OREGON HEALTH AND SCIENCE UNIVERSITY
OFFICE OF CLINICAL INTEGRATION AND EVIDENCE-BASED PRACTICE

Evidence-Based Practice Summary
Evidence Brief on the Efficacy of CardioCel® Patches

BACKGROUND AND RATIONALE

Congenital heart defects (CHD) are associated with considerable morbidity and mortality globally, with an incidence ranging from 8 to 13 per 1000 live births (Hoffman 2013; Marelli 2014; van der Linde D 2011). Additionally, CHDs are associated with the highest average hospital charges of all birth defects and the highest length of stay and mortality (Strange 2015). The ongoing need for repeat and revision surgery coupled with a lifelong burden of associated disease and comorbidity translates into significant public health impact and healthcare costs, which characteristically extend well beyond childhood. Of the $2.6 billion USD in hospital costs associated with birth defects in the United States during 2004, $1.4 billion (54%) was directly associated with the management and treatment of structural cardiovascular defects (Marelli 2014). A diverse range of cardiovascular patches for the correction of congenital defects in neonates and pediatric patients have been tested in clinical trials including the use of synthetic, autologous, and biological materials.

Summary of animal studies

Three previous animal studies have evaluated the effectiveness of the anticalcification ADPAT TEP process and the potential for remodelling in CardioCel®. A subcutaneous rat model, (Neethling 2014) demonstrated reduced calcification compared with bovine pericardium fixed with 0.6% glutaraldehyde, cryopreserved human pericardium rapidly fixed with 0.6% glutaraldehyde and ADAPT-treated cryopreserved human pericardium. Histological evaluation demonstrated the increasing host fibroblast number and the presence of functioning neo-capillaries on the edges of the explant without visible calcification (at 16 weeks). In a non-randomized, prospective study by the same investigators, using a juvenile sheep model, CardioCel® was used to replace the posterior mitral leaflet and 1 leaflet of the pulmonary valve (Brizard 2014). Histological evaluation after 7 months of implantation demonstrated a continuous endothelial lining that was visible on the blood interface with a few neo-capillaries, myofibroblasts, monocytes and cells with smooth muscle cell phenotype within the CardioCel®. CardioCel® has been used for complete tri-leaflet replacement of the aortic valve in a surgical sheep model (Meuris 2016). Echocardiography demonstrated good aortic valve function at 1 week, 3months and 6months after surgery. There was diminished mobility and macroscopic calcification in 1 of 9 cusps. Histology identified microscopic calcification of 2 additional cusps. The original CardioCel® structure was well preserved with evidence suggestive of early remodelling. (Bell 2019).

Worldwide Regulatory Approval:

The tissue-engineered scaffold CardioCel® has been cleared by the FDA and Canadian regulators for use in pericardial closure and repair of cardiac and vascular defects including intracardiac defects, septal defects, valve and annulus repair, great vessel reconstruction, peripheral vascular reconstruction and suture-line buttressing. It is CE marked according to the EU Medical Device Directive 93/42/EEC & 2007/47/EEC and currently being used in Australia as part of a Therapeutic Goods Administration authorized prescriber scheme for repair of congenital heart defects. It is anticipated that regulatory approvals will be sought for other international markets to provide a global solution to congenital heart defects patients (Strange 2015).

FDA CardioCel® Summary:

CardioCel® has a shelf life of 24 hours when stored between 2 – 25 degrees Celsius, and is supplied in three sizes: 4 x 4 cm, 5 x 8 cm and 14 x 7 cm. CardioCel® is indicated for use as a patient in pericardial closure and the repair of cardiac and vascular defects including intracardiac defects: septal defects, valve and annulus repair; great vessel reconstruction, peripheral vascular reconstruction and suture line buttressing. CardioCel® is manufactured from glutaraldehyde crosslinked bovine pericardium, which is the same material used for the predicate devices. CardioCel® is considered to be substantially equivalent to the predicates for the following reasons: Same raw material, same intended use, used in the same patient population, used in the same clinical environment, manufactured using the same principles of crosslinking with glutaraldehyde, used in the same anatomical region (cardiovascular system), intended to perform as a long term implant, maintaining the integrity of the area repaired, operates using the same fundamental scientific technology, supplied in several sizes, similar manufacturing process, similar sterilization method to one predicate, and similar packaging and labeling. CardioCel® was granted FDA's 510(k) Premarket notification of intent to market the device by determining the device is substantially equivalent to legally marketed predicate devices. Advisory, FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that the device compiles with all requirements of the Federal statutes and regulations (FDA 2014).

Patch comparisons

Several patches have received US FDA approval for use in repair of congenital heart defects. These products are cleared for use in a range of clinical conditions, including closure and repair of intracardiac defects, septal defects, valve and annulus repair, cardiac and vascular reconstruction and repairs, peripheral vascular reconstruction and repairs, great vessel reconstruction and repairs and suture-line buttressing. The table below provides a comparison of properties of bovine pericardium (BP) patches that are currently available. Similar to the ADAPT TEP, the engineering process use in the Edwards Bovine Pericardial Patch also removes phospholipids from the tissue. The crosslinking process in engineering CardioCel® uses modified monomeric glutaraldehyde (GA) as opposed to polymeric GA in other products and the subsequent sterilization and storage of CardioCel® is in a non-GA solution, which also minimizes cytotoxicity. Although, the ADAPT tissue is derived from BP, it no longer contains any cells or cell remnants/antigens of BP. Data from animal

studies seems to infer that an appropriate comparator may indeed be homologous/autologous pericardium (Neethling 2014; Strange 2015).

