Off-pump injectable versus on-pump conventional tissue valves for pulmonary valve replacement: the injectable valve implantation randomised trial (INVITE)

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ABSTRACT

Objectives To assess the effectiveness of injectable tissue pulmonary valve compared with standard pulmonary valve in patients requiring pulmonary valve replacement surgery.

Design A multicentre, single-blind, parallel two-group randomised controlled trial. Participants were blind to their allocation. Follow-up continued for 6 months. Randomised allocations were generated by a computer using block randomisation, stratified by centre.

Setting Two National Health Service secondary care centres in the UK.

Participants People aged 12–80 years requiring pulmonary valve replacement.

Interventions Participants were randomly allocated (1:1 ratio) to injectable pulmonary valve replacement (IPVR) without cardiopulmonary bypass (CPB) or standard pulmonary valve replacement (SPVR) with CPB.

Primary and secondary outcome measures The primary outcome was chest drainage volume over the first 24 hours after surgery. Secondary outcomes included in-hospital clinical outcomes; valve and heart function 6 months postsurgery and health-related quality of life 6 weeks and 6 months postsurgery.

Results Nineteen participants agreed to take part. Eleven were allocated to IPVR and eight to SPVR. The trial was stopped before the target sample size of 60 participants was reached due to challenges in recruitment. The primary analysis includes all randomised participants; there were no withdrawals. Chest drain volume 24 hours after surgery was on average 277.6 mL lower with IPVR (IPVR mean 340.0 mL; SPVR mean 633.8 mL; mean difference, −277.6; 95% CI, −484.0 to −71.2; p=0.005). There were no statistically significant differences in time to readiness for extubation (p=0.476), time to fitness for discharge (p=0.577) and time to first discharge from the intensive care unit (p=0.209). Six participants with IPVR required CPB. Safety profiles and quality of life scores were similar.

Conclusions IPVR reduced chest drain volume despite >50% of participants requiring CPB. There was no evidence of any other benefit of IPVR.

Trial registration number ISRCTN23538073.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Wide inclusion criteria, including children and adults (aged 12–80 years) to promote the applicability of the findings to a wide group of patients requiring pulmonary valve replacement.

⇒ Primary and secondary outcomes are objective clinical outcomes, important to patients, clinical teams and the National Health Service.

⇒ Procedures and data collection were standardised to minimise bias, although it was not possible to blind clinicians to treatment allocation.

⇒ Recruitment was terminated early after only 19 participants had been recruited so the primary outcome analysis was under powered and the study results should be treated with caution.

INTRODUCTION

Most children born with complex congenital heart disease (CHD) now reach adulthood due to advances in cardiac surgery and cardiology. Consequently, there are now more adults than children living with CHD. Many CHD patients require multiple operations throughout their lives to repair or replace poorly functioning pulmonary valves. The risk of major cardiac surgery increases with each operation and these patients suffer cumulative iatrogenic harm to the heart from repeated exposure to cardiopulmonary bypass (CPB) and cardioplegic myocardial arrest. Therefore, it is important to seek ways to minimise the harm from multiple operations.

‘Injectable’ self-expanding pulmonary tissue valves (BioPulmonic, Biointegral Surgical Inc (IPVs)) can be implanted without using CPB (off-pump) and with

In adults with poorly functioning pulmonary valves, surgical options include valve replacement and valve repair. The most conventional method of valve replacement is on-pump cardiac surgery with cardiopulmonary bypass (CPB) and cardioplegic myocardial arrest. This approach is associated with an increased risk of adverse events and complications and requires a longer period of recovery compared with surgery to replace or repair aortic and mitral valves. Furthermore, each operation and these patients suffer cumulative iatrogenic harm to the heart from repeated exposure to cardiopulmonary bypass (CPB) and cardioplegic myocardial arrest. Therefore, it is important to seek ways to minimise the harm from multiple operations.

‘Injectable’ self-expanding pulmonary tissue valves (BioPulmonic, Biointegral Surgical Inc (IPVs)) can be implanted without using CPB (off-pump) and with
minimal dissection around the heart through a median sternotomy. IPVs can always be implanted, whereas valves implanted percutaneously cannot always be used, for example, due to dilated right ventricular outlet tract (RVOT). Pulmonary valve replacement with a standard tissue valve (SPV) requires CPB (on-pump), often cardiopulmonary arrest and extensive heart dissection.

Case reports and small pilot studies have reported that IPVs are easy to implant and have satisfactory function. However, when the Injectable Valve Implantation Trial (INVITE) was conducted, no randomised controlled trial (RCT) had been conducted to evaluate valve replacement with IPV. We report the results of the first RCT comparing the effectiveness of IPVs with SPVs.

MATERIALS AND METHODS

Trial design
INVITE was conducted in two National Health Service (NHS) secondary care centres in the UK. Participants were randomly allocated to receive either standard pulmonary valve replacement (SPVR) with CPB or injectable pulmonary valve replacement (IPVR) without CPB in a 1:1 ratio. The protocol has been published elsewhere. We intended that at least two centres would take part.

Participants
Participants aged 12–80 years old undergoing pulmonary valve replacement (PVR), PVR with Atrial Septal Defect amenable to closure via cardiac catheter or PVR and RVOT reconstruction not requiring CPB were eligible for the trial. The required pulmonary valve annulus had to be at least adult size (25–31 mm). Patients requiring other anatomical heart corrections requiring CPB (including RVOT reconstruction) or an intracardiac shunt repair requiring CPB were excluded. Patients, or their parents/guardians if aged under 16 years, provided written informed consent; children aged 12–15 years provided written assent.

