The additional cost of gaining an additional QALY using MS rather than FS when imputed using the PMM method is £61,379, and the net monetary loss at a WTP of £20,000 is £1155.

Seemingly unrelated regression analysis of costs and QALYs, adjusted for baseline characteristics, showed that in terms of QALYS, MS was not statistically significantly different from FS. Table E25 also shows that the coefficient for cost was positive, indicating that MS was more costly than FS, and that this difference was statistically significant. Thus, MS is dominated by FS. The cost-effectiveness plane for the analysis is illustrated in Figure E4.

The probabilistic sensitivity analysis shows that at a WTP per QALY of £20,000, there is a 3.7% likelihood that MS is cost-effective compared with FS, and that this likelihood rises to 5.1% at a WTP of £30,000/QALY (Figure E5). The net monetary benefit of MS is negative across all WTP threshold values (Figure E6).

Deterministic sensitivity analyses showed that MS was either dominated or had a huge ICER (Table E26). The one exception to this was the complete-case analysis of cost-effectiveness, which found MS to be cost-effective. The intervention cost less but also had slightly worse outcomes in this sample size, which was limited to only 90 cases. The result indicates a saving of £10,000 for a loss of 1 QALY. The sample was not representative of those with missing data and included a larger proportion of females than the sample outside the complete-case analysis cost-effectiveness sample. The sensitivity analyses conducted using probabilistic sensitivity analysis consistently found FS to be a superior intervention to MS (Table E27). The cost-effectiveness planes for the sensitivity analyses are illustrated in Figure E7.

E-References

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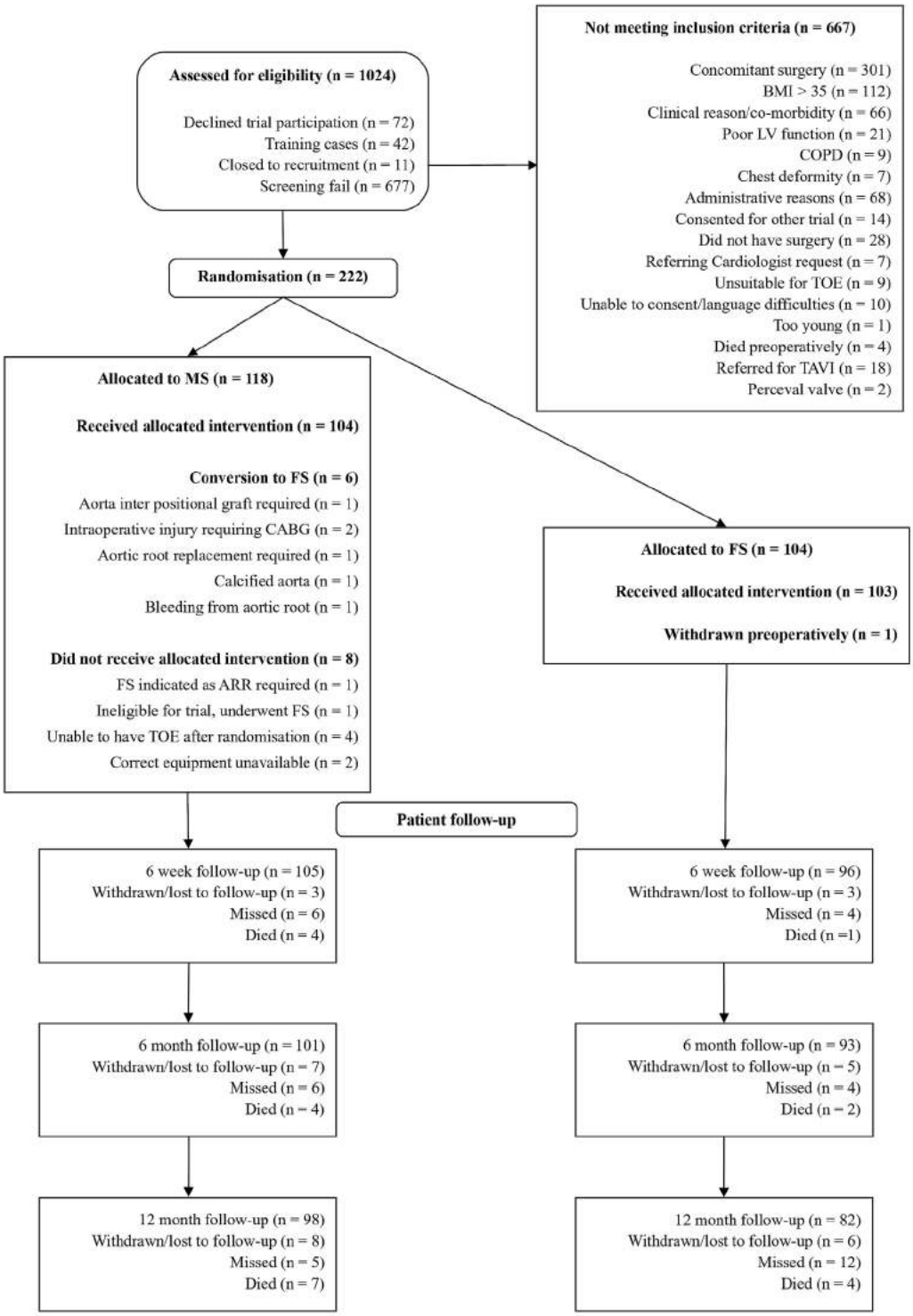

FIGURE E1. MiniStern Trial. CONSORT flow diagram. *BMI*, Body mass index; *LV*, left ventricular; *COPD*, chronic obstructive pulmonary/airway disease; *TOE*, transesophageal echocardiography; *TAVI*, transcutaneous aortic valve implantation; *MS*, mini-sternotomy; *FS*, full median sternotomy; *CABG*, coronary artery bypass grafting; *ARR*, aortic root replacement.

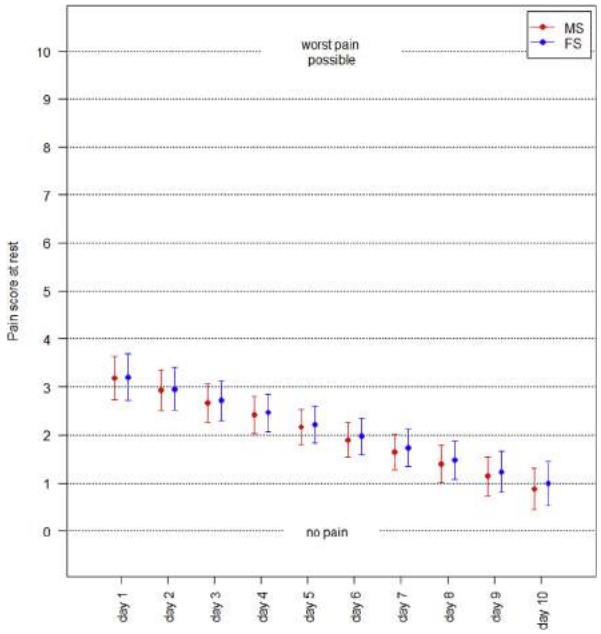

FIGURE E2. Forest plots of mean pain scores for the first 10 days following surgery, with 95% confidence intervals. Means on each day were adjusted for sex and valve type and were estimated from the complete-case analysis. *MS*, Mini-sternotomy; *FS*, full median sternotomy.

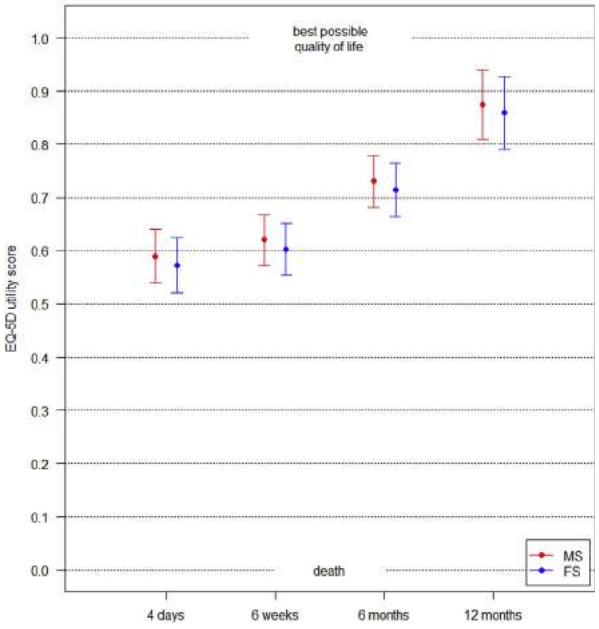

FIGURE E3. Forest plot of mean EQ-5D scores at each follow-up time, with 95% confidence intervals. Means at each follow-up time were adjusted for baseline EQ-5D, sex, and valve type and were estimated from the complete-case analysis. *MS*, Mini-sternotomy; *FS*, full median sternotomy.