Comparison table from Strange 2015 Expert Review:

Table 1. Comparison of commercially available bovine pericardium patches.

	CardioCel	CV peri-guard/ supple peri-guard	CorRestore patch	Edwards bovine pericardial patch	Glycar pericardial patch	Shelhigh no-react pericardial patch	PeriPatch sheet	CardioFix
Tissue treatment terminology	ADAPT® tissue engineering	Apex processing	N/A	XenoLogiX® treated	Encap	No React® aldehyde detoxification process (Heparin-surfactant)	N/A	PhotoFix®
Pericardium processing method	Modified monomeric GA treated	GA treated	GA treated	Buffered GA	GA treated	GA treated	GA treated	Dye-mediated photo-oxidation
Phospholipids removed from tissue	Yes	No	No	Yes	No	No	No	No
Sterilization method	ADAPT and propylene oxide	Ethanol and propylene oxide	GA	Formaldehyde surfactant	Formaldehyde and propylene oxide	GA fixed	Liquid alcohol sterilant	ETO
Storage medium	Propylene oxide	Propylene oxide	GA applied at specific temperature	Buffered GA	2% propylene oxide in water	Benzyl alcohol	2% GA/phosphate buffered solution	22% buffered ethanol
Patch size	4 × 4 cm 5 × 8 cm 14 × 7 cm	4 × 4 cm 6 × 8 cm 8 × 14 cm 10 × 16 cm	1.5 × 2 cm 2 × 3 cm 3 × 4 cm (Kit + Suture Strip 1.4 × 16 cm)	10 × 15 cm	2 × 9 cm	1 × 7 cm 2 × 7 cm 3 × 3 cm 5 × 5 cm 6 × 10 cm 8 × 14 cm	4 × 4 cm 4 × 6 cm 6 × 8 cm 8 × 14 cm 10 × 16 cm	1 × 1 cm 4 × 4 cm 6 × 8 cm 8 × 14 cm 10 × 16 cm 14 × 16 cm
Intended use	Permanent implantation in humans, and is indicated for repairing of congenital heart deformities and general soft tissue repair	Repair of pericardial structures and for use as a prosthesis for the surgical repair of soft tissue deficiencies which include: defects of the abdominal and thoracic wall, gastric binding, musde flap reinforcement, and hernias (including diaphragmatic, femoral, incisional, inguinal, lumbar, paracolostomy, scrotal and umbilical hernias	Intracardiac patch for cardiac reconstruction and repair	Augmenting the patient's own pericardium to assist in closure following open-heart surgery; intracardiac defects; septal defects and annulus repairs; cardiac and vascular reconstruction and repairs; peripheral vascular reconstruction and repairs; great vessel reconstruction and repairs; and suture-line buttressing	Repair of pericardial structures and for use as a prosthesis for the surgical repair of soft tissue deficiencies which include: defects of the abdominal and thoracic wall, gastric binding, musde flap reinforcement and hernias (including diaphragmatic, femoral, incisional, inguinal, lumbar, paracolostomy, scrotal and umbilical hernias	Intracardiac patch for cardiac reconstruction and repair	Intracardiac patch for cardiac reconstruction and repair	Intracardiac repair (ventricular repair using reinforced patch technique [i.e., minimum double thickness] and atrial repair); great vessel repair and suture-line buttressing using a reinforced patch technique for applications exposed to peak systolic pressure; and pericardial closure

GA: Glutaraldehyde; N/A: Not applicable.

ASK THE QUESTION

In adult and pediatric patients with congenital heart defects (CHD), what is the efficacy of the CardioCel® patches on patient outcomes (mortality, morbidity, additional procedures, complications, etc.)?

SEARCH FOR EVIDENCE

Appendix C

CRITICALLY ANALYZE THE EVIDENCE

Over 40 research articles were found mentioning CardioCel® when searching databases. Only seven studies were found directly researching CardioCel®'s efficacy in human populations, and one economic modeling study from the UK's National Health Service was found estimating CardioCel®'s cost-effectiveness. For the purposes of this appraisal, studies researching CardioCel® in laboratories or animal populations were summarized in the background, but were not included in the appraisal.

Efficacy in Pediatric Patients

The first study reporting on CardioCel®'s efficacy in humans was a single-center, prospective cohort study of 30 pediatric patients receiving the CardioCel® scaffold in South Africa. Study observed no patch-associated morbidity within one month of insertion and no echocardiographic evidence of calcification, bleeding, or failure at 18 to 36 months' post-surgery. In total, there were 5 deaths (2 in the 30-day postoperative period and 3 within the first 6 postoperative months). All deaths were deemed due to comorbid non-graft-related events. (Neethling 2013). A case series (Sobieraj 2016) from Poland evaluated the short-term results of CardioCel® bovine pericardial patch implantation in 8 patients during pediatric cardiac surgery. There were no hospital deaths. The new material exhibited satisfactory durability and elasticity during surgery, facilitating optimal adaption of the patch to the patient's tissues.
Level of Evidence: Very Low