Interventions
Eligible patients were randomised to either IPVR using an IPV (No-React Injectable BioPulmonic Valve; Biointegral Surgical) without CPB or SPVR using a stented SPV with CPB; both procedures were carried out through a median sternotomy. Participating surgeons were required to complete the first two cases with an experienced surgeon assisting for training purposes (online supplemental material 1).

For IPVR, the main pulmonary artery and front of the heart were dissected. A purse-string stitch was placed in the front of the infundibulum. The size of valve required was measured using an echocardiogram as the diameter of the main pulmonary artery (the IPV sits in the main pulmonary artery). If the main pulmonary artery was too big, it was made smaller using a stitch to plicate it. Having loaded the valve, the valve injector was inserted into the heart through the purse-string and the valve was deployed, then fixed into position using three fixation stitches. If the patient became unstable during surgery, CPB was instituted. The position and function of the valve was confirmed using transoesophageal echocardiography.

For SPVR, the heart was freed from scar tissue and CPB was started. The pulmonary artery was opened and the old valve removed. A new valve of the correct size was sewn into place, arresting the heart for a short period of time if necessary. A patch was used to close the heart over the new valve if necessary. CPB was discontinued when the heart had recovered from the effects of cardiopulmonary arrest. Other aspects of both procedures were completed in a standard manner. Participating sites used their locally agreed anticoagulation practices. All other aspects of participants’ care was performed according to standard practices in the hospital.

Outcomes
The primary outcome was postoperative blood loss (measured by chest drainage volume) in the first 24 postoperative hours. This outcome was chosen because it is objective (important since the care team could not be blind to allocation), measured as a continuous scaled quantity (requiring a smaller sample size than a binary outcome) and was considered to represent an important clinical benefit that could be clearly attributable to IPVR.

Secondary outcomes were prespecified and included postoperative time to ‘readiness for extubation’; duration of intensive care unit (ICU) stay; use of inotropic/vasodilator support; chest drain volume in the first 12 hours; blood products used in the first 24 hours; time to meet prespecified ‘fitness for discharge’ criteria; cardiac MRI assessment of the presence and degree of pulmonary regurgitation, end-diastolic volume and right ventricular ejection fraction at 6 months; echocardiography assessment of the presence and degree of pulmonary regurgitation and residual valve stenosis at 6 months; occurrence of valve-related complications during follow-up and health-related quality of life at 6 weeks and 6 months measured by EuroQol EQ-5D (or EQ-5D-Y in patients <18 years), SF36 (in patients >18 years) and child health questionnaires (CHQ, in patients <18 years), posted to participants. Criteria for classification as ‘fit for discharge’ (all had to be satisfied) were temperature, pulse, respiratory rate, oxygen saturation on air, white blood count, CRP within normal ranges and bowel function and physical mobility back to preoperative level.

Adverse events and reactions were recorded throughout the 6-month follow-up period. Serious adverse events (SAEs) after hospital discharge were collected by postal questionnaire at 6 weeks and 6 months. Unexpected SAEs were coded using the Medical Dictionary for Regulatory Activities (V.14.1; McLean, VA, USA).

Randomisation and blinding
Blocked randomised allocations were generated by a computer and stratified by centre before starting the trial. A research nurse randomised participants as close
to the planned operation as possible using an internet-based system, which only disclosed the treatment allocation after sufficient details had been entered to confirm eligibility and consent.

Participants and their parents/guardians were blind to allocation, the success of which was monitored at the 6 weeks and 6 months follow-up. It was not possible to blind the patient’s care team to allocation.

MRI and echocardiography data were recorded and analysed by researchers who were blind to allocation.

**Statistical methods**

A total target sample size of 60 was required to detect an approximate 50% reduction in chest drainage volume (effect size on logarithmic scale of −0.73) over the first 24 hours with 80% power and at a 5% significance level (two-tailed). The statistical analysis plan (SAP), written in advance of any analyses prespecified that formal statistical comparisons of treatment effects would only be made for the following outcomes: chest drainage volume in the first 24 hours postsurgery (primary outcome), time to readiness for extubation, time to first ICU discharge and time to fitness for discharge. The remaining secondary outcomes are described by treatment group only.

All analyses were performed on an intention-to-treat basis and directed by the SAP. Continuous data are summarised using mean and SD or median and IQR if distributions were skewed and categorical data as number and percentage. Chest drainage volume (primary outcome) was compared using linear regression (adjusted for centre fitted as a fixed effect) and time-to-event outcomes compared using Cox proportional hazards models (stratified by centre). For time to readiness for extubation, date/time extubated was analysed if date/time ready for extubation was not recorded. In the analysis of time to fitness for discharge, patients were censored on date of discharge if they were discharged prior to fitness for discharge criteria being met. A post-hoc sensitivity analysis was performed for the primary outcome after initial review of the data, adjusting for participant age and sex. Model fit was assessed and assumptions checked (including normal distribution of residuals for linear regression and proportional hazards assumption for time to event outcomes) using standard methods and transformations were performed or alternative methods sought if model fit was inadequate or model assumptions were not met. All analyses used the SPVR group as the reference group. Outcomes are reported as effect sizes with 95% CI and likelihood ratio tests were used to determine statistical significance. Adverse event frequencies were tabulated descriptively. All analyses were performed in Stata V.16.0 (StataCorp, LP, College Station, TX, USA).

**Public and patient involvement**

Members of the NIHR Bristol Biomedical Research Centre Patient Advisory Group were involved in the review of study materials to ensure suitability. In addition, trial results and dissemination plans were reviewed by the Young Persons Advisory Group, Parents Advisory Group and Patient Advisory Group.