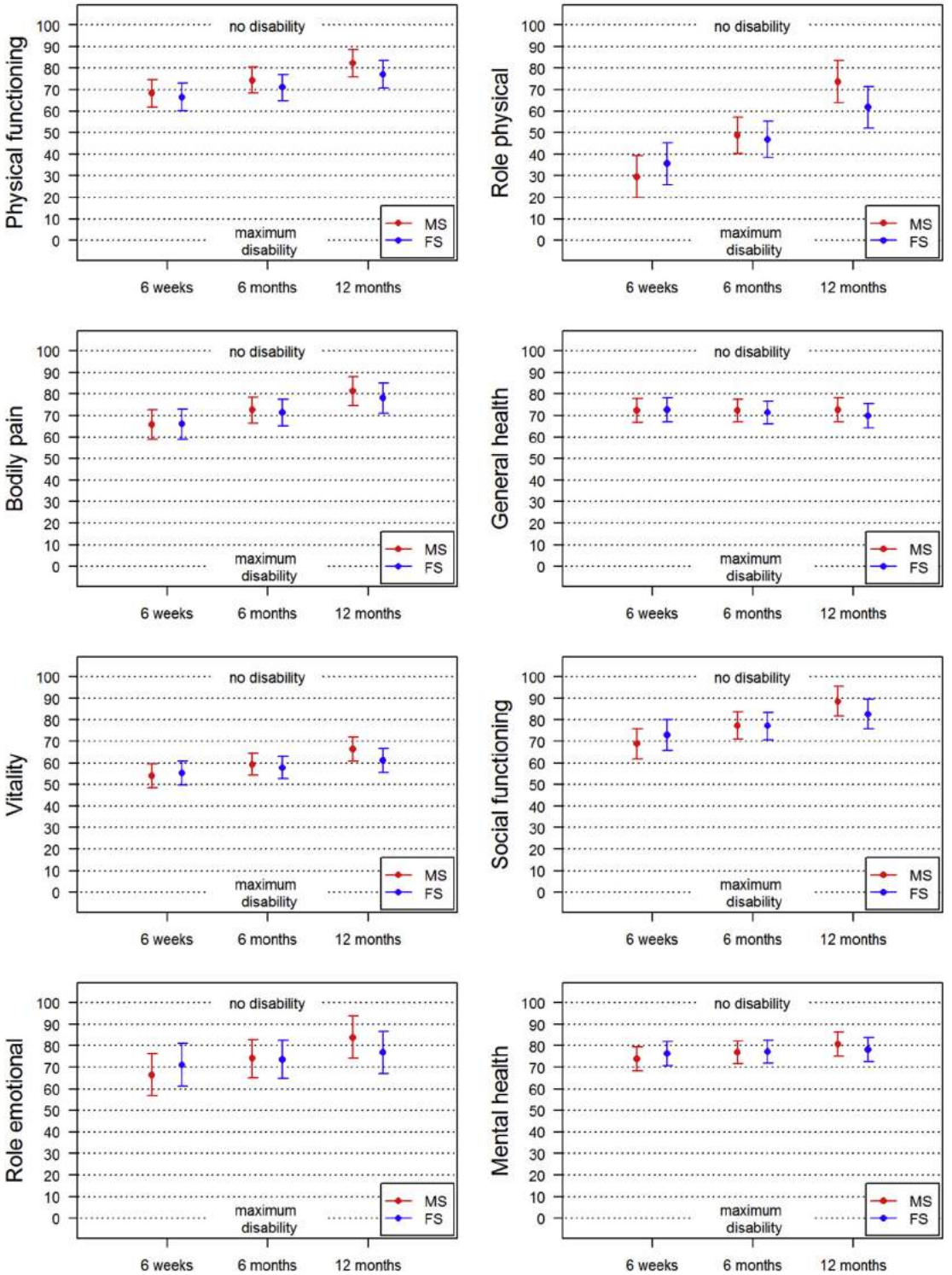

FIGURE E4. Forest plot of mean SF-36 domain scores at each follow-up time, with 95% confidence intervals. Means at each follow-up time were adjusted for baseline domain score, sex, and valve type and were estimated from the complete-case analysis. A score of 100 represents no disability, and a score of 0 represents maximum disability. *MS*, Mini-sternotomy; *FS*, full median sternotomy.

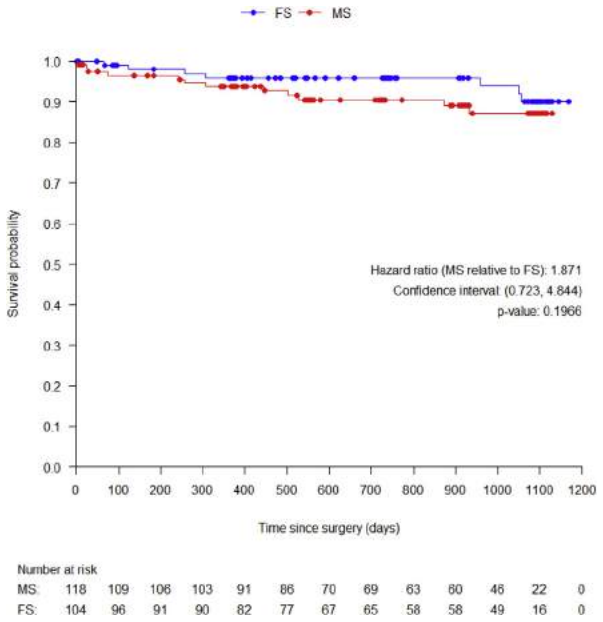

FIGURE E5. Kaplan–Meier curves for time to death by any cause. Patients are grouped by the treatment allocated to them. Patients with no fatal events recorded were censored at the last time known to be alive. Times of censoring are indicated by points on the curves. *MS*, Mini-sternotomy; *FS*, full median sternotomy.

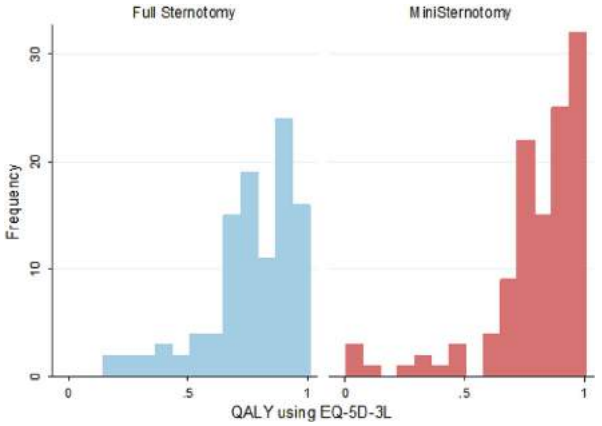

FIGURE E7. Distribution of quality-adjusted life-years. *QALY*, Quality-adjusted life-year.

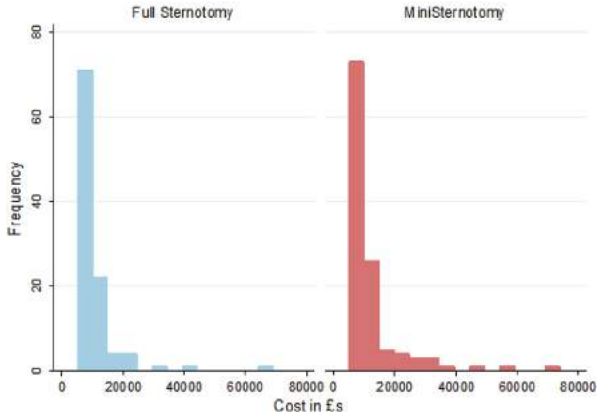

FIGURE E6. Distribution of total cost.

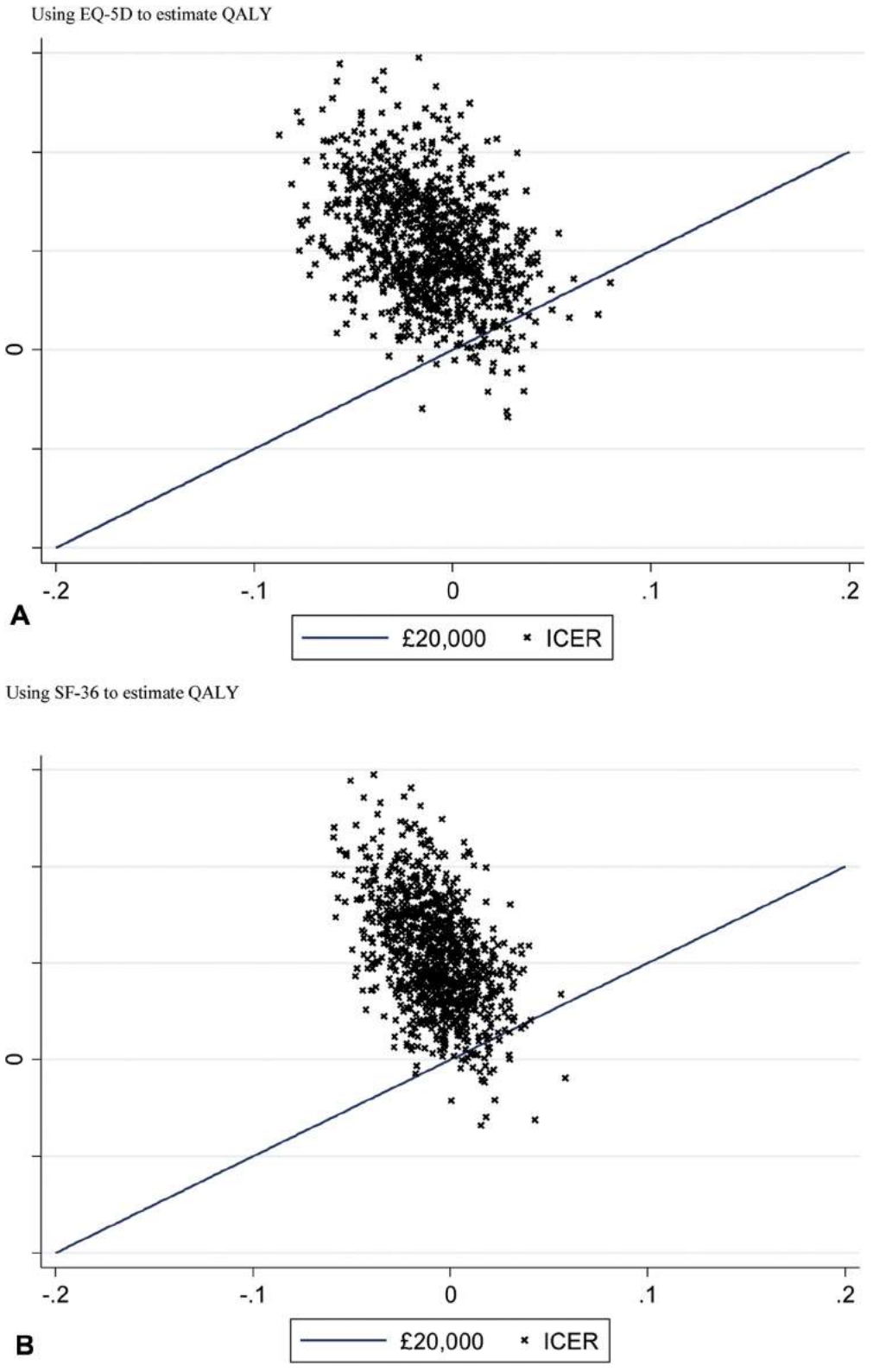

FIGURE E8. Cost-effectiveness plane, using the difference mini-sternotomy (*MS*) – full sternotomy (*FS*), adjusted for baseline. A, Using EQ-5D to estimate quality-adjusted life-years (*QALYs*). B, Using SF-36 to estimate QALYs. *ICER*, Incremental cost-effectiveness ratio.

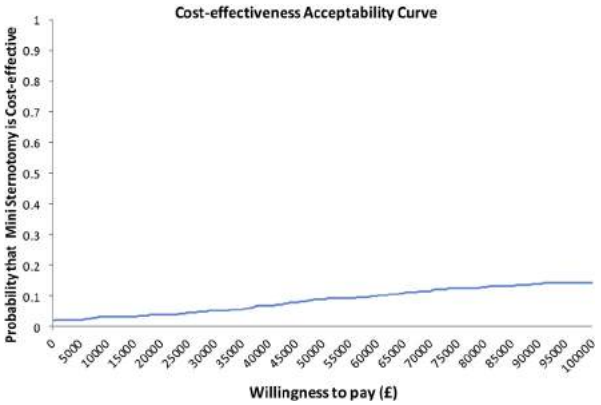

FIGURE E9. Cost-effectiveness acceptability curve (EQ-5D).

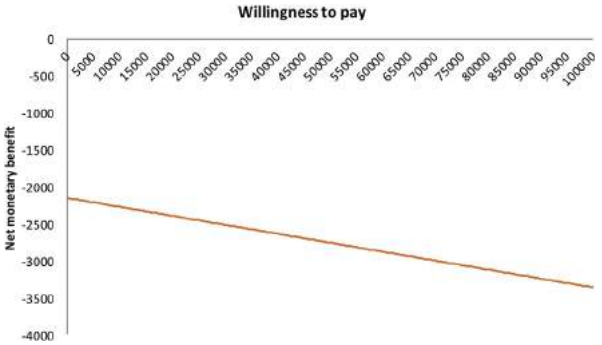

FIGURE E10. Net monetary benefit, controlling for baseline characteristics and missing data.