Performance at 24 months/2 years

Two studies were found reporting CardioCel®'s performance at 24 months/2 years. One observational study (Bell 2019) assessed the performance at 24 months of 135 patients receiving tissue-engineered bovine pericardium (CardioCel®) for the repair of congenital heart defects. Eight patients (5.9%) required reintervention in 12 instances (6.2%, 6 catheters and 6 surgical). There was no echocardiographic or radiological evidence of calcification in any patient. Ten of the reinterventions (83%) occurred within the first 12 months. All the reinterventions occurred within 36 months. Freedom from reintervention at both 12 and 24 months was 95% [confidence interval (CI) 91–97] and at 36 months was 94% (CI 89–97). Another retrospective study (Pavy 2018) included the initial results of 101

patients CardioCel® patch implantation in pediatric patients with congenital heart diseases. No infections and no intraoperative implantation difficulties were associated with the patch. The median follow-up period was 212 (range 4-726) days. The overall 30-day postoperative mortality was 3.8% (n = 4), none of which were related to graft failure. Five children were reoperated because of graft failure, 4 of whom had the patch implanted for aortic and were aged less than 10 days. The indications for patch implantation in the aortic position were aortopulmonary window, truncus arteriosus, coarctation and aortic arch hypoplasia repair.
Level of Evidence: Very Low

Efficacy in pediatric and adult populations
A retrospective study (Nordmeyer 2015) from Germany of 40 pediatric and adult patients reported the experience of aortic valve reconstruction using decellularized bovine pericardial patch material in congenital heart surgery. Nine of 40 (23%) patients experienced an event during follow-up (death: n = 1, 2.5%; reoperation: n = 8, 20%). Overall, the probability of freedom from reoperation or death was 97 ± 3%, 76 ± 9% and 57 ± 12% at 12, 24 and 36 months of FU, respectively. Reason for reoperation was stenosis in 3 (37.5%) patients, insufficiency in 4 (50%) patients and 1 (12.5%) patient was diagnosed with aortic valve endocarditis. Of the remaining 31 patients, 2 patients are scheduled for reoperation (aortic valve stenosis: n = 1 and aortic valve insufficiency: n = 1) and 9 patients exhibit worsening of aortic valve function with moderate aortic valve insufficient.
Level of Evidence: Very Low

Histological Findings
One observational study (Prabhu 2017) presented the histopathologic and immunohistochemical (IHC) findings of 6 human explants of CardioCel® patches that were used initially in operations for congenital heart defects in children. A variable inflammatory response was seen in the surrounding native tissue, but not within the CardioCel® graft in any of the explants. A neointimal layer of varying thickness developed on the visceral surface of 5 CardioCel® explants with endothelialization of the longest duration explant.
Level of Evidence: Very Low

Adverse Events
One case series (Kostolny 2018) described adverse events in 2 patients when neo-tricuspidization was performed in one case using CardioCel® leaflets and two cusps were formed from CardioCel® and grafted alongside one native leaflet in the other. Both patients developed bacterial endocarditis associated with varicella zoster virus infection and required a second surgical procedure.
Level of Evidence: Very Low

Cost
One economic modeling study (Velickovic 2018) was found evaluating the cost effectiveness of tissue engineered bovine tissue pericardium scaffold (CardioCel®) for the repair of congenital heart defects in comparison with surgery using xenogeneic, autologous,

and synthetic patches over a 40-year time horizon from the perspective of the UK National Health Service. According to the model predictions, CardioCel® was associated with reduced incidence of reoperation, increased quality adjusted life years (QALY), and costs savings compared to all other patches. Cost savings were greatest compared to synthetic patches. Estimated cost savings associated with CardioCel® were greatest within atrioventricular septal defect repair and lowest for ventricular septal defect repair. Based on the model, CardioCel® relative risk for re-operations is 0.938, 0.956 and 0.902 relative to xenogeneic, autologous, and synthetic patches, respectively.
Level of Evidence: Very Low

Expert Commentary
Additionally, the following Expert commentary (Strange 2015) was found concluding: The ADAPT TEP (CardioCel®) may have a number of potential advantages over existing technologies used in many forms of bioprosthetic implants, notably, the lack of foreign body response seen with non-crosslinked tissue grafts, resulting in increased biocompatibility. In addition, there is no evidence to date of chronic inflammation as occurs with non-crosslinked tissue or synthetic grafts. There has been evidence of controlled healing and host cell infiltration further supporting biocompatibility and durability. To date, there has been no evidence of tissue degeneration or calcification.

Evidence Brief Conclusion
Overall, there is very low level of evidence found on the efficacy of CardioCel® in patients with congenital heart defects. The majority of patients included in the studies were pediatric patients, with one study including a small amount of adult patients. The level of evidence was downgraded due to imprecision and design limitations. Consistency was not able to be determined based on the studies currently published. Further research is needed on CardioCel® to increase confidence in the results currently published.