**RESULTS**

**Recruitment**

Between April 2016 and October 2018, 80 patients at University Hospitals Bristol and Weston NHS Foundation Trust and University Hospital Southampton NHS Foundation Trust were screened for inclusion in the trial. Thirty-two (40.0%) were ineligible. Thirty-four of 48 eligible patients screened were approached. Nineteen consented to participate and were randomised; 8 (42.1%) were allocated to SPVR and 11 (57.9%) to IPVR (figure 1). Of the 19 randomised participants, 15 were 16 years or older (8 SPVR, 7 IPVR). The Trial Steering Committee recommended that recruitment must stop before reaching the target sample size because it was not feasible to reach the target during the period for which funding was available (full recruitment was estimated to require another 5 years).

The analysis of the primary outcome includes all randomised participants. There were nine protocol deviations: four patients did not receive cell saver set up (two SPVR and two IPVR) and five patients (all IPVR) were unblinded to treatment allocation (online supplemental table 1). Safety data and health status questionnaires were available for 18 of 19 participants at 6 weeks and for all participants at 6 months. Two participants did not have 6 month echocardiography or MRI data available (both IPVR).

**Baseline data**

By chance, participants allocated to IPVR were younger (median age, 23.6 vs 29.7 years), included fewer males (45.5% vs 75.0%) and were less likely to have a family history of cardiac disorders (9.1% vs 50.0%) than participants allocated to SPVR (table 1—baseline and intraoperative characteristics).

**Operative and postoperative details**

Intraoperative characteristics by treatment allocation are presented in table 1—baseline and intraoperative characteristics and online supplemental table 2. Approximately half of all participants received intraoperative inotropes/vasodilators. CPB was instituted in 6/11 (54.5%) participants in the IPVR group; reasons for instituting CPB are described in the footnote of table 1—baseline and intraoperative characteristics.

Postoperative details including blood results and reoperations are presented in online supplemental table 3 and postoperative echocardiographic and MRI assessments are presented in online supplemental table 4 and table 5 respectively.

**Primary outcome**

Chest drain volume in the first 24 hours postsoperative was lower in the IPVR group (mean 340.0 (SD 167.3) in the
Assessed for eligibility (n=80)
(64 adults, 16 paediatrics)

Patients excluded (n=61: 49 adults, 12 paediatrics):

Ineligible (n=32: 27 adults, 5 paediatrics): 1
Patient is not aged 12-80 years with an adult size valve (n=4), Patient is not undergoing one of the following: a) PVR b) PVR with ASD which is amenable to closure via cardiac catheter c) PVR with RVOT reconstruction that does not require CPB is using an injectable valve (n=6), Patient is a prisoner or adult lacking capacity to consent (n=3), Patient has pulmonary valve or artery stenosis requiring patch reconstruction of the pulmonary arteries using CPB (n=12), Patient having an intra-cardiac shunt that would require CPB despite using an injectable valve (n=2), Patient has a RVOT reconstruction that would require CPB despite using an injectable valve (n=11), Patient requires other anatomical heart corrections that would require CPB despite using an injectable valve (n=8) Patient has active endocarditis (n=3), Patient unable to give assent/consent (n=3)

PIL not sent (n=5: 3 adults, 2 paediatrics):
Consultant decision (n=2), Different consultant (n=1), Not an NXY patient (n=1), Surgeon not yet trained in procedure (n=1)

Not approached (n=9: 5 adults, 4 paediatrics):
Surgeon not yet trained in procedure (n=2), Patient not keen (n=1), No longer on list for cardiac surgery (n=1), Poor command of English (n=1), Trial ended (n=1), Discussed by cardiologist at clinic and decided to go for standard care (n=1), Family did not wish to take part (n=1), No trained surgeon available on original listed date (n=1)

Did not consent (n=15: 14 adults, 1 paediatric):
Wants standard care (n=4), Not interested (n=4), Personal reasons (n=3), No reason given (n=2), Trial now closed to recruitment (n=2)

Randomised (n=19)
(15 adults, 4 paediatrics)

Allocated to SPVR (n=8):
(8 adults, 0 paediatrics)
Withdrawals pre-surgery
Deaths pre-surgery (n=0)
Underwent surgery and included in analysis population (n=8)
Number of protocol deviations: 2 (in 2 patients)
Withdrawals post-surgery
Deaths post-surgery (n=0)

6-week follow up
QoL questionnaire completed (n=8)

6-month follow up
MRI (n=8)
Echo (n=8)
QoL questionnaire (n=8)

Allocated to IPVR (n=11):
(7 adults, 4 paediatrics)
Withdrawals pre-surgery
Deaths pre-surgery (n=0)
Underwent surgery and included in analysis population (n=11)
Number of protocol deviations: 7 (in 6 patients)
Withdrawals post-surgery
Deaths post-surgery (n=0)

6-week follow up
QoL questionnaire completed (n=10)

6-month follow up
MRI (n=9)
Echo (n=9)
QoL questionnaire (n=11)

Figure 1  CONSORT diagram showing patient flow through the study. 1 Some patients may be ineligible for more than one reason. ASD, atrial septal defect; CONSORT, Consolidated Standards of Reporting Trials; CPB, cardiopulmonary bypass; Echo, echocardiography; IPVR, injectable pulmonary valve replacement; PIL, patient information leaflet; QoL, quality of life; RVOT, right ventricular outflow tract; SPVR, standard pulmonary valve replacement.
### Table 1  Baseline and intraoperative characteristics