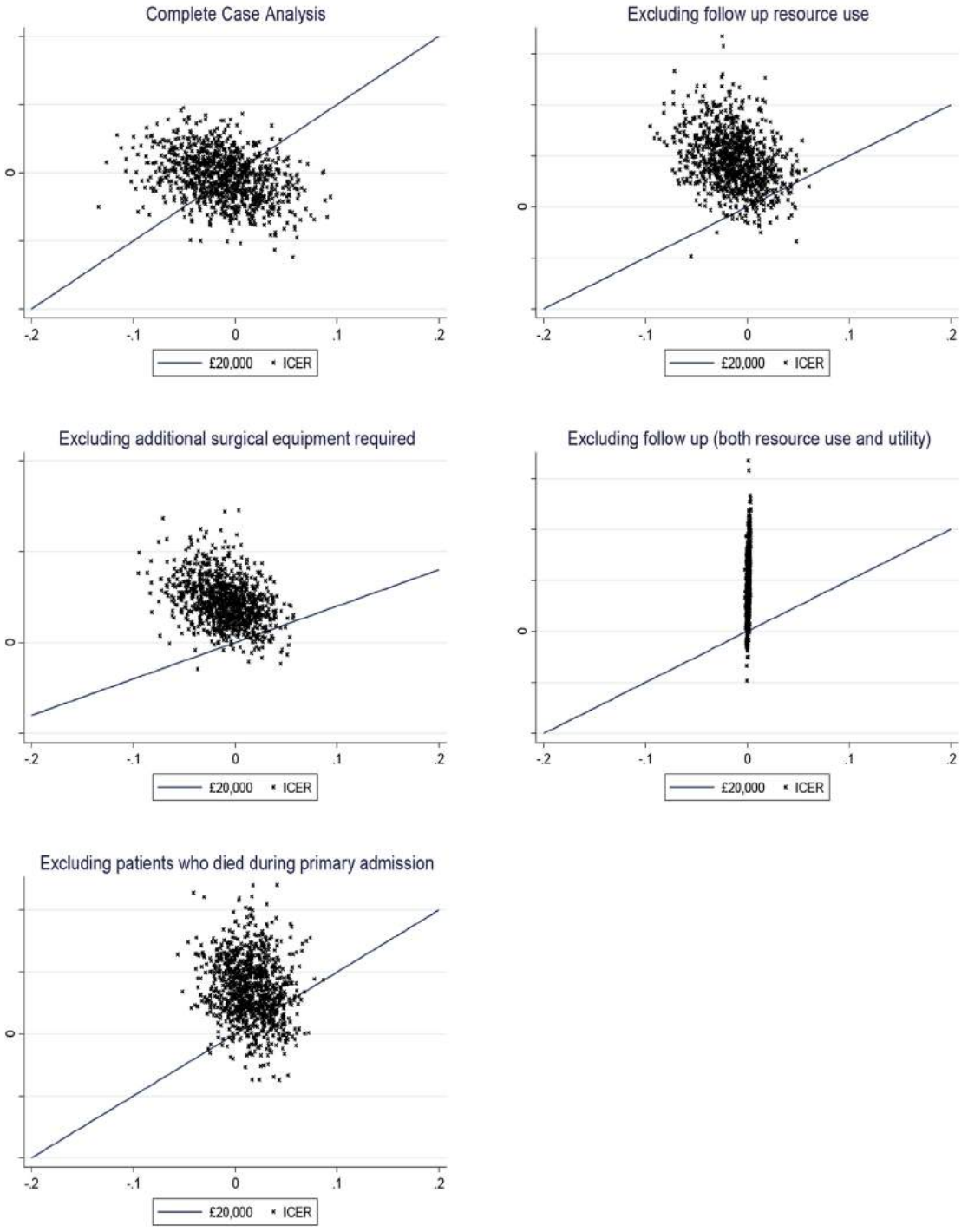

FIGURE E11. Sensitivity analyses using the difference mini-sternotomy (MS) – full sternotomy (FS), adjusted for baseline. *ICER*, Incremental cost-effectiveness ratio.

TABLE E1. Patients who underwent redo sternotomy, crossed over from mini sternotomy to full sternotomy, or were randomized but deemed ineligible

Operation	Allocated treatment	Description	Per-protocol population	Safety population
Redos	FS	Return to theatre for ventricular septal defect closure and redo AVR	As FS	As FS
	FS	Return to theatre for tamponade and cardiac arrest; redo sternotomy for tamponade	As FS	As FS
	MS	Return to theatre for tamponade MA bleed; conversion to FS	As MS	As MS
	MS	Return to theatre for bleeding; redo FS	As MS	As MS
	MS	Return to theatre for tamponade; evacuation of clot/pericardial effusion; conversion to FS	As MS	As MS
	MS	Return to theatre for cardiac arrest and tamponade; emergency resternotomy (FS), tamponade, and aortotomy repair	As MS	As MS
	MS	Return to theatre for pericardial collection and early tamponade; PEA arrest; reexploration on bypass; completion of FS	As MS	As MS
	MS	Second return to theatre, attempted weaning of ECMO and placement of RVAD; removal of blood clot; redo sternotomy	As MS	As MS
Crossovers	MS	Aortic root replacement required, FS indicated	Excluded	As FS
	MS	FS indicated as unable to perform TOE	Excluded	As FS
	MS	Aorta interposition graft required	Excluded	As MS
	MS	FS indicated as unable to have TOE	Excluded	As FS
	MS	CABG required due to intraoperative injury	Excluded	As MS
	MS	CABG required due to intraoperative injury	Excluded	As MS
	MS	FS indicated as unable to perform TOE	Excluded	As FS
	MS	Required aortic root replacement, conversion to FS	Excluded	As MS
	MS	Patient randomized too early; unable to insert TOE probe	Excluded	As FS
	MS	Did not have correct equipment in theatre	Excluded	As FS
	MS	Mini-sternotomy equipment not available	Excluded	As FS
	MS	Bleeding	Excluded	As MS
	MS	Patient had calcified aorta; nowhere to cannulate safely	Excluded	
Ineligible	FS	Withdrawn from trial by surgeon preoperatively (but postrandomization); AVR and myectomy required	Excluded	Excluded
	FS	Poor-quality baseline echocardiogram, with no assessment of LV function	Excluded	As FS
	MS	Surgeon had not checked echocardiography report until after randomization; FS performed	Excluded	As FS

FS, Full sternotomy; *AVR*, aortic valve replacement; *MS*, mini-sternotomy; *MA*, internal mammary artery; *PEA*, pulseless electrical activity; *ECMO*, extracorporeal membrane oxygenation; *RVAD*, right ventricular assist device; *TOE*, transesophageal echocardiography; *CABG*, coronary artery bypass grafting; *LV*, left ventricular.

TABLE E2. Additional summaries of in-hospital endpoints, Kaplan–Meier estimates

Endpoint	Mini-sternotomy (n = 118)	Full sternotomy (n = 104)
Time to discharge (d)		
Mean (SE)	9.5 (0.6)	8.6 (0.5)
Median (95% CI)	7 (6-8)	7 (6-8)
Time to fit for discharge (d)		
Mean (SE)	8.5 (0.5)*	7.5 (0.3)*
Median (95% CI)	6 (5-7)	6 (6-7)
Time to first mobilization (d)		
Mean (SE)	5.7 (0.5)*	4.9 (0.3)*
Median (95% CI)	4 (3-4)	4 (–)†
Time to mediastinal drain removal (h)		
Mean (SE)	48.1 (4.8)*	30.0 (1.7)
Median (95% CI)	26.1 (22.8-42.6)	22.5 (22.0-22.9)
Time to first extubation (h)		
Mean (SE)	13.1 (1.7)*	10.5 (0.7)
Median (95% CI)	9.2 (8.7-9.9)	8.3 (8.0-9.2)

The table presents the Kaplan–Meier estimates of in-hospital endpoints. Censoring of longest time to event for some endpoints led to underestimation of means and standard errors (highlighted with asterisks). A confidence interval for median time to mobilization could not be estimated. Table E5 shows the number of pain scores obtained on each of the 10 days following surgery. The denominator used for each percentage is the number of patients known to be alive and in hospital on the given day. *SE*, Standard error; *CI*, confidence interval. *Censoring of longest time to event for some endpoints led to underestimation of means and SEs. †A CI for median time to mobilization could not be estimated.

TABLE E3. Additional summaries of operative endpoints

Endpoint	Mini-sternotomy (n = 118)	Full sternotomy (n = 104)
Theatre time (min)		
Mean (SE)	201.2 (3.9)	181.0 (4.6)
Median (95% CI)	191 (187-205)	176 (170-180)
CPB time (min)		
Mean (SE)	82.0 (1.9)	69.5 (2.3)
Median (95% CI)	80 (77-86)	66 (59-74)
Cross-clamp time (min)		
Mean (SE)	65.5 (1.5)	52.4 (1.6)
Median (95% CI)	65 (61-69)	49 (45-53)
Surgery duration (min)		
Mean (SE)	165.5 (3.4)	145.7 (4.3)
Median (95% CI)	163 (155-172)	148.5 (134-153)
Total theatre time, including repeats/readmissions (min)		
Mean (SE)	221.1 (9.5)	191.2 (6.1)
Median (95% CI)	196 (189-210)	178.5 (171-188)
Total CPB time, including repeats/readmissions (min)		
Mean (SE)	85.1 (2.6)	71.1 (2.8)
Median (95% CI)	82 (77-87)	66 (59-74)
Total cross-clamp time, including repeats/readmissions (min)		
Mean (SE)	66.1 (1.6)	53.5 (2.0)
Median (95% CI)	66 (61-70)	49 (45-53)
Volume of blood lost in the first 12 postoperative hours (mL)		
Mean (SD)	310.4 (342.5)	323.2 (267.8)
Median (IQR)	225 (150-325)	250 (175-375)
Transfusion of packed red cells in the first 48 postoperative hours (mL)		
Number of transfused patients (%)	50 (42)	51 (49)
Mean (SD) in transfused patients	625.3 (513.2)	442.4 (265.3)
Median (IQR) in transfused patients	500 (300-644)	303(284-569)
Transfusion of clotting products in the first 48 postoperative hours (mL)		
Number of transfused patients (%)	11 (9)	4 (4)
Mean (SD) in transfused patients	920.5 (1438.4)	753.0 (672.5)
Median (IQR) in transfused patients	332 (183-1050)	625 (209-1297)

All estimates for time-to-event endpoints are Kaplan–Meier estimates. Time data were complete, except for durations of 7 surgeries (3 min-sternotomy [MS], 4 full median sternotomy [FS]) that were not recorded and thus were censored at 1 minute. Blood data were missing for only 1 patient (FS group, withdrawn before surgery). Blood transfusion and clotting products data for 7 patients at the Freeman Hospital were recorded in units and converted to milliliters (1 unit of packed red cells = 300 mL; 1 unit of platelets = 245 mL; 1 unit of fresh-frozen plasma = 280 mL). Transfusion data were explored using logistic regression models, including fixed effects for treatment, valve, and sex and a random surgeon effect. These analyses did not show a statistically significant difference between MS and FS patients in either need for blood transfusion (MS/FS odds ratio [OR], 0.797; 95% CI, 0.453-1.402; $P = .4310$) or the need for transfusion of clotting products (MS/FS OR, 2.616; 95% CI, 0.801-8.541; $P = .1112$). *SE*, Standard error; *CI*, confidence interval; *CPB*, cardiopulmonary bypass; *SD*, standard deviation; *IQR*, interquartile range.