GRADE Table Templates

BODY OF EVIDENCE APPRAISAL TABLE FOR:
Population: Pediatric Patients
Modality: CardioCel®
Outcome: Efficacy

Quality (certainty) of evidence for: (outcome)
☐ High
☐ Moderate
☐ Low
☒ Very Low

Risk of Bias across studies:	**Lower Quality Rating if:**	**Other Considerations:**
☐ High ☒ Medium ☐ Low	☐ Studies inconsistent (*wide variation of treatment effect across studies, population, interventions, or outcomes varied*) - **UNKNOWN** ☐ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☒ Studies are imprecise (*when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain)*	Lower Quality Rating if: ☐ Publication Bias (*e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)* Increase Quality Rating if: ☐ Large effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect

Study Acronym; Author; Year Published; Location	**Aim of Study**	**Patient Population**	**Study Methods**	**Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)**	**Design Limitations**
Author: Neethling, W.M., et al. Year Published: 2013 Location: University Hospital, Medical School, University of Free State in Bloemfontein, South Africa. Journal: *Interactive Cardiovascular & Thoracic Surgery*	To evaluate the safety, efficacy and clinical performance of the tissue-engineered ADAPT(R) bovine pericardial patch (ABPP) in paediatric patients with a range of congenital cardiac anomalies.	**Size:** 30 paediatric patients **Inclusion Criteria**: Patients were eligible for inclusion if they had symptoms and anatomy sufficient to warrant application of the ABPP as a bioprosthetic substitute during surgical repair procedures during open-heart surgery. Specifically, this involved ASD, VSD, atrioventricular septal defect (AVSD), aortic root enlargement and RVOT reconstruction. Patients undergoing concomitant procedures such as coronary artery bypass or valve	**Type:** Non-randomized prospective study **Intervention**: Paediatric patients underwent surgery for insertion of the ABPP. Primary efficacy measures included early (<30 day) morbidity; incidence of device-related complications; haemodynamic performance derived from echocardiography assessment at 6- and 12-month follow-up and magnetic resonance imaging findings in 10 randomly selected patients at 12 months. Secondary measures included device-handling characteristics; shape	**Results:** In the 30-day postoperative period, no graft-related morbidity was observed. In total, there were 5 deaths (2 in the 30-day postoperative period and 3 within the first 6 postoperative months). All deaths were deemed due to comorbid non-graft-related events. Echocardiography assessment at 6 and 12 months revealed intact anatomical and haemodynamically stable repairs without any visible calcification of the patch. Magnetic resonance imaging assessment in 10 patients at	**Study Limitations:** ☐ None **Non-Randomized Studies** ☒ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up

		replacement were also eligiblefor inclusion.	and sizing characteristics and perioperative implant complications. The Aristotle complexity scoring system was used to score the complexity level of all surgical procedures. Patients completing the 12-month study were eligible to enter a long-term evaluation study.	12 months revealed no signs of calcification. Fisher's exact test demonstrated that patients undergoing more complex, higher risk surgical repairs (Aristotle complexity score >8) were significantly more likely to die (P = 0.0055, 58% survival compared with 100% survival for less complex surgical repairs). In 19 patients, echocardiographic data were available at 18–36 months with no evidence of device calcification, infection, thromboembolic events or device failure.	
Author: Sobieraj, M. et al. Year Published: 2016 Location: Poznan University of Medical Sciences, Poznan, Poland Journal: *Kardiochir Torakochirurgia Pol*	To evaluate the short-term results of CardioCel® bovine pericardial patch implantation during pediatric cardiac surgery	**Size:** 8 patients **Patient Characteristics** 	**Type:** Case Series **Intervention**: Preliminary analysis of the effects of the CardioCel® pericardial patch in pediatric patients undergoing congenital heart defect correction requiring the use of the implant. The patients underwent three types of procedures: aortic arch reconstruction, repair of supravalvular aortic stenosis, and pulmonary artery reconstruction.	**Results:** The age of patients ranged from 10 days to 14 years. There were no hospital deaths. The new material exhibited satisfactory durability and elasticity during surgery, facilitating optimal adaption of the patch to the patient's tissues. No significant bleeding was reported from the suture site, The median duration of follow-up was 58 days. During the follow-up, there was no symptoms of pseudoaneurysm formation, patch thickening or calcification in the areas where the pericardial patches were implanted. No clinical or laboratory symptoms of infection were observed in locations where the new material was applied.	**Study Limitations:** ☐ None **Non-Randomized Studies** ☒ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☒ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up

References:

1. Neethling, W. M., et al. (2013). "Evaluation of a tissue-engineered bovine pericardial patch in paediatric patients with congenital cardiac anomalies: initial experience with the ADAPT-treated CardioCel(R) patch." Interactive Cardiovascular & Thoracic Surgery **17**(4): 698-702.
2. Sobieraj, M., et al. (2016). "Application of the CardioCel® bovine pericardial patch - a preliminary report." Kardiochir Torakochirurgia Pol **13**(3): 210-212.

BODY OF EVIDENCE APPRAISAL TABLE FOR:
Population: Pediatric Patients
Modality: CardioCel®
Outcome: Performance at 24 months/2 years

Quality (certainty) of evidence for: (outcome)
☐ High
☐ Moderate
☐ Low
☒ Very Low

Risk of Bias across studies:	**Lower Quality Rating if:**	**Other Considerations:**
☐ High ☒ Medium ☐ Low	☐ Studies inconsistent (*wide variation of treatment effect across studies, population, interventions, or outcomes varied*) ☐ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☒ Studies are imprecise (*when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain)*	Lower Quality Rating if: ☐ Publication Bias (*e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)* Increase Quality Rating if: ☐ Large effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect

Study Acronym; Author; Year Published; Location	**Aim of Study**	**Patient Population**	**Study Methods**	**Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)**	**Design Limitations**
Author: Bell, D., et al. Year Published: 2019 Location: Australia Journal: *Interactive Cardiovascular & Thoracic Surgery*	To assess the performance of tissue-engineered bovine pericardium (CardioCel®) at 24 months and beyond when using for the repair of congenital heart defects	**Size:** 135 patients (140 procedures and 195 implants) **Inclusion Criteria**: (i) Congenital cardiac anomaly in patients aged 1 day – 18 years and (ii) CardioCel® used as a cardiovascular tissue substitute	**Type:** Observational Study **Intervention**: Between October 2012 and November 2014, CardioCel® was implanted in eligible patients. Applications included the closure of septal defects (98, 50.3%), repair of pulmonary arteries (63, 32.3%), intra-atrial/intraventricular baffles (10, 5.1%), repair of systemic arteries (15, 7.7%), valve repair (5, 2.6%), repair of systemic veins (3, 1.5%) and Fontan operation (1, 0.5%).	**Results:** Eight patients (5.9%) required reintervention in 12 instances (6.2%, 6 catheters and 6 surgical). There was no echocardiographic or radiological evidence of calcification in any patient. Ten of the reinterventions (83%) occurred within the first 12 months. All the reinterventions occurred within 36 months. Freedom from reintervention at both 12 and 24 months was 95% [confidence interval (CI) 91–97] and at 36 months was 94% (CI 89–97). There was no statistical difference in	**Study Limitations:** ☐ None ***Non-Randomized Studies*** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☒ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up

			There were 19 (13.6%) procedures performed in neonates, 77 (55%) in infants and 44 (31.4%) in children older than 365 days.	freedom from reintervention when stratified by age or patch position.	
Author: Pavy, C., et al. Year Published: 2018 Location: UK Journal: *Interactive Cardiovascular & Thoracic Surgery*	To present the initial 2-year results of CardioCel® patch implantation in paediatric patients with congenital heart diseases	**Size:** 101 patients had surgical repair using a CardioCel® patch **Inclusion Criteria**: <18 years old and operated for congenital heart disease	**Type:** Retrospective Study **Intervention**: This was a single-center study with prospectively collected data of all patients aged 18 years and under operated for congenital heart disease. The patch was introduced in 2014, with clinical practice committee approval and a special consent in case of an Ozaki procedure. Standard follow-up was performed with systematic clinical exams and echocardiograms. In case of reoperation or graft failure, the patch was removed and sent for a histological examination.	**Results:** Mean age was 22 (+/-36.3) months, and the mean weight was 9.7 (+/-10.3) kg. No infections and no intraoperative implantation difficulties were associated with the patch. The median follow-up period was 212 (range 4-726) days. The overall 30-day postoperative mortality was 3.8% (n = 4), none of which were related to graft failure. Five children were reoperated because of graft failure, 4 of whom had the patch implanted for aortic and were aged less than 10 days. The indications for patch implantation in the aortic position were aortopulmonary window, truncus arteriosus, coarctation and aortic arch hypoplasia repair. The median time between the first and the second operation for graft failure was 245 (range 5-480) days.	**Study Limitations:** ☐ None **Non-Randomized Studies** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☒ Failure to adequately control confounding ☒ Incomplete or inadequately short follow-up

References:

1. Bell, D., et al. (2019). "Durability of tissue-engineered bovine pericardium (CardioCel(R)) for a minimum of 24 months when used for the repair of congenital heart defects." Interactive Cardiovascular & Thoracic Surgery **28**(2): 284-290.
2. Pavy, C., et al. (2018). "Initial 2-year results of CardioCel(R) patch implantation in children." Interactive Cardiovascular & Thoracic Surgery **26**(3): 448-453.

BODY OF EVIDENCE APPRAISAL TABLE FOR:
Population: Pediatric and Adult Patients
Modality: CardioCel®
Outcome: Efficacy

Quality (certainty) of evidence for: (outcome) ☐High ☐ Moderate ☐ Low ☒ Very Low					
Risk of Bias across studies: ☐ High ☒ Medium ☐ Low		**Lower Quality Rating if:** ☐ Studies inconsistent (*wide variation of treatment effect across studies, population, interventions, or outcomes varied*) - **UNKNOWN** ☐ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☒ Studies are imprecise (*when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain)*		**Other Considerations:** Lower Quality Rating if: ☐ Publication Bias (*e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)* Increase Quality Rating if: ☐ Large effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect	
Study Acronym; Author; Year Published; Location	**Aim of Study**	**Patient Population**	**Study Methods**	**Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)**	**Design Limitations**
Author: Nordmeyer, S. et al. Year Published: 2018 Location: Berlin, Germany Journal: *European Journal of Cardio-Thoracic Surgery*	To report the experience of AVR using decellularized bovine pericardial patch material in congenital heart surgery	**Size:** 40 patients **Inclusion Criteria**: None **Exclusion Criteria**: None **There were no specific patient selection criteria.*	**Type:** Retrospective Study **Intervention**: Data of all consecutive patients who underwent aortic valve reconstruction (AVR) using decellularized bovine pericardial patch material were reviewed. Emphasis was placed on the combined end points of reoperation or death and echocardiographic parameters early after operation and at FU for the assessment of aortic valve appearance and performance and left ventricular function. The surgical team decided on the material that would be used for AVR on an individual basis. Factors that were taken into account for this decision included the underlying aortic valve morphology and the planned reconstruction technique (e.g. cusp extension versus cusp replacement).	**Results:** Nine of 40 (23%) patients experienced an event during follow-up (death: n = 1, 2.5%; reoperation: n = 8, 20%). Overall, the probability of freedom from reoperation or death was 97 ± 3%, 76 ± 9% and 57 ± 12% at 12, 24 and 36 months of FU, respectively. Reason for reoperation was stenosis in 3 (37.5%) patients, insufficiency in 4 (50%) patients and 1 (12.5%) patient was diagnosed with aortic valve endocarditis. Of the remaining 31 patients, 2 patients are scheduled for reoperation (aortic valve stenosis: n = 1 and AI: n = 1) and 9 patients exhibit worsening of aortic valve function with moderate AI. Freedom from developing combined end point [death/reoperation/moderate degree of aortic valve	**Study Limitations:** ☐ None **Non-Randomized Studies** ☒ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☒ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up