<table>
<thead>
<tr>
<th></th>
<th>Randomised to SPVR (n=8)</th>
<th>Randomised to iPVR (n=11)</th>
<th>Overall (n=19)</th>
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<tbody>
<tr>
<td><strong>Baseline characteristics</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Age at randomisation (years)</td>
<td>29.7 (21.3, 36.2)</td>
<td>23.6 (14.4, 43.7)</td>
<td>25.8 (18.0, 39.3)</td>
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<td>Sex</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
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<tr>
<td>Body Mass Index</td>
<td>26.7 (7.2)</td>
<td>22.6 (4.7)</td>
<td>24.3 (6.0)</td>
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<tr>
<td>NYHA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>3/8 (37.5%)</td>
<td>2/11 (18.2%)</td>
<td>5/19 (26.3%)</td>
</tr>
<tr>
<td>II</td>
<td>3/8 (37.5%)</td>
<td>7/11 (63.6%)</td>
<td>10/19 (52.6%)</td>
</tr>
<tr>
<td>III</td>
<td>2/8 (25.0%)</td>
<td>2/11 (18.2%)</td>
<td>4/19 (21.1%)</td>
</tr>
<tr>
<td><strong>Heart rhythm</strong></td>
<td></td>
<td></td>
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<tr>
<td>Sinus rhythm</td>
<td>6/8 (75.0%)</td>
<td>10/11 (90.9%)</td>
<td>16/19 (84.2%)</td>
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<tr>
<td>Heart block</td>
<td>1/8 (12.5%)</td>
<td>0/11 (0.0%)</td>
<td>1/19 (5.3%)</td>
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<tr>
<td>Atrial fibrillation/flutter</td>
<td>0/8 (0.0%)</td>
<td>1/11 (9.1%)</td>
<td>1/19 (5.3%)</td>
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<tr>
<td>Sinus Bradycardia</td>
<td>1/8 (12.5%)</td>
<td>0/11 (0.0%)</td>
<td>1/19 (5.3%)</td>
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<tr>
<td><strong>Bloods</strong></td>
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<tr>
<td>Haemoglobin (g/L)</td>
<td>146.6 (10.6)</td>
<td>138.4 (12.1)</td>
<td>141.8 (11.9)</td>
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<td>Platelets (x10^9/L)</td>
<td>251.0 (51.4)</td>
<td>256.8 (77.7)</td>
<td>254.4 (66.2)</td>
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<tr>
<td>Creatinine (µmol/L)</td>
<td>80.5 (12.7)</td>
<td>71.7 (20.5)</td>
<td>75.4 (17.8)</td>
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<td><strong>Cardiac condition</strong></td>
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<tr>
<td>PA/IVS</td>
<td>1/8 (12.5%)</td>
<td>0/11 (0.0%)</td>
<td>1/19 (5.3%)</td>
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<td>DORV</td>
<td>0/8 (0.0%)</td>
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<td>2/19 (10.5%)</td>
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<td>PA/VSD</td>
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<td>Pulmonary stenosis</td>
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<td>2/11 (18.2%)</td>
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<tr>
<td>Tetralogy of fallot</td>
<td>4/8 (50.0%)</td>
<td>7/11 (63.6%)</td>
<td>11/19 (57.9%)</td>
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<td>Other*</td>
<td>1/8 (12.5%)</td>
<td>2/11 (18.2%)</td>
<td>3/19 (15.8%)</td>
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<tr>
<td><strong>O₂ saturations (%)</strong></td>
<td>98.9 (1.4)</td>
<td>98.1 (1.6)</td>
<td>98.4 (1.5)</td>
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<td><strong>Medical history</strong></td>
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<tr>
<td>Chronic pulmonary disease</td>
<td>0/8 (0.0%)</td>
<td>1/11 (9.1%)</td>
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<td>Previous cardiac surgery</td>
<td>8/8 (100.0%)</td>
<td>10/11 (90.9%)</td>
<td>18/19 (94.7%)</td>
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<td>Family history (cardiac)</td>
<td>4/8 (50.0%)</td>
<td>1/11 (9.1%)</td>
<td>5/19 (26.3%)</td>
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<td>Pulmonary hypertension</td>
<td>0/8 (0.0%)</td>
<td>1/11 (9.1%)</td>
<td>1/19 (5.3%)</td>
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<tr>
<td>Neurological dysfunction</td>
<td>0/8 (0.0%)</td>
<td>0/11 (0.0%)</td>
<td>0/19 (0.0%)</td>
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<td>Renal dysfunction</td>
<td>1/8 (12.5%)</td>
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<td>Smoking</td>
<td>No</td>
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<td>Ex-smoker (&gt;1 month)</td>
<td>0/8 (0.0%)</td>
<td>1/11 (9.1%)</td>
<td>1/19 (5.3%)</td>
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<tr>
<td>Yes</td>
<td>2/8 (25.0%)</td>
<td>0/11 (0.0%)</td>
<td>2/19 (10.5%)</td>
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<td><strong>Drugs on admission</strong></td>
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<tr>
<td>Heparin/lexane†</td>
<td>0/8 (0.0%)</td>
<td>0/7 (0.0%)</td>
<td>0/15 (0.0%)</td>
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<td>Antiarrhythmic†</td>
<td>0/8 (0.0%)</td>
<td>0/7 (0.0%)</td>
<td>0/15 (0.0%)</td>
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<td>Diuretics†</td>
<td>0/8 (0.0%)</td>
<td>1/7 (14.3%)</td>
<td>1/15 (6.7%)</td>
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<td>Amiodarone†</td>
<td>0/6 (0.0%)</td>
<td>0/7 (0.0%)</td>
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<tr>
<td>PPIs†</td>
<td>0/8 (0.0%)</td>
<td>0/7 (0.0%)</td>
<td>0/15 (0.0%)</td>
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<td>Aspirin</td>
<td>0/8 (0.0%)</td>
<td>0/11 (0.0%)</td>
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<td>Warfarin</td>
<td>1/8 (12.5%)</td>
<td>1/11 (9.1%)</td>
<td>2/19 (10.5%)</td>
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<td>ACE inhibitors</td>
<td>2/8 (25.0%)</td>
<td>1/11 (9.1%)</td>
<td>3/19 (15.8%)</td>
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<td>Angiotensin 11 blockers</td>
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<td>Sildenafil</td>
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<tr>
<td>Other†</td>
<td>5/8 (62.5%)</td>
<td>3/11 (27.3%)</td>
<td>8/19 (42.1%)</td>
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<tr>
<td><strong>Preop echocardiographic assessment</strong></td>
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<tr>
<td>LV function</td>
<td>Good</td>
<td>4/8 (50.0%)</td>
<td>10/11 (90.9%)</td>
</tr>
<tr>
<td>Mildly impaired</td>
<td>4/8 (50.0%)</td>
<td>1/11 (9.1%)</td>
<td>5/19 (26.3%)</td>
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<tr>
<td>RV function</td>
<td>Good</td>
<td>5/8 (62.5%)</td>
<td>8/11 (72.7%)</td>
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<tr>
<td>Mildly impaired</td>
<td>1/8 (12.5%)</td>
<td>3/11 (27.3%)</td>
<td>4/19 (21.1%)</td>
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Table 1 Continued