TABLE E4. Results from cox models and log-rank tests for primary and secondary endpoints

Endpoint	MS/FS HR (95% CI)	*P* value, null hypothesis, HR = 1	Log-rank test statistic	*P* value, log-rank test
Primary analyses				
Time to discharge	0.874 (0.668-1.143)	.3246	0.157	.6924
Time until fit	0.907 (0.688-1.197)	.4914	0.340	.5597
Per-protocol analyses of primary endpoints				
Time to discharge	0.868 (0.656-1.147)	.3194	0.200	.6544
Time until fit	0.915 (0.688-1.218)	.5443	0.217	.6415
Sensitivity analyses: age included as an effect in the Cox models				
Time to discharge	0.866 (0.661-1.135)	.2985	0.157	.6924
Time until fit	0.902 (0.683-1.192)	.4685	0.340	.5597
Sensitivity analyses: EuroSCORE included as an effect in the Cox models				
Time to discharge	0.885 (0.676-1.159)	.3753	0.157	.6924
Time until fit	0.936 (0.709-1.236)	.6400	0.340	.5597
Sensitivity analyses: censoring times taken as event times				
Time to discharge	0.884 (0.677-1.153)	.3625	0.189	.6639
Time until fit	0.888 (0.680-1.160)	.3844	0.765	.3819
Sensitivity analysis: patients assumed to be fit at discharge				
Time until fit	0.879 (0.671-1.151)	.3480	0.703	.4018
Secondary endpoint analyses				
Time until first mobilization	0.899 (0.680-1.187)	.4518	0.303	.5819
Time until drain removal	0.587 (0.442-0.778)	.0002	5.838	.0157
Time until first extubation	0.856 (0.655-1.120)	.2582	0.359	.5488
Exploratory analyses				
Surgery duration	0.660 (0.500-0.872)	.0035	17.892	<.0001
CPB time	0.592 (0.448-0.782)	.0002	24.871	<.0001
Cross-clamp time	0.451 (0.340-0.597)	<.0001	42.539	<.0001
Theatre time	0.665 (0.503-0.879)	.0042	16.806	<.0001
Total CPB time including repeats/readmissions	0.547 (0.414-0.723)	<.0001	20.176	<.0001
Total cross-clamp time including repeats/readmissions	0.458 (0.346-0.608)	<.0001	34.352	<.0001
Total theatre time including repeats/readmissions	0.698 (0.531-0.918)	.0102	5.657	.0174
Time to death by any cause	1.871 (0.723-4.844)	.1966	0.7309	.3926

The table presents the results of all analyses performed for the primary and secondary time-to-event endpoints, including unplanned, exploratory analyses of secondary endpoints. All secondary endpoint analyses, sensitivity analyses, and exploratory analyses were performed using the intent-to-treat population. All log-rank tests were stratified by valve, sex, and surgeon. All Cox models included valve, sex, and treatment as fixed effects and surgeon as a random effect. Exploratory analysis of time to all-cause death included age as a fixed effect in the Cox model. Mean imputation was used for missing EuroSCORE data at baseline (1 MS). *MS*, Mini-sternotomy; *FS*, full median sternotomy; *HR*, hazard ratio; *CI*, confidence interval; *CPB*, cardiopulmonary bypass.

TABLE E5. Pain at rest scores in the first 10 days following surgery

Day	Mini-sternotomy (n = 118)	Full sternotomy (n = 104)
Day 1		
Mean (SD)	3.5 (2.5)	3.7 (2.4)
Number (%)	100 (85)	82 (80)
Day 2		
Mean (SD)	3 (2.3)	3.1 (2.5)
Number (%)	89 (75)	81 (79)
Day 3		
Mean (SD)	2.7 (2.3)	2.4 (2.3)
Number (%)	91 (77)	83 (81)
Day 4		
Mean (SD)	2.4 (2.1)	2.4 (2.4)
Number (%)	94 (80)	84 (82)
Day 5		
Mean (SD)	2 (1.9)	2.1 (2)
Number (%)	90 (79)	80 (79)
Day 6		
Mean (SD)	1.8 (1.7)	2.1 (2)
Number (%)	69 (77)	61 (76)
Day 7		
Mean (SD)	1.5 (1.8)	1.8 (2)
Number (%)	46 (69)	42 (78)
Day 8		
Mean (SD)	1.2 (1.4)	1.7 (1.6)
Number (%)	40 (77)	35 (76)
Day 9		
Mean (SD)	1 (1.8)	0.8 (1.5)
Number (%)	25 (57)	18 (47)
Day 10		
Mean (SD)	0.7 (1)	1.3 (2)
Number (%)	18 (47)	12 (43)

The denominator used for each percentage is the number of patients known to be alive and in the hospital on the given day. *SD*, Standard deviation.

TABLE E6. EQ-5D utility scores up to the 12-month follow-up

Time	Mini-sternotomy (n = 118)	Full sternotomy (n = 104)
Baseline		
Mean (SD)	0.77 (0.19)	0.70 (0.24)
Number (%)	105 (89)	95 (91)
Day 4		
Mean (SD)	0.47 (0.29)	0.39 (0.28)
Number (%)	92 (78)	89 (86)
Discharge		
Mean (SD)	0.60 (0.24)	0.58 (0.24)
Number (%)	103 (87)	88 (85)
6 wk		
Mean (SD)	0.74 (0.23)	0.71 (0.21)
Number (%)	106 (90)	88 (85)
6 mo		
Mean (SD)	0.83 (0.25)	0.83 (0.23)
Number (%)	105 (89)	95 (91)
12 mo		
Mean (SD)	0.83 (0.29)	0.78 (0.28)
Number (%)	103 (87)	84 (81)

For patients who died, EQ-5D scores were taken to be 0 following death. Percentages presented in the table were calculated as the number of scores recorded (including the 0s) divided by the number of patients randomized to the group. The difference in mean baseline score was potentially due to the imbalance in sex; the full sternotomy group had a greater proportion of females, who reported lower quality of life on average. *SD*, Standard deviation.

TABLE E7. SF-36 domain scores up to the 12-month follow-up

Domain	Mini-sternotomy (n = 118)	Full sternotomy (n = 104)
Bodily pain		
Baseline		
Mean (SD)	70 (25)	64 (28)
Number (%)	104 (88)	96 (92)
6 wk		
Mean (SD)	61 (24)	60 (23)
Number (%)	105 (89)	90 (87)
6 mo		
Mean (SD)	79 (27)	74 (28)
Number (%)	104 (88)	94 (90)
12 mo		
Mean (SD)	76 (31)	72 (32)
Number (%)	99 (84)	86 (83)
General health		
Baseline		
Mean (SD)	62 (20)	58 (22)
Number (%)	104 (88)	94 (90)
6 wk		
Mean (SD)	70 (20)	66 (20)
Number (%)	104 (88)	91 (88)
6 mo		
Mean (SD)	71 (24)	66 (24)
Number (%)	103 (87)	94 (90)
12 mo		
Mean (SD)	68 (26)	62 (26)
Number (%)	100 (85)	86 (83)
Mental health		
Baseline		
Mean (SD)	74 (18)	67 (21)
Number (%)	104 (88)	95 (91)
6 wk		
Mean (SD)	72 (22)	73 (19)
Number (%)	104 (88)	91 (88)
6 mo		
Mean (SD)	80 (21)	74 (22)
Number (%)	103 (87)	94 (90)
12 mo		
Mean (SD)	76 (26)	73 (23)
Number (%)	100 (85)	86 (83)
Physical functioning		
Baseline		
Mean (SD)	54 (26)	47 (28)
Number (%)	105 (89)	96 (92)
6 wk		
Mean (SD)	63 (22)	56 (23)
Number (%)	105 (89)	91 (88)
6 mo		
Mean (SD)	78 (27)	70 (28)
Number (%)	104 (88)	94 (90)
12 mo		
Mean (SD)	74 (30)	67 (31)
Number (%)	100 (85)	86 (83)
Role emotional		
Baseline		
Mean (SD)	67 (40)	55 (46)
Number (%)	104 (88)	94 (90)
6 wk		
Mean (SD)	60 (44)	63 (43)
Number (%)	104 (88)	90 (87)
6 mo		
Mean (SD)	81 (35)	72 (42)
Number (%)	104 (88)	94 (90)
12 mo		
Mean (SD)	76 (39)	71 (42)
Number (%)	98 (83)	85 (82)
Role physical		
Baseline		
Mean (SD)	33 (41)	23 (38)
Number (%)	103 (87)	96 (92)
6 wk		
Mean (SD)	19 (32)	20 (33)
Number (%)	103 (87)	90 (87)
6 mo		
Mean (SD)	65 (42)	59 (44)
Number (%)	103 (87)	94 (90)
12 mo		
Mean (SD)	64 (44)	52 (46)
Number (%)	98 (83)	85 (82)
Social functioning		
Baseline		
Mean (SD)	66 (30)	61 (29)
Number (%)	104 (88)	94 (90)
6 wk		
Mean (SD)	66 (29)	68 (27)
Number (%)	104 (88)	91 (88)
6 mo		
Mean (SD)	85 (26)	78 (28)
Number (%)	102 (86)	93 (89)
12 mo		
Mean (SD)	81 (30)	78 (30)
Number (%)	98 (83)	85 (82)
Vitality		
Baseline		
Mean (SD)	46 (25)	40 (23)
Number (%)	104 (88)	95 (91)
6 wk		
Mean (SD)	50 (22)	48 (22)
Number (%)	104 (88)	90 (87)
6 mo		
Mean (SD)	64 (23)	57 (23)
Number (%)	103 (87)	94 (90)
12 mo		
Mean (SD)	60 (26)	54 (26)
Number (%)	100 (85)	86 (83)

An in-house implementation of the standard scoring algorithm for the developmental version of the SF-36 was used. For the patients who died, SF-36 scores were taken to be 0 following death. Percentages presented in the table were calculated as the number of scores recorded (including the 0s) divided by the number of patients randomized to the group. The differences in mean baseline scores were potentially due to the imbalance in sex; the full sternotomy group had a greater proportion of females, who reported lower quality of life on average. *SD*, Standard deviation.