				dysfunction (aortic valve stenosis, AI)] after AVR was 92 ± 5%, 55 ± 9% and 28 ± 9% at 12, 24 and 36 months, respectively.	

References:

1. Nordmeyer, S., et al. (2018). "Results of aortic valve repair using decellularized bovine pericardium in congenital surgery." European Journal of Cardio-Thoracic Surgery **54**(6): 986-992.

BODY OF EVIDENCE APPRAISAL TABLE FOR:
Population: Pediatric Patients
Modality: CardioCel®
Outcome: Histological Findings

Quality (certainty) of evidence for: (outcome)
☐ High
☐ Moderate
☐ Low
☒ Very Low

Risk of Bias across studies:	**Lower Quality Rating if:**	**Other Considerations:**
☒ High ☐ Medium ☐ Low	☐ Studies inconsistent (*wide variation of treatment effect across studies, population, interventions, or outcomes varied*) - **UNKNOWN** ☐ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☒ Studies are imprecise (*when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain)*	Lower Quality Rating if: ☐ Publication Bias (*e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)* Increase Quality Rating if: ☐ Large effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect

Study Acronym; Author; Year Published; Location	**Aim of Study**	**Patient Population**	**Study Methods**	**Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)**	**Design Limitations**
Author: Prabhu, S. et al. Year Published: 2017 Location: Brisbane, Australia Journal: *Semin Thorac Cardiovasc Surg*	To present the histopathologic and immunohistochemical (IHC) findings of 6 human explants of CardioCel® patches that were used initially in operations for congenital heart defects in children.	**Size:** Six explants from 140 patients undergoing CardioCel® implants **Inclusion Criteria**: (1) a congenital cardiac anomaly in patients aged 1 day to 18 years, (2) CardioCel® used as a cardiovascular tissue substitute, and (3) subsequent surgery (any indication) with an	**Type:** Retrospective Study **Intervention**: CardioCel® explants were evaluated histologically using hematoxylin and eosin, Masson trichrome, and immunohistochemical staining. Clinical data of all patients were collected from electronic	**Results:** A variable inflammatory response was seen in the surrounding native tissue, but not within the CardioCel® graft in any of the explants. A neointimal layer of varying thickness developed on the visceral surface of 5 CardioCel® explants with endothelialization of the longest duration explant. A	**Study Limitations:** ☐ None **Non-Randomized Studies** ☒ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☒ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up

		explantation of a CardioCel® patch (partial or complete).	health records and paper charts.	granulation tissue layer developed on the parietal surface of the graft (consistently thicker than the neointima). Maintained collagen fiber architecture (laminated) and variable fibroblastic invasion (which increased with the age of the implant) were identified in all 6 cases. Scattered capillary vessels were noted in the majority of the explants with new collagen fibers in one, suggesting early remodeling. Calcium was seen in 1 explant at the interface of the graft and inflammatory response on its parietal surface. Evidence of graft remodeling was noted in the majority of the explants without inflammatory cells or calcification within the explanted graft material. A noticeable feature was the differential thickness of the host reaction to the parietal compared with the visceral surface of the graft.	

References:

1. Prabhu, S., et al. (2017). "Histologic Evaluation of Explanted Tissue-Engineered Bovine Pericardium (CardioCel®)." Semin Thorac Cardiovasc Surg **29**(3): 356-363.

BODY OF EVIDENCE APPRAISAL TABLE FOR:
Population: Pediatric Population
Modality: CardioCel®
Outcome: Adverse Events

Quality (certainty) of evidence for: (outcome)
☐ High
☐ Moderate
☐ Low
☒ Very Low

Risk of Bias across studies:	**Lower Quality Rating if:**	**Other Considerations:**
☒ High ☐ Medium ☐ Low	☐ Studies inconsistent (*wide variation of treatment effect across studies, population, interventions, or outcomes varied*) - **UNKNOWN** ☐ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☒ Studies are imprecise (*when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain)*	Lower Quality Rating if: ☐ Publication Bias (*e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)* Increase Quality Rating if: ☐ Large effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect

Study Acronym; Author; Year Published; Location	**Aim of Study**	**Patient Population**	**Study Methods**	**Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)**	**Design Limitations**
Author: Kostolny, M. et al. Year Published: 2018 Location: UK Journal: *World J Pediatr Congenit Heart Surg*	To describe the management and clinical course of two children with congenital bicuspid aortic valve	**Size:** 2 patients **Inclusion Criteria**: None **Exclusion Criteria**: None	**Type:** Case Series **Intervention**: Describe adverse events in 2 patients when neo-tricuspidization was performed in one case using CardioCel® leaflets and two cusps were formed from CardioCel® and grafted alongside one native leaflet in the other.	**Results:** Both patients developed bacterial endocarditis associated with varicella zoster virus infection and required a second surgical procedure.	**Study Limitations:** ☐ None **Non-Randomized Studies** ☒ Failure to develop and apply appropriate eligibility criteria ☒ Flawed measurement of both exposure and outcome ☒ Failure to adequately control confounding ☒ Incomplete or inadequately short follow-up

References:

1. Kostolny, M., et al. (2018). "Infective Endocarditis Associated With Varicella Zoster Virus Following Aortic Valve Repair." World J Pediatr Congenit Heart Surg: 2150135118769322.