<table>
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<tr>
<th></th>
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<th>Randomised to IPVR (n=11)</th>
<th>Overall (n=19)</th>
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<tbody>
<tr>
<td>Intraoperative characteristics</td>
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<tr>
<td>Bypass data</td>
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<td></td>
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<tr>
<td>Bypass required§</td>
<td>8/8 (100.0%)</td>
<td>6/11 (54.5%)</td>
<td>14/19 (73.7%)</td>
</tr>
<tr>
<td>If yes: myocardial protection</td>
<td>5/7 (71.4%)</td>
<td>2/6 (33.3%)</td>
<td>7/13 (53.8%)</td>
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<tr>
<td>None</td>
<td>2/7 (28.6%)</td>
<td>4/6 (66.7%)</td>
<td>6/13 (46.2%)</td>
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<tr>
<td>Inotropes/vasodilators (intraoperative)</td>
<td>4/8 (50.0%)</td>
<td>5/11 (45.5%)</td>
<td>9/19 (47.4%)</td>
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</table>

Operative details

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<thead>
<tr>
<th></th>
<th>SPVR (n=8)</th>
<th>IPVR (n=11)</th>
<th>Overall (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main pulmonary artery modified</td>
<td>Plicated</td>
<td>2/8 (25.0%)</td>
<td>4/11 (36.4%)</td>
</tr>
<tr>
<td>Enlarged</td>
<td>2/8 (25.0%)</td>
<td>1/11 (9.1%)</td>
<td>3/19 (15.8%)</td>
</tr>
<tr>
<td>No change</td>
<td>4/8 (50.0%)</td>
<td>6/11 (54.5%)</td>
<td>10/19 (52.6%)</td>
</tr>
</tbody>
</table>

Data are presented as median (IQR), mean (SD) or n (%).

*Other cardiac conditions: transposition of the great arteries VSD (n=1: SPVR), primary pulmonary regurgitation (n=1: IPVR), mild A.R. Pulmonary regurgitation acquired (n=1: IPVR), TGA for paediatric patients (n=4).
‡Levothyroxine NovoLan (n=1: IPVR), Metformin, Bisoprolol, Sitagliptin and Glimepiride (n=1: SPVR), Co-Codamol (n=1: SPVR), Lymecycline (n=1: SPVR), Dianette (n=1: IPVR), cod liver oil and sea kelp (n=1: IPVR).§Reasons for requirement of bypass in patients randomised to IPVR: During chest opening, a laceration was made in the heart. This required urgent cardiopulmonary bypass to stabilise the patient. The valve position was not perfect after it had been deployed and it is not possible to retrieve the valve without going on bypass. The reason the valve position was not perfect was because the patient’s main pulmonary artery was very short and to get the valve in without obstructing his right branch PA meant it had to be deployed more proximally. After deployment of the valve, it was identified that the valve had deployed too proximally. It was functioning well but there was concerns that it would not be stable. Due to the design of the prosthesis, it was not possible to manipulate it into a better position and therefore the decision was made that the valve should be placed in a perfect position. Cardiopulmonary bypass was therefore used to place the valve in such a position, and it was fixed there with excellent short-term and medium-term result. There was an episode of VF while opening the chest. When the valve was implanted, it was felt that it had not opened completely due to areas of calcification in the RVOT/PA. The decision was therefore made to go on bypass and ensure the valve was properly deployed. The valve was implanted because of the large size of the outflow tract, it became twisted and required removal. A further attempt was made to place the valve but on this occasion, the valve embolised. Cardiopulmonary bypass was instigated to retrieve the valve, then implant it in the correct position. Calcification of RVOT meant off-bypass injection of pulmonary valve was not feasible, therefore valve was replaced on CPB.
¶Norepinephrine: SPVR 1/8 (12.5%), IPVR 2/11 (18.2%); Dopamine: SPVR 0/8 (0.0%), IPVR 4/11 (36.4%); Milrinone: SPVR 1/8 (12.5%), IPVR 2/11 (18.2%); Dobutamine: SPVR 2/8 (25.0%), IPVR 0/11 (0.0%); Enoximone: SPVR1/8 (12.5%), IPVR 0/11 (0.0%); GTN: SPVR 1/8 (12.5%), IPVR 0/11 (0.0%).ACE, angiotensin-converting-enzyme; CPB, cardiopulmonary bypass; DORV, double outlet right ventricle; GTN, glyceryl trinitrate; IPVR, injectable pulmonary valve replacement; LV, left ventricular; NYHA, New York Heart Association; PA/IVS, pulmonary atresia with intact ventricular septum; PA/VSD, pulmonary atresia with ventricular septal defect; PPIs, proton pump inhibitors; RV, right ventricular; RVOT, right ventricular outflow tract; SPVR, standard pulmonary valve replacement; VF, ventricular fibrillation.