TABLE E8. Estimated treatment effects (MS-FS) and treatment–time interactions for SF-36 domain scores up to 12 months, EQ-5D utility scores up to 12 months, and pain scores up to discharge

Parameter	Effect (MS – FS)	95% CI	*P* value
Pain at rest (n = 219)			
Treatment effect	0.0	(−0.7 to 0.6)	.9766
Treatment–time (d) interaction	0.0	(−0.1 to 0.1)	.8190
EQ-5D utility scores (n = 197)			
Treatment effect	0.02	(−0.03 to 0.07)	.5148
Treatment–time (mo) interaction	0.00	(−0.01 to 0.01)	.9731
SF-36 physical functioning (n = 192)			
Treatment effect	1.2	(−6.2 to 8.7)	.7414
Treatment–time (mo) interaction	0.3	(−0.2 to 0.9)	.2387
SF-36 role physical (n = 190)			
Treatment effect	−8.3	(−21.1 to 4.5)	.2025
Treatment–time (mo) interaction	1.7	(0.3 to 3.1)	.0169
SF-36 bodily pain (n = 191)			
Treatment effect	−0.7	(−9.1 to 7.8)	.8792
Treatment–time (mo) interaction	0.3	(−0.5 to 1.1)	.4331
SF-36 general health (n = 189)			
Treatment effect	−1.0	(−7.5 to 5.5)	.7710
Treatment–time (mo) interaction	0.3	(−0.2 to 0.8)	.2224
SF-36 vitality (n = 190)			
Treatment effect	−2.1	(−8.8 to 4.5)	.5273
Treatment–time (mo) interaction	0.6	(0.1 to 1.2)	.0293
SF-36 social functioning (n = 189)			
Treatment effect	−5.5	(−14.1 to 3.1)	.2093
Treatment–time (mo) interaction	1.0	(0.2 to 1.7)	.0183
SF-36 role emotional (n = 189)			
Treatment effect	−6.2	(−18.6 to 6.2)	.3255
Treatment–time (mo) interaction	1.1	(−0.1 to 2.3)	.0699
SF-36 mental health (n = 190)			
Treatment effect	−3.2	(−9.7 to 3.4)	.3431
Treatment–time (mo) interaction	0.5	(−0.0 to 1.0)	.0702

The table shows the results of complete-case analyses of questionnaire data, under a missing completely at random assumption, including only patients with at least 1 analyzable follow-up questionnaire. For each analysis, the number in parentheses is the number of patients used to fit the model. For pain and SF-36 scores, some random effects were estimated to have a variance of 0 and were excluded from the models (surgeon effect for pain and both the surgeon effect and random slope for the SF-36). The slope (time coefficient) was estimated to be negative for pain and positive for all EQ-5D and SF-36 scores. This suggests improvement over time in each score. Evidence of greater rate of improvement over time for patients in the mini-sternotomy group (statistically significant, positive interaction term) was seen for 3 SF-36 domains (role physical, vitality, and social functioning), but not for others. *MS*, Mini-sternotomy; *FS*, full sternotomy; *SF-36*, Short Form Health Survey; *CI*, confidence interval.

TABLE E9. Estimated treatment effects (MS-FS) and treatment–time interactions for SF-36 domain scores up to 12 months, EQ-5D utility scores up to 12 months, and pain scores up to discharge, after multiple imputation of missing scores

Parameter	Effect (MS – FS)	95% CI	*P* value
Pain at rest			
Treatment effect	0.0	(−0.7 to 0.6)	.9059
Treatment–time (d) interaction	0.0	(−0.1 to 0.1)	.9685
EQ-5D utility scores			
Treatment effect	0.01	(−0.04 to 0.06)	.8203
Treatment–time (mo) interaction	0.00	(−0.01 to 0.01)	.9094
SF-36 physical functioning			
Treatment effect	2.0	(−4.9 to 8.9)	.5744
Treatment–time (mo) interaction	0.2	(−0.3 to 0.8)	.3996
SF-36 role physical			
Treatment effect	−6.6	(−18.7 to 5.4)	.2808
Treatment–time (mo) interaction	1.5	(0.1 to 2.8)	.0310
SF-36 bodily pain			
Treatment effect	−0.1	(−9.0 to 7. 7)	.9748
Treatment–time (mo) interaction	0.3	(−0.4 to 1.1)	.4091
SF-36 general health			
Treatment effect	1.1	(−5.0 to 7.3)	.7175
Treatment–time (mo) interaction	0.2	(−0.3 to 0.7)	.3373
SF-36 vitality			
Treatment effect	−0.5	(−6.9 to 5.9)	.8798
Treatment–time (mo)interaction	0.4	(−0.2 to 1.0)	.1733
SF-36 social functioning			
Treatment effect	−4.4	(−12.4 to 3.5)	.2756
Treatment–time (mo) interaction	0.7	(0.0 to 1.5)	.0589
SF-36 role emotional			
Treatment effect	−4.6	(−16.4 to 7.2)	.4415
Treatment–time (mo) interaction	0.8	(−0.4 to 2.0)	.1790
SF-36 mental health			
Treatment effect	−2.5	(−8.6 to 3.5)	.4113
Treatment–time (mo) interaction	0.4	(−0.1 to 0.9)	.1195

The table presents the results from analyzing the questionnaire data using multiple imputation to handle missing observations, under a missing at random assumption. For each analysis, missing data were imputed from models that included all other variables used in the analysis, along with Canadian Cardiovascular Society grade and New York Heart Association grade as auxiliary variables. The method used was multiple imputation by chained equations with predictive mean matching. Estimates from 100 imputed datasets were combined using Rubin rules. Pain was imputed only for patients known to be alive and hospitalized, not for patients who had died or had already been discharged. Evidence of a greater rate of improvement over time for MS patients (statistically significant, positive interaction term) was seen for only 1 SF-36 domain. *MS*, Mini-sternotomy; *FS*, full sternotomy; *SF-36*, Short Form Health Survey; *CI*, confidence interval.

TABLE E10. Summary of heart function (LVEF) and respiratory function (FEV_1)

Parameter	Mini-sternotomy (n = 118)	Full sternotomy (n = 104)
FEV_1 (Liters)		
Baseline visit		
Mean (SD)	2.3 (0.7)	2.3 (0.8)
Median (IQR)	2.2 (1.8-2.7)	2.2 (1.7-2.6)
Number	115	101
Discharge		
Mean (SD)	1.6 (0.6)	1.6 (0.6)
Median (IQR)	1.5 (1.2-1.8)	1.5 (1.2-1.9)
Number	82	69
6-wk visit		
Mean (SD)	2.1 (0.8)	2.1 (0.7)
Median (IQR)	2 (1.5-2.5)	1.9 (1.6-2.5)
Number	92	84
6-mo visit		
Mean (SD)	2.2 (0.7)	2.1 (0.7)
Median (IQR)	2.1 (1.7-2.6)	1.9 (1.4-2.4)
Number	91	82
LVEF (%)		
Baseline visit		
Mean (SD)	61.9 (9.1)	62.4 (8.6)
Median (IQR)	62.5 (57.5-67.5)	63 (57.5-67.0)
Number	117	101
Discharge		
Mean (SD)	59.9 (9.7)	59 (10.2)
Median (IQR)	62 (55.0-65.0)	58 (55.0-64.5)
Number	106	96
6-mo visit		
Mean (SD)	61.2 (8.1)	61.8 (9.7)
Median (IQR)	61 (56.0-67.5)	62.5 (56.3-68.0)
Number	97	88

No analyses were planned for these endpoints. *FEV_1*, Forced expiratory volume in 1 second (measured by hand-held spirometry); *SD*, standard deviation; *IQR*, interquartile range; *LVEF*, left ventricular ejection fraction (measured by echocardiography).

TABLE E11. Frequency of nonfatal SAEs within 1 year of surgery, by treatment received

Nonfatal SAE	Mini-sternotomy (n = 110), % (number)	Full sternotomy (n = 111), % (number)	Total (n = 221), % (number)
Cardiac (including atrial fibrillation, conduction problems, need for permanent pacemaker)	43 (29)	27 (21)	70 (50)
Respiratory	20 (14)	9 (8)	29 (22)
Injury/procedural	19 (11)	7 (6)	26 (17)
Noncardiorespiratory infection (including wound)	7 (7)	12 (9)	19 (16)
Urinary	11 (10)	8 (6)	19 (16)
Surgical and medical procedures	9 (6)	7 (7)	16 (13)
Nervous system	8 (8)	7 (7)	15 (15)
Cardiorespiratory infection (including endocarditis, device-related infections, chest infection)	9 (9)	6 (5)	15 (14)
Vascular	9 (9)	1 (1)	10 (10)
Psychiatric	5 (5)	5 (5)	10 (10)
Gastrointestinal, diarrhea	7 (6)	3 (3)	10 (9)
Gastrointestinal, other	7 (7)	1 (1)	8 (8)
General disorders	4 (4)	3 (2)	7 (6)
Metabolic	2 (2)	3 (2)	5 (4)
Blood/lymph	4 (3)	1 (1)	5 (4)
Neoplasms	1 (1)	1 (1)	2 (2)
Hepatitis/cholecystitis	1 (1)	1 (1)	2 (2)
Musculoskeletal	2 (2)	0 (0)	2 (2)
Skin/tissue	0 (0)	1 (1)	1 (1)
Eye	0 (0)	1 (1)	1 (1)
Immune	0 (0)	1 (1)	1 (1)
Total	168 (56)	105 (46)	273 (102)

Among the nervous system SAEs recorded in the table, stroke was sustained by 3 full sternotomy recipients and 2 mini-sternotomy recipients. No patient sustained more than 1 stroke. *SAE*, Serious adverse effect.

TABLE E12. Frequency of nonfatal SAEs within 1 year of surgery at each level of severity, expectedness, and relatedness, by treatment received

Nonfatal SAE	Mini-sternotomy (n = 110), % (number)	Full sternotomy (n = 111), % (number)	Total (n = 221), % (number)
Cardiorespiratory			
Severity			
Severe	26 (14)	14 (11)	40 (25)
Moderate	34 (24)	24 (18)	58 (42)
Mild	12 (11)	4 (4)	16 (15)
Expectedness			
Expected	69 (38)	42 (30)	111 (68)
Unexpected	3 (2)	0 (0)	3 (2)
Relatedness			
Probably related	4 (4)	2 (2)	6 (6)
Possibly related	50 (30)	32 (25)	82 (55)
Unrelated	18 (13)	8 (6)	26 (19)
Total	72 (38)	42 (30)	114 (68)
Noncardiorespiratory			
Severity			
Severe	40 (21)	24 (15)	64 (36)
Moderate	43 (29)	31 (21)	74 (50)
Mild	13 (11)	8 (5)	21 (16)
Expectedness			
Expected	68 (34)	45 (27)	113 (61)
Unexpected	28 (15)	18 (15)	46 (30)
Relatedness			
Probably related	9 (5)	5 (5)	14 (10)
Possibly related	37 (22)	30 (20)	67 (42)
Unrelated	50 (27)	28 (20)	78 (47)
Total	96 (41)	63 (34)	159 (75)

The only unexpected events in the mini-sternotomy (MS) group were a bilateral pleural effusion in 1 patient, and bronchial aspiration and periarrest event in 1 patient. Both patients recovered completely. Exploratory analysis in the safety population, using logistic regression (with fixed treatment, valve, and sex effects and a random surgeon effect), did not show a statistically significant difference between MS and full sternotomy (FS) recipients in the odds of sustaining a nonfatal SAE within the first year (MS/FS odds ratio [OR], 1.559, 95% confidence interval [CI], 0.895-2.715; $P = .1161$). An exploratory Poisson regression (with a fixed effect for treatment and a random patient effect) did show a greater rate of such SAEs for MS recipients (MS/FS rate ratio, 1.615; 95% CI, 1.070-2.437; $P = .0225$). There were 7 cases of pericardial tamponade (4 in FS recipients and 3 in MS recipients; only 1 per patient), but logistic regression (without the random surgeon effect) did not produce a statistically significant result (MS/FS OR, 0.680; 95% CI, 0.146-3.178; $P = .6229$). *SAE*, Significant adverse effect.