BODY OF EVIDENCE APPRAISAL TABLE FOR: Population: Pediatric and Adult Modality: CardioCel® Outcome: Cost
Quality (certainty) of evidence for: (outcome) ☐ High ☐ Moderate ☐ Low ☒ Very Low

Risk of Bias across studies: ☐ High ☒ Medium ☐ Low	**Lower Quality Rating if:** ☐ Studies inconsistent (*wide variation of treatment effect across studies, population, interventions, or outcomes varied*) - **UNKNOWN** ☐ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☒ Studies are imprecise (*when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain)*	**Other Considerations:** Lower Quality Rating if: ☐ Publication Bias (*e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)* Increase Quality Rating if: ☐ Large effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect

Study Acronym; Author; Year Published; Location	**Aim of Study**	**Patient Population**	**Study Methods**	**Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)**	**Design Limitations**
Author: Velickovic, V.M., et al. Year Published: 2018 Location: UK Journal: *PLoS ONE*	To evaluate the cost effectiveness of tissue engineered bovine tissue pericardium scaffold (CardioCel®) for the repair of congenital heart defects in comparison with surgery using xenogeneic, autologous, and synthetic patches over a 40-year time horizon from the perspective of the UK National Health Service	**Size:** 49 studies **Exclusion Criteria**: Studies that reported calcification rates for a prosthesis, conduits, and valved conduits and not for patch or scaffolds.	**Type:** Economic Modeling Study **Intervention**: A six-state Markov state-transition model to model natural history of disease and difference in the interventional effect of surgeries depending on patch type implanted. Patches differed regarding their probability of re-operation due to patch calcification, based on a systematic literature review. Transition probabilities were based on the published literature, other clinical inputs were based on UK registry data, and cost data were based on UK sources and the published literature. Incremental cost-effectiveness ratio (ICER) was determined as incremental costs per quality adjusted life years (QALY) gained. A 40-year analytic time-horizon and adopted the payer perspective. Comprehensive sensitivity analyses were performed.	**Results:** According to the model predictions, CardioCel® was associated with reduced incidence of reoperation, increased QALY, and costs savings compared to all other patches. Cost savings were greatest compared to synthetic patches. Estimated cost savings associated with CardioCel® were greatest within atrioventricular septal defect repair and lowest for ventricular septal defect repair. Based on the model, CardioCel® relative risk for re-operations is 0.938, 0.956 and 0.902 relative to xenogeneic, autologous, and synthetic patches, respectively. 	**Study Limitations:** ☒ None **Economic Evaluation** ☐ The research question is not clearly stated ☐ The perspective of interest is not clear (ie., societal, patient, health system, payer) ☐ The source(s) of effectiveness estimates are not clearly stated ☐ The primary outcome measures are not clearly stated ☐ The methods for the estimation of quantities and unit costs are not described

References:

1. Velickovic, V. M., et al. (2018). "Congenital heart defect repair with ADAPT tissue engineered pericardium scaffold: An early-stage health economic model." PLoS ONE [Electronic Resource] **13**(9): e0204643.

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Appendix A. GRADE criteria for rating a body of evidence on an intervention

Developed by the GRADE Working Group

Grades and interpretations:

High: Further research is very unlikely to change our confidence in the estimate of effect. Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low: Any estimate of effect is very uncertain.

Type of evidence and starting level

Randomized trial–high Observational study–low Any other evidence–very low

Criteria for increasing or decreasing level

Reductions Study quality has serious (–1) or very serious (–2) problems Important inconsistency in evidence (–1) Directness is somewhat (–1) or seriously (–2) uncertain Sparse or imprecise data (–1) Reporting bias highly probable (–1) **Increases** Evidence of association† strong (+1) or very strong (+2) †Strong association defined as significant relative risk (factor of 2) based on consistent evidence from two or more studies with no plausible confounders Very strong association defined as significant relative risk (factor of 5) based on direct evidence with no threats to validity.

Appendix B. Trustworthy Guideline rating scale

The University of Pennsylvania's Center for Evidence-Based Practice Trustworthy Guideline rating scale is based on the Institute of Medicine's "Standards for Developing Trustworthy Clinical Practice Guidelines" (IOM), as well as a review of the AGREE Enterprise and Guidelines International Network domains.

The purpose of this scale is to focus on the weaknesses of a guideline that may reduce the trust a clinical user can have in the guideline, and distinguish weaknesses in documentation (e.g. guide-line does not have a documented updating process) from weaknesses in the guidance itself (e.g. recommendations are outdated). Current quality scales like AGREE emphasize documentation. They are important checklists for developers of new guidelines, but are less useful for grading existing guidelines. These scales also are harder for clinicians and other persons who are not methodology experts to apply, and their length discourages their use outside formal technology assessment reports. This new scale is brief, balanced, and easy and consistent to apply.