Figure 2 Primary and secondary outcome treatment effects. Post-hoc sensitivity analysis: primary analysis additionally adjusted for participant age and sex. ICU, intensive care unit; IPVR, injectable pulmonary valve replacement; MD, mean difference; SPVR, standard pulmonary valve replacement.
IPVR group vs 633.8 mL (SD 249.8) in the SPVR group). The mean difference was −277.6 mL (95% CI −484.0 to −71.2, p-value 0.005; figure 2 and online supplemental table 6). A post-hoc sensitivity analysis adjusting for participant age and sex estimated a similar mean difference (−286.6, 95% CI −512.6 to −60.7, p-value 0.005).

Secondary outcomes
Kaplan-Meier graphs of time to readiness for extubation, time to first ICU discharge and time to fitness for discharge are shown in online supplemental figure 1. Median times to readiness for extubation and ICU discharge were longer for the SPVR group but not significantly different to the IPVR group (extubation: median 7.5 hours (IQR 5.6 to 16.1) in the IPVR group vs 6.8 hours (IQR 4.8 to 7.7) in the SPVR group; ICU discharge: median 23.0 hours (IQR 16.5 to 62.1) vs 17.0 hours (IQR 8.6 to 32.2)). Median time to fitness for discharge also did not differ significantly between groups (median 7 days (IQR 4 to –) in the IPVR group vs 8 days (IQR 5 to –) in the SPVR group). Treatment estimates are summarised in online supplemental table 7. Assumptions underpinning all models fitted were met.

Other secondary clinical outcomes are described in table 2. Postoperative inotropes were given in slightly more participants randomised to IPVR compared with SPVR (72.7% vs 62.5%), but the average total dose in the first 24 hours was similar (median 1.1 mg/kg (IQR 0.0 to 1.8) in the IPVR group vs 1.9 mg/kg (IQR 0.0 to 3.3) in the SPVR group). Chest drain volume in the first 12 hours was lower in the IPVR group (mean 215.0 mL (101.5) in the IPVR group vs 293.8 mL (121.6) in the SPVR group). Only one participant in the IPVR group received blood products (fresh frozen plasma) in the first 24 hours. Echocardiography and MRI findings were unremarkable and did not suggest any differences between groups.

Quality of life in adult participants was similar in the two groups (online supplemental table 8), although the number in the IPVR group was reduced because four were <16 years. No paediatric participants were randomised to SPVR precluding a comparison between groups on the CHQ.

Postoperative complications
Valve-related complications occurred in 4/11 (36.4%) participants who had IPVR, two during their index admission (one reoperation for valve-related issues during their index admission, 1 valve-related sepsis) and two posthospital discharge (one endocarditis, 1 valve related sepsis) and 1/8 (12.5%) participants who had SPVR (one residual valve stenosis post hospital discharge; table 2).

Overall, 32 postoperative complications were recorded in 13 participants: 12 complications in five of eight (62.5%) participants in the SPVR group and 20 complications in eight of 11 (72.7%) participants in the IPVR group (online supplemental table 9, 10). Of these complications, 12 (4 SPVR vs 8 IPVR) were classed as SAEs. There were no deaths.

DISCUSSION
INVITE is the first RCT comparing the effectiveness of IPVs and SPVs. The trial did not recruit the prespecified target number, as discussed below. There were four main findings. Mean chest drain volume in the first 24 hours after surgery, the primary outcome, was lower in the IPVR group than the SPVR group. There were no differences in times to extubation, readiness for first ICU discharge or fitness for discharge from hospital. Other clinical outcomes, including the incidence of complications and quality of life were similar in both groups. All implanted IPVs and SPVs were functioning satisfactorily 6 months after surgery.

Findings in the context of previous studies
IPVs are relatively new surgical prostheses used mainly in Europe. The appeal of IPVR is that the valve can be implanted off-pump, avoiding complications associated with CPB. IPVR reduces dissection around the heart, which is suggested to reduce operation time and postoperative bleeding. However, previous studies demonstrating that IPVs are easy to implant and have satisfactory function were case reports/series and a small non-randomised pilot study.1–9 There is a high risk that patients in the case studies/series were highly selected, limiting the applicability of the information reported.

The case reports/series had small sample sizes, ranging from 1 to 12 and follow-up ranged from the index admission to 42 months. Only two studies report use of CPB in patients receiving IPVs; in these studies eight out of 19 patients receiving IPVs received CPB;7–9 six were described as having CPB for simultaneous/additional cardiac procedures and two because the patients (children) were too small (<30 kg). Only three studies reported any complications; in one study, one of four patients had a valve migration after 4 months and required reoperation,1 in a second study, one of six patients had a paravalvular leak and a homograft was implanted 2 days after implanting the IPV8 and in a third study, two of 12 patients had a mild paravalvular leak.9

Our pilot study which prompted INVITE also reported that none of six patients having IPVR required CPB and there were no significant complications with its use.3 In this pilot study, an IPVR group (six patients) was compared with a SPVR group (seven patients). Mean operating time was almost 2 hours less with IPVR, and the median postoperative chest drain volume was over 200 mL less. Patients in the IPVR group did not require any blood product, compared with a median of three units in the SPVR group. No patient had a paravalvular leak or more than mild pulmonary regurgitation at early follow-up, suggesting that IPVR is a safe and efficacious surgical strategy. However, potential selection of patients for IPVR or SPVR in the pilot study means estimates of differences between groups are at high risk of bias. We designed a pragmatic study which aimed to recruit patients who would have been eligible for IPVR in usual care. One eligibility criterion, excluding patients...
undergoing other procedures requiring CPB, is the only criterion that might be considered to be inconsistent with this aim but was applied to ensure that effects could be attributed to the valves being studied. We cannot rule out the possibility that surgeons selected the patients they recruited to offer randomisation but there was no evidence of eligible patients not being approached (from a rigorous screening log at the centre that recruited most participants).