TABLE E13. Frequency of paraprosthetic regurgitation, by treatment received

Parameter	Mini-sternotomy (n = 110)	Full sternotomy (n = 111)	Total (n = 221)
Discharge			
No regurgitation	84	85	169
Mild regurgitation	19	16	35
Moderate regurgitation	0	0	0
Severe regurgitation	0	0	0
Total	101	103	204
6-mo visit			
No regurgitation	77	82	159
Mild regurgitation	18	10	28
Moderate regurgitation	0	0	0
Severe regurgitation	0	0	0
Total	95	92	187

Paraposthetic regurgitation was explored using logistic regressions at each time point. These were performed as complete-case analyses in the safety population. Logistic regression models included fixed treatment, valve and sex effects, and a random surgeon effect. They did not show a statistically significant difference between mini-sternotomy (MS) recipients and full sternotomy (FS) recipients in the odds of regurgitation, either at discharge (MS/FS odds ratio [OR], 1.163, confidence interval [CI], 0.553-2.445; $P = .6883$) or at 6 mo (MS/FS OR, 1.880; 95% CI, 0.798-4.430; $P = .1480$).

TABLE E14. All wound infections within the first year after surgery, by treatment received

Treatment	Relationship	Description
FS	Possibly related	Superficial sternal wound infection
FS	Possibly related	Sternal wound infection; returned to theatre for debridement and wires removed
FS	Possibly related	Sternal wound infection
FS	Possibly related	Sternal wound breakdown; debridement and excision of sinuses; peripherally inserted central catheter for 6 wk; intravenous antibiotics
FS	Possibly related	Drain site wound infection
FS	Possibly related	Wound infection, small area at lower end of sternum
FS	Possibly related	Small sternal wound infection
FS	Probably related	Sternal wound infection
FS	Probably related	Sternal wound infection
FS	Possibly related	Sternal wound infection
FS	Probably related	Sternal wound infection
FS	Possibly related	Sternal wound infection; antibiotic therapy initiated
FS	Possibly related	Sternal wound infection requiring hospital admission; treated with antibiotics
FS	Possibly related	Wound infection treated with antibiotics and daily dressing changes
MS	Possibly related	Readmission, wound infection, intravenous/oral flucloxacillin
MS	Possibly related	Methicillin-resistant *Staphylococcus aureus* sternal wound infection
MS	Probably related	Sternal wound infection; admitted with fever, chest pain, shortness of breath, and discharging sternal wound; intravenous flucloxacillin initiated; swab taken; VAC dressing applied
MS	Possibly related	Wound infection at base of sternotomy; wound swab taken, *Klebsiella pneumoniae* grown; amoxycillin initiated

In total, 4 MS recipients and 13 FS recipients sustained wound infections within 1 year of surgery (1 FS recipient sustained 2 infections). No patient who received a mechanical valve sustained a wound infection. The odds of wound infection were explored via logistic regression (complete-case analysis in the safety population, with fixed treatment and sex effects and a random surgeon effect). The odds of suffering at least 1 wound infection were estimated to be lower for MS recipients than for FS recipients (MS/FS odds ratio, 0.312; 95% confidence interval, 0.097-1.005; $P = .0511$). Only 2 infections were categorized as deep (1 MS and 1 FS). *FS*, Full sternotomy; *MS*, mini-sternotomy.

TABLE E15. All deaths

	Treatment received	Treatment allocated	Cause	Relationship to treatment	Days from surgery to death
Cardiorespiratory	FS	FS	Endocarditis and sepsis	Possibly related	124
	FS	FS	Lung infection	Unrelated	1050
	FS	FS	Respiratory failure, pneumonia, chronic lymphocytic leukemia	Unrelated	1057
	MS	MS	Cardiac arrest and pericardial tamponade 2 days after surgery; heart failure and left anterior pneumothorax 3 days after surgery	Possibly related	3
	MS	MS	Type 2 respiratory failure and shock, multiorgan failure	Possibly related	24
	MS	MS	Postoperative arrest in high-dependency unit on day of surgery; heart failure 26 days after surgery	Possibly related	26
	MS	MS	Lower respiratory tract infection; type 2 respiratory failure; non–ST-elevation myocardial infarction during hospital admission	Unrelated	75
	MS	MS	Endocarditis, infected valve; refused all treatment, including antibiotics; palliation only	Possibly related	241
	MS	MS	Exacerbation of chronic obstructive pulmonary disease	Unrelated	307
	MS	MS	Ischaemic heart disease	Unrelated	502
	MS	MS	Myocardial infarction	Unrelated	933
Noncardiorespiratory	FS	FS	Sepsis	Unrelated	66
	FS	FS	Metastatic prostate cancer	Unrelated	256
	FS	FS	B cell lymphoma	Unrelated	308
	FS	FS	Embolus of left common femoral artery, advanced colorectal cancer, AS, congestive heart failure	Unrelated	958
	MS	MS	Metastatic bladder cancer	Unrelated	257
	MS	MS	Death due to malignant tumor of esophagus	Unrelated	445
	MS	MS	Diffuse large B cell lymphoma	Unrelated	527
	MS	MS	Spontaneous subdural hemorrhage	Unrelated	873

The table shows that none of the patients who died were considered crossovers from MS to FS; however, there were 3 deaths among patients who were allocated to and received MS but who were returned to the theatre for redo FS. These were the deaths, all categorized as cardiorespiratory, occurring at 3, 26, and 933 days after surgery. *FS*, Full sternotomy; *MS*, mini-sternotomy; *AS*, ankylosing spondylitis.

TABLE E16. Unit costs

Item	Source	Consultation time/code	Mean (SD), £, 2014/15
General practitioner visits	PSSRU 2015. 10.8b	Per patient contact lasting 17.2 min	65.00 (13.00)
General practitioner home visits	PSSRU 2015. 10.8b	Per patient contact lasting 11.7 min	45.00 (9.00)
Nurse (general practitioner practice) visits	PSSRU 2015. 10.6	Per patient contact 15.5 min	14.47 (2.89)
Nurse (specialist community) home visits	PSSRU 2015. 10.4	Per patient contact 15.5 min	19.38 (3.88)
Physiotherapy (outpatient)	NHS Ref 2014-15	Code: WF01A	16.13 (3.23)
Occupational therapy (outpatient)	NHS Ref 2014-15	Code: WF01A	16.67 (3.33)
Physiotherapy (inpatient)	PSSRU 2015. 13.1	Per patient contact lasting 20 min	12.67 (2.53)
Occupational therapy (inpatient)	PSSRU 2015. 13.2	Per patient contact lasting 20 min	12.67 (2.53)
Physiotherapy (home)	PSSRU 2015. 8.4.1	Per patient contact lasting 20 min	27.00 (5.40)
Theatre use	Papworth estimate		20.00 (4.00)
Horizontal surgical saw	Papworth estimate	20-year life span and are used in 255 surgeries in every 5 y	3138.22 (3.1)
Pediatric internal cardioversion paddles			161.71 (0.2)
Internal paddle handle			670.00 (0.7)
Reprocessing cost of defibrillator paddles for each surgery*		Per patient	2.40 (2.40)
Single-use saw blade for mini-sternotomy		Per patient	15.80 (15.80)
Single-use saw blade for full sternotomy		Per patient	48.00 (48.00)
Adult critical care	NHS Ref 2014-15	Total/weighted average	1274.92 (583.33)
Specialized ward	NHS Ref 2014-15	Code: SD01A	387.96 (77.59)
General ward	NHS Ref 2014-15	Code: SD03A	103.01 (20.60)
Rehabilitation	PSSRU (1.3) 2015		158.57 (31.71)
24-h blood pressure monitoring	Lovibond et al, 2011[E3]		61.47 (12.29)
Radiography (chest)	Auguste et al, 2011[E4]		3.46 (0.69)
Transthoracic echocardiography	NHS Ref 2014-15	Simple echocardiography	83.94 (16.79)
Transesophageal echocardiography	NHS Ref 2014-15	Complex echocardiography	128.49 (25.70)
Stress echocardiography	NHS Ref 2014-15	Complex echocardiography	128.49 (25.70)
24-h electrocardiography	NHS Ref 2014-15	Electrocardiography monitoring	140.69 (28.14)
12-h electrocardiography	NHS Ref 2014-15	Electrocardiography monitoring	140.69 (28.14)
Exercise tolerance test	NHS Ref 2014-15	Electrocardiography monitoring	140.69 (28.14)
Magnetic resonance imaging	NHS Ref 2014-15	Total/weighted average	146.15 (56.64)
Full pulmonary function testing	NHS Ref 2014-15	Code: DZ52Z	55.32 (11.06)
Cardiac rehabilitation	NHS Ref 2014-15	Code: VC38Z	97.84 (19.57)
Cardiology clinic	NHS Ref 2014-15	Code: WF01A	123.02 (24.60)
Pacemaker	NHS Ref 2014-15	Code: EY08E	76.32 (15.26)
Blood tests	NHS Ref 2014-15	Code: DAPS08	3.46 (0.69)
Arrhythmia clinic	NHS Ref 2014-15	Total/weighted average	131.14 (26.23)
Wound clinic	NHS Ref 2014-15	Code: N25AF/AN	54.93 (10.99)
Accident and emergency visit	NHS Ref 2014-15	Total/weighted average	140.59 (141.05)
Computed tomography scan	NHS Ref 2014-15	Total/weighted average	122.31 (48.86)

SD, Standard deviation; *PSSRU*, Personal Social Services Research Unit; *NHS*, National Health Service. *The lead clinician confirmed that the defibrillator is not routinely used, that the cost of paddles should apply to 30% of patients, and that the cost of external defibrillator plates should be excluded for mini-sternotomy, because the plate is used only when it is not possible to insert the paddles.

TABLE E17. Summary of resource use (without imputation)

Primary admission costs	Unit of measurement	Full sternotomy		Mini-sternotomy	
		Observations	Mean (SD) resource use/ patient	Observations	Mean (SD) resource use/ patient
Theatre	Minutes	104	191.19 (62.15)	118	221.11 (102.65)
Critical care (intensive therapy unit)	Hours	103	34.67 (57.17)	118	55.24 (94.69)
Cardiac ward	Days	103	7.09 (4.31)	118	6.90 (3.87)
Rehabilitation*	Days	103	2.45 (11.90)	117	1.68 (10.27)
Acute hospital*	Days	103	0.90 (4.97)	117	0.74 (5.09)
Physiotherapy (inpatient)	Days	103	5.90 (4.21)	117	5.90 (5.16)
Occupational therapy (inpatient)	Days	103	0.17 (0.58)	118	0.24 (0.69)
Follow-up (postdischarge)					
Intensive therapy unit	Days	81	0.00 (0.00)	94	0.03 (0.31)
General ward	Days	92	2.87 (14.37)	101	0.86 (3.43)
Cardiac ward	Days	92	0.40 (1.49)	100	1.15 (4.32)
24-h blood pressure monitoring	Number of tests	80	0.16 (0.56)	94	0.19 (1.26)
Radiography (chest)	Number of tests	80	0.49 (0.89)	94	0.64 (0.90)
Computed tomography scan	Number of tests	80	0.14 (0.52)	94	0.15 (0.51)
Transthoracic echocardiography	Number of tests	80	0.41 (0.69)	94	0.55 (0.84)
Transesophageal echocardiography	Number of tests	80	0.03 (0.22)	92	0.03 (0.18)
Stress echocardiography	Number of tests	80	0.01 (0.11)	93	0.01 (0.10)
24-h electrocardiography	Number of tests	80	0.11 (0.39)	94	0.15 (0.46)
12-h electrocardiography	Number of tests	80	0.69 (0.91)	94	0.90 (1.18)
Exercise tolerance test	Number of tests	80	0.08 (0.27)	93	0.06 (0.25)
Magnetic resonance imaging	Number of tests	79	0.03 (0.16)	94	0.05 (0.23)
Full pulmonary function testing	Number of tests	80	0.05 (0.22)	94	0.03 (0.18)
Blood test	Number of tests	81	0.05 (0.22)	94	0.06 (0.35)
Accident and emergency visit	Number of visits	80	0.09 (0.28)	94	0.22 (0.51)
Arrhythmia clinic	Number of visits	80	0.03 (0.16)	94	0.00 (0.00)
Cardiac rehabilitation	Number of visits	79	0.84 (2.76)	93	0.32 (1.43)
Cardiology clinic	Number of visits	79	0.48 (0.68)	94	0.49 (0.73)
General practitioner home visits	Number of visits	79	0.23 (0.64)	94	0.30 (0.75)
General practitioner visits	Number of visits	80	2.00 (2.34)	94	2.20 (2.31)
Nurse (specialist community) home visits	Number of visits	80	0.31 (1.12)	94	0.39 (1.18)
Nurse (general practice) visits	Number of visits	80	2.10 (10.02)	92	0.75 (1.46)
Occupational therapy (outpatient)	Number of visits	80	0.11 (0.71)	94	0.06 (0.62)
Pacemaker	Number of visits	79	0.08 (0.68)	93	0.06 (0.38)
Physiotherapy (home)	Number of visits	80	0.05 (0.35)	94	0.00 (0.00)
Physiotherapy (outpatient)	Number of visits	80	0.04 (0.19)	94	0.01 (0.10)
Wound clinic	Number of visits	80	0.06 (0.29)	94	0.02 (0.15)