We do not attempt to convert the results of this assessment into a numeric score. Instead we present a table listing the guidelines and how they are rated on each standard. This facilitates qualitative understanding by the reader, who can see for what areas the guideline base as a whole is weak or strong as well as which guidelines are weaker or stronger.

1. Transparency

A	Guideline development methods are fully disclosed.
B	Guideline development methods are partially disclosed.
C	Guideline development methods are not disclosed.

The grader must refer to any cited methods supplements or other supporting material when evaluating the guideline. Methods should include:

Who wrote the initial draft
How the committee voted on or otherwise approved recommendations

Evidence review, external review and methods used for updating are not addressed in this standard.

2. Conflict of interest

A	Funding of the guideline project is disclosed, disclosures are made for each individual panelist, and financial or other conflicts do not apply to key authors of the guideline or to more than 1 in 10 panel members).
B	Guideline states that there were no conflicts (or fewer than 1 in 10 panel members), but does not disclose funding source.
C	Lead author, senior author, or guideline panel members (at least 1 in 10) have conflict of interest, or guideline project was funded by industry sponsor with no assurance of independence.

NR	Guideline does not report on potential conflict of interests.

For purposes of this checklist, conflicts of interest include employment by, consulting for, or holding stock in companies doing business in fields affected by the guideline, as well as related financial conflicts. This definition should not be considered exclusive. As much as anything, this is a surrogate marker for thorough reporting, since it may be assumed that guideline projects are funded by the sponsoring organization and many authors think it unnecessary to report a non-conflict.

3. Guideline development group

A	Guideline development group includes 1) methodological experts and clinicians and 2) representatives of multiple specialties.
B	Guideline development group includes one of the above, but not both.
C	Guideline developers all from one specialty or organization, and no methodologists.
NR	Affiliations of guideline developers not reported

The purpose of this standard is to ensure that supporters of competing procedures, or clinicians with no vested interest in utilization of one procedure or another, are involved in development of the guideline. Both AGREE II and IOM call for patient or public involvement: very few guideline panels have done so to date, so this is not necessary for guidelines to be rated A. Involvement of methodologists or HTA specialists in the systematic review is sufficient involvement in the guideline development group for our purposes. In the absence of any description of the guideline group, assume the named authors are the guideline group.

4. Systematic review

A	Guideline includes a systematic review of the evidence or links to a current review.
B	Guideline is based on a review which may or may not meet systematic review criteria.
C	Guideline is not based on a review of the evidence.

In order to qualify as a systematic review, the review must do all of the following:

Describe itself as systematic or report search strategies using multiple databases
Define the scope of the review (including key questions and the applicable population)
Either include quantitative or qualitative synthesis of the data or explain why it is not indicated

Note: this element does not address the quality of the systematic review: simply whether or not it exists. Concerns about quality or bias of the review will be discussed in text, where the analyst will explain whether the weaknesses of the review weaken the validity or reliability of the guideline.

Note: a guideline may be rated B on this domain even if the review on which it is based is not available to us. This potential weakness of the guideline should be discussed in text of the report.

5. Grading the supporting evidence

A	Specific supporting evidence (or lack thereof) for each recommendation is cited and graded
B	Specific supporting evidence (or lack thereof) for each recommendation is cited but the recommendation is not graded.
C	Recommendations are not supported by specific evidence.

To score a B on this domain there should be specific citations to evidence tables or individual references for each relevant recommendation in the guideline, or an indication that no evidence was available. Any standardized grading system is acceptable for purposes of this rating. If a guideline reports that there is no evidence available despite a thorough literature search, it may be scored B on this domain, or even A if evidence for other recommendations is cited and graded.

6. Recommendations

A	Considerations for each recommendation are documented (i.e. benefits and harms of a particular action, and/or strength of the evidence); and recommendations are presented in an actionable form.
B	Either one or the other of the above criteria is met.
C	Neither of the above criteria are met

In order to be actionable, the guideline should specify the specific population to which the guideline applies, the specific intervention in question, and the circumstances under which it should be carried out (or not carried out). The language used in the recommendations should also be consistent with the strength of the recommendation (e.g. directive and active language like “should” or “should not” for strong recommendations, and passive language like “consider” for weak recommendations). A figure or algorithm is considered actionable as long as it is complete enough to incorporate all the applicable patients and interventions. Please see the forthcoming NICE manual (24) for a good discussion of actionability in guidelines.

7. External review

A	Guideline was made available to external groups for review.
B	Guideline was reviewed by members of the sponsoring body only.
C	Guideline was not externally reviewed.
NR	No external review process is described.

8. Updating and currency of guideline

A	Guideline is current and an expiration date or update process is specified.
B	Guideline is current but no expiration date or update process is specified.
C	Guideline is outdated.

A guideline is considered current if it is within the developers' stated validity period, or if no period or expiration data is stated, the guideline was published in the past three years (NOTE: the specific period may be changed at the analyst's discretion, based on whether the technology is mature and whether there is a significant amount of recent evidence). A guideline must address new evidence when it is updated. A guideline which is simply re-endorsed by the panel without searching for new evidence must be considered outdated

Appendix C. Search Strategy

Database: Ovid MEDLINE(R) without Revisions <1996 to April 2019>
Search Strategy:

Keywords:
1 CardioCel® AND
2 Bovine pericardium patches AND
3 Congenital heart defects OR
4 Aortic Valve Defects