Notwithstanding the difference observed for the primary outcome in INVITE, these findings contrast with those reported here: six of 11 (55%) IPVR participants

Table 2  Clinical secondary outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Randomised to SPVR (n=8)</th>
<th>Randomised to IPVR (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inotropes/vasodilators (postop)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any postoperative inotropes*</td>
<td>5/8 (62.5%)</td>
<td>8/11 (72.7%)</td>
</tr>
<tr>
<td>Total dose during 24 hours postop (mg/kg)†</td>
<td>1.0 (0.0, 3.3)</td>
<td>1.1 (0.0, 1.8)</td>
</tr>
<tr>
<td>Total duration of postoperative inotropic support (hours)‡</td>
<td>16.1 (0.0, 29.1)</td>
<td>19.2 (0.0, 29.4)</td>
</tr>
<tr>
<td>Chest drain volume in the first 0–12 hours (mL)</td>
<td>293.8 (121.6)</td>
<td>215.0 (101.5)</td>
</tr>
<tr>
<td>Blood products used in the first 24 hours postoperative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any blood products used</td>
<td>0/8 (0.0%)</td>
<td>1/1 (9.1%)</td>
</tr>
<tr>
<td>FFP</td>
<td></td>
<td>1/1 (100.0%)</td>
</tr>
<tr>
<td>Cardiac MRI assessment of valve and heart function at 6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of pulmonary regurgitation</td>
<td>4/8 (50.0%)</td>
<td>7/9 (77.8%)</td>
</tr>
<tr>
<td>Degree of pulmonary regurgitation (%)§</td>
<td>0.8 (0.3, 1.1)</td>
<td>3.2 (1.4, 7.9)</td>
</tr>
<tr>
<td>End-diastolic volume (absolute)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV (mL)¶</td>
<td>146.6 (122.8, 172.4)</td>
<td>115.6 (110.1, 130.5)</td>
</tr>
<tr>
<td>RV (mL)¶</td>
<td>178.8 (169.5, 201.2)</td>
<td>159.8 (131.9, 205.0)</td>
</tr>
<tr>
<td>Right ventricular ejection fraction (%)¶</td>
<td>49.1 (43.3, 51.1)</td>
<td>45.2 (39.5, 48.4)</td>
</tr>
</tbody>
</table>

Echocardiography assessment of valve function at 6 months

| Presence of pulmonary regurgitation          | 3/8 (37.5%)              | 5/9 (55.6%)               |
| Degree of pulmonary regurgitation            |                          |                           |
| Mild                                         | 2/2 (100.0%)             | 4/4 (100.0%)              |
| Residual valve stenosis                      | 1/8 (12.5%)              | 0/9 (0.0%)                |
| Peak velocity (m/s)¶                         | 2.6 (0.5)                | 2.4 (0.4)                 |

Valve related complications during follow-up

| Any valve-related complication               | 1/8 (12.5%)              | 4/11 (36.4%)              |
| Prehospital discharge                        |                          |                           |
| Reoperation for valve-related issues         | 0/8 (0.0%)               | 1/1 (9.1%)                |
| Valve-related sepsis                         | 0/8 (0.0%)               | 1/1 (9.1%)                |
| Posthospital discharge                       |                          |                           |
| Residual valve stenosis                      | 1/8 (12.5%)              | 0/9 (0.0%)                |
| Valve related sepsis                         | 0/8 (0.0%)               | 1/1 (9.1%)                |
| Endocarditis                                 | 0/8 (0.0%)               | 1/1 (9.1%)                |

Data are presented as median (IQR), mean (SD) or n (%).

* Norepinephrine: SPVR 1/8 (12.5%), IPVR 5/11 (45.5%); Dopamine: SPVR 0/8 (0.0%), IPVR 3/11 (27.3%); Milrinone: SPVR 1/8 (12.5%), IPVR 2/11 (18.2%); Dobutamine: SPVR 2/8 (25.0%), IPVR 2/11 (18.2%); Enoximone: SPVR 1/8 (12.5%), IPVR 0/11 (0.0%); GTN: SPVR 3/8 (37.5%), IPVR 3/11 (27.3%).

†Zero if no postoperative inotropes received. Norepinephrine excluded from total dose. Dose calculated for the first 24 hours postoperative.

6 patients received at least one inotrope for >24 hours (3 SPVR: 1 Dopamine, 1 Dopamine and Milrinone, 1 GTN; 3 IPVR: 2 Dobutamine, 1 Enoximone and GTN).

‡Zero if no postoperative inotropes received.

§A wave corrected.

¶Missing data (SPVR, IPVR): Data missing for 2 patients (0, 2).

FFP, fresh frozen plasma; GTN, glyceryl trinitrate; ICU, intensive care unit; IPVR, injectable pulmonary valve replacement; LV, left ventricular; RV, right ventricular; SPVR, standard pulmonary valve replacement.
required CPB, four due to issues with implanting or deploying the IPV. A further four of 11 (36.4%) IPV participants had valve-related complications, one of which required reoperation for severe, pulmonary regurgitation and implantation of a SPV.