SD, Standard deviation. *Discharged to convalescence/long term care/acute hospital instead of to home.

TABLE E18. Missing follow-up resource use

Follow-up resource use	Full sternotomy, number	Mini-sternotomy, number	Total, number
6 wk			
Missing	3	4	7
Lost to follow-up	4	6	10
Dead	1	4	5
Observations	96	104	200
6 mo			
Missing	2	5	7
Lost to follow-up	8	9	17
Dead	2	6	8
Observations	92	98	190
12 mo			
Missing	9	4	13
Lost to follow-up	11	13	24
Dead	4	7	11
Observations	80	94	174
Total	104	118	222

TABLE E19. Incomplete data and imputation

Resource use	Full sternotomy				Mini-sternotomy			
	Complete	Incomplete	Imputed	Total	Complete	Incomplete	Imputed	Total
Primary admission								
Theatre time (min)	104	0	0	104	118	0	0	118
Critical care stay (h)	103	1	1	104	118	0	0	118
Cardiac ward stay (d)	103	1	1	104	118	0	0	118
Rehabilitation days*	103	1	1	104	117	1	1	118
Acute hospital days*	103	1	1	104	117	1	1	118
Physiotherapy visits	103	1	1	104	117	1	1	118
Occupational therapy visits	103	1	1	104	118	0	0	118
Follow-up (postdischarge)								
Postdischarge intensive therapy unit days	81	23	23	104	94	24	24	118
Postdischarge general ward stay	92	12	12	104	101	17	17	118
Postdischarge cardiac ward stay	92	12	12	104	100	18	18	118
24 h blood pressure monitoring	80	24	24	104	94	24	24	118
Radiography (chest)	80	24	24	104	94	24	24	118
Computed tomography scan	80	24	24	104	94	24	24	118
Transthoracic echocardiography	80	24	24	104	94	24	24	118
Transesophageal echocardiography	80	24	24	104	92	26	26	118
Stress echocardiography	80	24	24	104	93	25	25	118
24-h electrocardiography	80	24	24	104	94	24	24	118
12-h electrocardiography	80	24	24	104	94	24	24	118
Exercise tolerance test	80	24	24	104	93	25	25	118
Magnetic resonance imaging	79	25	25	104	94	24	24	118
Pulmonary function testing	80	24	24	104	94	24	24	118
Blood tests	81	23	23	104	94	24	24	118
Accident and emergency visit	80	24	24	104	94	24	24	118
Arrhythmia clinic	80	24	24	104	94	24	24	118
Cardiac rehabilitation	79	25	25	104	93	25	25	118
Cardiology clinic	79	25	25	104	94	24	24	118
General practitioner home visits	79	25	25	104	94	24	24	118
General practitioner visits	80	24	24	104	94	24	24	118
Nurse (specialist community) home visits	80	24	24	104	94	24	24	118
Nurse (general practice) visits	80	24	24	104	92	26	26	118
Occupational therapy	80	24	24	104	94	24	24	118
Pacemaker	79	25	25	104	93	25	25	118
Physiotherapy (home)	80	24	24	104	94	24	24	118
Physiotherapy	80	24	24	104	94	24	24	118
Wound clinic	80	24	24	104	94	24	24	118
EQ-5D score								
Baseline	95	9	9	104	105	13	13	118
4 d postoperation	89	15	15	104	92	26	26	118
Discharge	88	16	16	104	103	15	15	118
6-wk follow-up	88	16	16	104	106	12	12	118
6-mo follow-up	95	9	9	104	105	13	13	118
12-mo follow-up	84	20	20	104	103	15	15	118
SF-6D score								
Baseline	89	15	15	104	101	17	17	118
6-wk follow-up	88	16	16	104	102	16	16	118
6-mo follow-up	90	14	14	104	102	16	16	118
12-mo follow-up	82	22	22	104	91	27	27	118

SF-6D, Short-Form Six-Dimension. *Acute hospital days: Indicate postoperative hospital stay in the parent surgical unit/hospital (Papworth or Freeman Hospital, UK). Rehabilitation days: Indicate stay in a local district general hospital/nursing home/convalescence home prior after transfer from the surgical unit but prior to final discharge home.

TABLE E20. Summary of resource use

Primary admission costs	Unit of measurement	Full sternotomy		Mini-sternotomy	
		Observations	Mean (SD) resource use/ patient	Observations	Mean (SD) resource use/ patient
Theatre	Minutes	104	191.19 (62.15)	118	221.11 (102.65)
Critical care (intensive therapy unit)	Hours	104	34.52 (56.91)	118	55.24 (94.69)
Cardiac ward	Days	104	7.07 (4.29)	118	6.90 (3.87)
Rehabilitation*	Days	104	2.42 (11.84)	118	1.66 (10.22)
Acute hospital*	Days	104	0.89 (4.95)	118	0.77 (5.08)
Physiotherapy (inpatient)	Days	104	5.88 (4.20)	118	5.94 (5.15)
Occupational therapy (inpatient)	Days	104	0.17 (0.58)	118	0.24 (0.69)
Follow-up (postdischarge)					
Intensive therapy unit	Days	104	0.00 (0.00)	118	0.03 (0.28)
General ward	Days	104	2.61 (13.55)	118	0.77 (3.20)
Cardiac ward	Days	104	0.38 (1.43)	118	1.19 (4.14)
24-h blood pressure monitoring	Number of tests	104	0.18 (0.52)	118	0.17 (1.13)
Radiography (chest)	Number of tests	104	0.55 (0.87)	118	0.61 (0.83)
Computed tomography scan	Number of tests	104	0.16 (0.48)	118	0.16 (0.49)
Transthoracic echocardiography	Number of tests	104	0.42 (0.66)	118	0.56 (0.79)
Transesophageal echocardiography	Number of tests	104	0.02 (0.20)	118	0.05 (0.19)
Stress echocardiography	Number of tests	104	0.01 (0.10)	118	0.01 (0.09)
24-h electrocardiography	Number of tests	104	0.13 (0.41)	118	0.16 (0.44)
12-h electrocardiography	Number of tests	104	0.72 (0.85)	118	0.94 (1.17)
Exercise tolerance test	Number of tests	104	0.07 (0.24)	118	0.06 (0.23)
Magnetic resonance imaging	Number of tests	104	0.02 (0.15)	118	0.06 (0.22)
Full pulmonary function testing	Number of tests	104	0.06 (0.22)	118	0.03 (0.16)
Blood testing	Number of tests	104	0.06 (0.21)	118	0.07 (0.33)
Accident and emergency visit	Number of visits	104	0.13 (0.31)	118	0.24 (0.50)
Arrhythmia clinic	Number of visits	104	0.02 (0.14)	118	0.00 (0.00)
Cardiac rehabilitation	Number of visits	104	1.07 (2.78)	118	0.34 (1.36)
Cardiology clinic	Number of visits	104	0.47 (0.62)	118	0.52 (0.72)
General practitioner home visits	Number of visits	104	0.27 (0.64)	118	0.25 (0.68)
General practitioner visits	Number of visits	104	2.00 (2.16)	118	2.17 (2.18)
Nurse (specialist community) home visits	Number of visits	104	0.38 (1.06)	118	0.47 (1.22)
Nurse (general practice) visits	Number of visits	104	1.93 (8.83)	118	0.71 (1.32)
Occupational therapy	Number of visits	104	0.15 (0.70)	118	0.05 (0.55)
Pacemaker	Number of visits	104	0.06 (0.59)	118	0.08 (0.39)
Physiotherapy (home)	Number of visits	104	0.05 (0.32)	118	0.00 (0.00)
Physiotherapy	Number of visits	104	0.05 (0.20)	118	0.02 (0.11)
Wound clinic	Number of visits	104	0.06 (0.28)	118	0.03 (0.15)

SD, Standard deviation. *Discharged to convalescence/long-term care/acute hospital instead of home.

TABLE E21. Summary of deterministic sensitivity and scenario analyses undertaken

Sensitivity analyses	Rationale
Complete-case analysis	Including only respondents with no missing values across all variables and across follow-up; results in sample requiring no missing value imputation
Excluding patients who died during primary admission	Patients who died during primary admission were the main cost driver and required substantial surgical time and cardiac care to assess whether excluding these patients would change recommendations.
Excluding additional equipment cost required	Assuming that the additional equipment required for the surgeries already exists in the trusts.
Excluding follow-up resource use	To test the assumption that the cost difference between the two arms were accrued during primary admission, to allow comparison with literature that missed these costs, but still retain benefits as captured in other studies
Excluding follow-up resource use and utility data	Data up to discharge had few missing values; also to assess impact of having a shorter cutoff time point for trial (as wider literature had) but provide a less biased analysis that measures benefits but not costs.
Use SF-6D utility values	SF-6D values used as an alternative construction for QALYs

SF-6D, Short-Form Six-Dimension; *QALY*, quality-adjusted life-year.

TABLE E22. Costs per patient up to 12 months postrandomization (with imputation), 2015

		Full sternotomy		Mini-sternotomy	
Parameter	Mean unit cost, £	Observations	Mean (SD) cost per patient, £	Observations	Mean (SD) cost per patient, £
Primary admission costs					
Additional surgical items					
Horizontal surgical saw	3138.2	104	0.0 (0.0)	118	3.1 (0.0)
Single-use saw blade for mini-sternotomy	48.0	104	0.0 (0.0)	118	48.0 (0.0)
Single-use saw blade for full sternotomy	15.8	104	15.8 (0.0)	118	0.0 (0.0)
Pediatric internal cardioversion paddles	161.7	104	0.0 (0.0)	118	0.2 (0.0)
Reprocessing defibrillator paddles for each surgery	2.4	104	2.4 (0.0)	118	2.4 (0.0)
Internal paddle handle	670.0	104	0.0 (0.0)	118	0.7 (0.0)
Cost of additional surgical items*		104	16.52 (0.0)	118	52.0 (0.0)
Theatre	20.0	104	3823.8 (1243.0)	118	4422.2 (2053.0)
Critical care (intensive therapy unit)	1274.9	104	1833.8 (3023.2)	118	2934.2 (5029.9)
Cardiac ward	388.0	104	2743.7 (1664.0)	118	2676.3 (1499.9)
Rehabilitation†	158.6	104	384.2 (1877.6)	118	263.4 (1621.3)
Acute hospital†	388.0	104	346.9 (1918.9)	118	297.5 (1971.3)
Physiotherapy (inpatient)	12.7	104	74.5 (53.2)	118	75.2 (65.3)
Occupational therapy (inpatient)	12.7	104	2.1 (7.3)	118	3.0 (8.7)
Subtotal (primary admission)	–	104	9225.7 (6510.8)	118	10,723.9 (8850.2)
Post-primary admission costs					
Hospital admission					
Intensive therapy unit	1274.9	104	0.0 (0.0)	118	32.4 (352.1)
General ward	103.0	104	268.4 (1395.4)	118	79.4 (329.5)
Cardiac ward	388.0	104	149.2 (554.8)	118	463.6 (1606.4)
Tests					
24-h blood pressure monitoring	61.5	104	10.9 (32.0)	118	10.2 (69.5)
Radiography (chest)	3.5	104	19.4 (30.9)	118	21.6 (29.5)
Computed tomography scan	122.3	104	19.4 (58.6)	118	19.7 (59.8)
Transthoracic echocardiography	83.9	104	35.1 (55.2)	118	46.9 (66.6)
Transesophageal echocardiography	128.5	104	2.5 (25.2)	118	6.5 (24.3)
Stress echocardiography	128.5	104	1.2 (12.6)	118	1.1 (11.8)
24-h electrocardiography	140.7	104	18.3 (57.2)	118	22.7 (62.3)
12-h electrocardiography	140.7	104	101.5 (119.6)	118	132.9 (165.0)
Exercise tolerance test	140.7	104	9.5 (34.0)	118	8.9 (32.6)
Magnetic resonance imaging	146.2	104	3.5 (21.3)	118	9.3 (32.5)
Full pulmonary function testing	55.3	104	3.2 (12.4)	118	1.6 (9.1)
Blood tests	3.5	104	0.0 (0.1)	118	0.0 (0.1)

(Continued)

TABLE E22. Continued

Parameter	Mean unit cost, £	Full sternotomy Observations	Full sternotomy Mean (SD) cost per patient, £	Mini-sternotomy Observations	Mini-sternotomy Mean (SD) cost per patient, £
Health care visits					
Accident and emergency visit	140.6	104	18.9 (43.0)	118	33.4 (70.4)
Arrhythmia clinic	131.1	104	2.5 (18.1)	118	0.0 (0.0)
Cardiac rehabilitation	97.8	104	104.4 (271.9)	118	33.6 (133.4)
Cardiology clinic	123.0	104	57.4 (76.3)	118	63.6 (88.1)
General practitioner home visits	45.0	104	12.1 (28.9)	118	11.3 (30.4)
General practitioner visits	65.0	104	129.7 (140.6)	118	141.3 (141.8)
Nurse (specialist community) home visits	19.4	104	7.3 (20.6)	118	9.0 (23.6)
Nurse (general practice) visits	14.5	104	28.0 (127.7)	118	10.3 (19.2)
Occupational therapy (outpatient)	16.7	104	2.5 (11.7)	118	0.8 (9.2)
Pacemaker	76.3	104	4.4 (44.9)	118	6.1 (29.5)
Physiotherapy (home)	27.0	104	1.4 (8.6)	118	0.0 (0.0)
Physiotherapy (outpatient)	16.1	104	0.8 (3.4)	118	0.3 (1.9)
Wound clinic	54.9	104	3.4 (15.2)	118	1.6 (8.3)
Subtotal (post-primary admission)	–	104	1014.9 (1777.5)	118	1168.2 (2077.9)
Drugs (total)	–	104	379.4 (548.2)	118	441.4 (976.7)
Total cost	–	104	10,620.0 (7623.8)	118	12,333.5 (9864.2)

SD, Standard deviation. *Mean cost per patient estimated by assuming that the saw, paddle, and handle have a 20-year life span and are used in 255 surgeries over a 5-year period. Defibrillator (paddle, handle and sterilization) cost applicable in only 30% of cases. †Discharged to convalescence/long-term care/acute hospital instead of home.

TABLE E23. Summary of utility values and QALYs

Test	Full sternotomy Observations	Full sternotomy Mean (SD) utility	Mini-sternotomy Observations	Mini-sternotomy Mean (SD) utility
EQ-5D				
Baseline	104	0.6988 (0.24)	118	0.7793 (0.18)
4 d postoperation	104	0.3721 (0.29)	118	0.4430 (0.28)
Discharge	104	0.5815 (0.23)	118	0.5940 (0.25)
6-wk follow-up	104	0.6930 (0.21)	118	0.7195 (0.24)
6-mo follow-up	104	0.8272 (0.22)	118	0.8322 (0.24)
12-mo follow-up	104	0.7584 (0.29)	118	0.8253 (0.29)
EQ-5D QALYs	104	0.7699 (0.19)	118	0.7978 (0.21)
SF-6D				
Baseline	104	0.6418 (0.11)	118	0.6802 (0.12)
6-wk follow-up	104	0.6327 (0.10)	118	0.6356 (0.14)
6-mo follow-up	104	0.7184 (0.16)	118	0.7332 (0.19)
12-mo follow-up	104	0.6868 (0.19)	118	0.7058 (0.23)
SF-6D QALYs	104	0.6847 (0.12)	118	0.6989 (0.16)

SD, Standard deviation; *QALY*, quality-adjusted life-years; *SF-6D*, Short-Form Six-Dimension.

TABLE E24. Comparison of costs and QALYS (raw data, with imputation)

Parameter	Full sternotomy (n = 104)	Mini-sternotomy (n = 114)
Total costs over 12 mo, £, mean (SD)	10,620 (7624)	12,334 (9864)
Incremental cost at 12 mo (MS-FS), £		1714
Total EQ-5D 3L QALYs, mean (SD)	0.7699 (0.19)	0.7978 (0.21)
Incremental EQ-5D 3L QALYs (MS-FS)		0.0279
ICER, £		61,379
INMB at WTP of £20,000/QALY, £		−1155
INMB at WTP of £30,000/QALY, £		−876

SD, Standard deviation; *MS*, mini-sternotomy; *FS*, full sternotomy; *QALY*, quality-adjusted life-year; *ICER*, incremental cost-effectiveness ratio; *INMB*, incremental net monetary benefit; *WTP*, willingness to pay.

TABLE E25. Regression estimates of costs and QALYs

Dependent variable	Coefficient	SE	*P* value	95% CI
EQ-5D QALYs				
Mini-sternotomy	−0.0040	0.0245	.87	−0.0520 to 0.0440
Male sex	0.0250	0.0246	.31	−0.0231 to 0.0732
Age	−0.0051	0.0014	.00	−0.0078 to −0.0024
Baseline EQ-5D score	0.3037	0.0590	.00	0.1880 to 0.4194
Tissue valve	0.0794	0.0459	.08	−0.0107 to 0.1694
Constant	0.7391	0.1093	.00	0.5249 to 0.9533
Total cost (£)				
Mini-sternotomy	2010.22	1201.57	.09	−344.82 to 4365.25
Male sex	−1275.52	1205.23	.29	−3637.73 to 1086.70
Age	98.32	67.58	.15	−34.13 to 230.77
Baseline EQ-5D score	−983.50	2896.40	.73	−6660.34 to 4693.33
Tissue valve	−853.43	2254.14	.71	−5271.45 to 3564.60
Constant	5704.71	5362.01	.29	−4804.64 to 16,214.06

SE, Standard error; *CI*, confidence interval; *QALY*, quality-adjusted life-year.

TABLE E26. Deterministic sensitivity analysis using difference MS-FS, adjusted for baseline

Parameter	Obs	Incremental cost over 12 months (MS-FS), £, mean (SE)	Incremental QALYs over 12 months (MS-FS), £, mean (SE)	ICER, £	INMB at £20,000 per QALY, £	INMB at £30,000 per QALY, £
Missing values imputed by PMM	222	2010 (1202)	−0.0040 (0.0245)	Dominated	−2089.26	−2128.78
Using SF-6D QALYs	222	2010 (1202)	−0.0017 (0.0178)	Dominated	−2044.44	−2061.55
Assuming there is no additional equipment required for the 2 procedures	222	1975 (1202)	−0.0040 (0.0245)	Dominated	−2053.73	−2093.26
Excluding follow-up resource use	222	1664 (1060)	−0.0040 (0.0245)	Dominated	−1742.98	−1782.50
Complete-case analysis	90	−150 (661)	−0.0145 (0.0334)	10,333.62	−139.89	−284.60
Excluding patients who died during primary admission	219	1408 (1128)	0.0172 (0.0216)	81,905.62	−1064.40	−892.46
Including costs and QALY data only up to discharge	222	1664 (1060)	0.0013 (0.0009)	1,316,409.02	−1638.66	−1626.02

Obs, Observed number of patients; *MS*, mini-sternotomy; *FS*, full sternotomy; *SE*, standard error; *QALY*, quality-adjusted life-year; *ICER*, incremental cost-effectiveness ratio; *INMB*, incremental net monetary benefit; *PMM*, predictive mean matching; *SF-6D*, Short-Form Six-Dimension.

TABLE E27. Probabilistic sensitivity analysis using difference MS-FS, adjusted for baseline

Parameter	Obs	Incremental cost over 12 months (MS-FS), £, mean (SE)	Incremental QALYs over 12 months (MS-FS), £, mean (SE)	ICER, £	INMB at £20,000, £	INMB at £30,000, £
Missing values imputed by PMM and adjusted	1000	2154 (36)	−0.0122 (0.0008)	Dominated	−2396.99	−2518.59
Using SF-6D QALYs	1000	2154 (36)	−0.0075 (0.0006)	Dominated	−2303.03	−2377.66
Assuming there is no additional equipment required for the two procedures	1000	2245 (40)	−0.0096 (0.0008)	Dominated	−2437.25	−2533.50
Excluding follow-up resource use	1000	1835 (35)	−0.0131 (0.0008)	Dominated	−2096.58	−2227.15
Complete-case analysis	1000	−111 (22)	−0.0121 (0.0011)	9170.78	−130.56	−251.12
Excluding patients who died during primary admission	1000	1433 (32)	0.0147 (0.0007)	97,425.25	−1138.55	−991.50
Including costs and QALY data only up to discharge	1000	1835 (35)	0.0008 (0.0000)	2,415,384.92	−1820.25	−1812.65

Obs, Observed number of patients; *MS*, mini-sternotomy; *FS*, full sternotomy; *SE*, standard error; *QALY*, quality-adjusted life-year; *ICER*, incremental cost-effectiveness ratio; *INMB*, incremental net monetary benefit; *PMM*, predictive mean matching; *SF-6D*, Short-Form Six-Dimension.