We have found no report of IPV use after 2015, when Grohmann et al reported reviewing seven patients who had undergone an IPV 1–7 years previously. Six of seven patients had undergone valve rereplacement, three requiring repeat surgery and three having percutaneous valve-in-valve implantations. This finding is not directly relevant to INVITE, which had approval to follow participants only for 6 months, but suggests that IPVs should be used with caution.

There are three possible explanations for the difference in short-term findings between INVITE and previous studies: inclusion criteria for the INVITE trial were insufficiently selective; previous studies reported highly selected patients or chance due to the small numbers reported in all studies. We reject the first possibility since two surgeons who implanted IPVs in the pilot study performed IPVR in INVITE. We cannot distinguish between the two other possibilities.

Discussion of clinical experiences with IPVR

Avoiding CPB was expected to benefit patients in the IPVR group by hastening recovery and lowering the risk of major complications after the operation. However, CPB was instituted in six of 11 patients (54.5%) in the IPVR group. Four patients required CPB due to malpositioning of the IPV in various ways: sometimes, the valve slipped forwards and became lodged in the branch pulmonary artery; sometimes, the valve deployed too proximally within the RVOT and full expansion could not be achieved resulting in RVOT obstruction; occasionally, the valve twisted during deployment resulting in non-coaxial orientation with resultant obstruction. The chief reason for these was the inflexibility of the delivery process that depended on the surgeon controlling the distal migration of the device using their fingers at the bifurcation of the pulmonary artery; if delivery was not controlled in this way, the IPV was not restrained in any way until fully extruded from the introduction trochar. A similar experience has previously been reported.6 However, after successful deployment and positioning, the IPV could be securely anchored into place. Surgeon experience and familiarity will also play a role.

The requirement for CPB on occasion does not preclude successful use of the IPV, which can be easily and securely sutured into place having opened the pulmonary artery. However, using CPB for IPVR has cost implications as decreasing the potential benefit from avoiding CPB.

Strengths/limitations

The main strength of INVITE is the randomised design, allowing an unbiased comparison between IPVR and SPVR. This strength remains despite the trial failing to reach its recruitment target. A further strength was the inclusion of all patients for whom IPVR is proposed to be a viable PVR strategy, to promote the applicability of the findings to a wide group of patients requiring PVR.

The main limitations were as follows:

1. Recruitment was very much lower than the target, reducing the power to detect differences between groups and making it difficult to interpret the observed treatment effects.
2. The small number of participants also led to chance imbalances between groups. However, the treatment effect for the primary outcome was essentially unchanged after adjusting for age and sex.
3. The wide age range of participants required age-appropriate instruments for patient-reported quality-of-life. Since all paediatric participants were allocated to IPVR, this may have biased the quality-of-life comparison in an unpredictable manner.
4. The surgical team could not be blind to allocation and five participants or their families were unblinded (one preoperatively, four postoperatively before hospital discharge), all in the IPVR group. This could have led to bias in the assessment of subjective outcomes. However, the primary and some other outcomes were objective.

A key finding is the difficulty of conducting a multicentre, surgical interventional trial using a novel prosthesis in the current surgical environment. Recruitment progressed much more slowly than expected for two main reasons. First, only one site (other than Bristol) agreed to participate despite considerable efforts to recruit other national centres. Informal discussions with potential participating surgeons identified interprofessional differences of opinion about the new technique as a significant contributing factor. Second, there were fewer than expected eligible patients; the majority of eligible participants who were approached consented to take part.

In the UK more than 200 PVRs are performed each year. We therefore expected to enrol the requisite number of patients well within the planned timeframe. However, many patients had other abnormalities that made them ineligible, including need for pulmonary artery reconstruction and closure of residual intra-cardiac shunts.

CONCLUSIONS

Chest drain volume in the first 24 hours was lower with IPVR than SPVR, although estimated with a high degree of uncertainty due to the small sample size. The difference in volume may have been influenced by chance differences in baseline characteristics. Other outcomes did not differ statistically or clinically. Our data are consistent with surgeons failing to adopt IPVR over the time since the trial was designed. Conducting multicentre surgical trials of novel devices remains challenging.

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Contributors AP, the study Chief Investigator, devised the trial concept and designed the study along with BR, MT, CR, LC, and GA. AP is acting as guarantor. RH aided in drafting the trial protocol, managed the study and prepared the first draft of the manuscript. TW-S also managed the trial and helped draft the initial manuscript. MC, AP, SS, NV and GA were participating surgeons and delivered the trial interventions. KS and KW screened and recruited patients and collected study data. MRI data were analysed by MH. RE statistically analysed the study data, prepared the trial results and contributed to the drafting of the manuscript. The manuscript was reviewed by all authors before submission.

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Competing interests Pierson Ltd agreed to provide the injectable tissue valves (BioPulmonic, Biointegral Surgical) used in the trial at a discounted rate. Pierson Ltd paid for travel-related expenses for Stefano Marianeschi to visit the trial centres and provide injectable pulmonary valve replacement training.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by NHS South West Research Ethics Committee—ref 15/SW/0179. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data generated from this study will be stored in a publicly available repository: https://doi.org/10.5523/bris.2qzgq1f0thgn27bxa528sfqg3 for all participants who consented for their data to be shared for future ethically approved research. Individual deidentified participant data, associated meta data and additional related documents (eg, statistical analysis plan) will be available after publication of the main results of the study, indefinitely. Requests for data access will be reviewed by the appropriate University of Bristol data access committee. The requirements for access include an affiliated institution; ethical approval and evidence of any funding and/or sponsorship.

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