Transcatheter closure of patent ductus arteriosus

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MSAC application 1330

Assessment report

Contracted Assessment Report for Application 1330 - Transcatheter closure of a patent ductus arteriosus

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Electronic copies of the report can be obtained from the Medical Service Advisory Committee's Internet site at http://www.msac.gov.au/

Enquiries about the content of the report should be directed to the above address. This report is a technical report for use by the Medical Services Advisory Committee (MSAC) to inform its deliberations. MSAC is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC's advice does not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

This report was prepared by the Department of Health and Ageing

This report should be referenced as follows:

Department of Health and Ageing (2013). Transcatheter closure of patent ductus arteriosus. MSAC Application 1330, Assessment Report. Commonwealth of Australia, Canberra, ACT.

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EXECUTIVE SUMMARY

Background

An application requesting Medicare Benefits Schedule (MBS) listing of transcatheter closure of patent ductus arteriosus (PDA) was received from the Cardiac Society of Australia and New Zealand (CSANZ) by the Department of Health and Ageing in September 2012. Transcatheter closure of PDA has been established in the public health system in Australia, predominantly in the public sector, since the 1990s. The CSANZ (the applicant) indicates that transcatheter closure is standard therapy for treatment of PDA. However, the intervention has not previously been considered by the Medical Services Advisory Committee (MSAC). There are no MBS items available for transcatheter closure of PDA.

The decision analytic protocol (DAP) for transcatheter closure of PDA was considered by the Protocol Advisory Sub-Committee (PASC) of the MSAC in December 2012 and made available for public consultation in 2013. Feedback was received from the Australian and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS), and the applicant.

This report is based on the final DAP which incorporates the consultation feedback. The clinical research question for public funding is "In the treatment of patients with clinically significant PDA, what is the safety, effectiveness and cost effectiveness of transcatheter closure of the patent duct compared to surgical ligation?"

Medical condition

During foetal life, the ductus arteriosus is a normal structure that allows most of the blood leaving the right ventricle to bypass the pulmonary circulation and pass into the aortic arch. Typically, only about 10% of the right ventricular output passes through the pulmonary vascular bed. (Kim et al 2011).

The failure of the ductus arteriosus to close is a congenital disorder referred to as PDA and is either an isolated lesion or may be present in association with other defects. When the PDA fails to close there is a persistent shunt from the aorta to the pulmonary artery which results in increased pulmonary blood flow and volume loading of the left atrium and left ventricle.

What is congenital heart disease?

Congenital heart disease is any disorder of the heart or central blood vessels that is present at birth. It can take many forms and includes abnormalities of the heart or heart valves, such as holes between the pumping chambers of the heart, or valves that do not open or close properly; defects, such as the narrowing of major blood vessels, like the aorta and pulmonary artery; or combinations of disorders. Symptoms may appear at birth, or sometime thereafter, and can include breathlessness or a failure to attain normal growth and development. Most children with congenital heart disease are treated with surgery or catheter-based techniques, usually in infancy or early childhood (Hurst et al 2001).

Congenital heart disease constitutes one of the leading causes of death in the first year of life. Among babies born in Australia in 2003, ventricular septal defect (VSD) was the most commonly reported congenital heart condition, with 630 cases recorded, followed by PDA (406), atrial septal defect (ASD) (402) and pulmonary stenosis (134) (AIHW 2011).

Clinical presentation of patients with a PDA

Patients can present at any age. Three-week to 6-week-old infants can present with tachypnoea, diaphoresis, inability or difficulty with feeding, and weight loss or no weight gain. A PDA with a moderate-to-large left-to-right shunt may be associated with a hoarse cry, cough, lower respiratory tract infections, atelectasis (collapse of lung tissue), or pneumonia. With large defects, the patient may have a history of feeding difficulties and poor growth during infancy, described as failure to thrive.

The typical child with a PDA is asymptomatic. At times, the patient may report decreased exercise tolerance or pulmonary congestion in conjunction with a murmur.

Adults with a PDA that has gone undiagnosed may present with signs and symptoms of heart failure, atrial arrhythmia, or even differential cyanosis limited to the lower extremities (Medscape 2011).

Hospitalisations

In 2007–08, there were 5,802 hospitalisations in Australia with congenital heart disease as a principal diagnosis. The highest rate of hospitalisation was for ASD (6 hospitalisations per 100,000 persons), followed by VSD (2 per 100,000), Tetralogy of Fallot (1.3 per 100,000) and PDA (1.2 per 100,000). Note that hospitalisations data in this report are based on 'episodes of care' rather than the number of people hospitalised with a condition (AIHW).

AIHW procedures data for 2009-10 indicate that there were 550 procedures performed for closure of PDA of which 29% (160 procedures) were performed percutaneously.

Indications for percutaneous closure

The vast majority of PDAs are detected and closed in early childhood. Indications for transcatheter closure of a PDA in infancy include symptoms of congestive heart failure, failure to thrive, and evidence of left ventricular volume overload (Dimas 2010).

Occasionally PDAs present in later life with an asymptomatic cardiac murmur, breathlessness, endarteritis, or rarely with impaired cardiac function or pulmonary hypertension. Adult duct anatomy differs frequently from the common childhood pattern making transcatheter closure technically much more complex (Bentham 2012).

Proposed MBS funding

The applicant has indicated that the technique involved in the procedure and the devices utilised most closely resemble those of MBS item 38272 which covers transcatheter closure of ASD. MBS item 38272 has a schedule fee of $912.30 as of 1 November 2012.

However, the applicant has also provided a draft item descriptor including a proposed Schedule fee of $963.90. For the purposes of this report, the proposed fee for transcatheter closure of ASD will be used for the financial evaluation of transcatheter closure of PDA.
It should be noted that the proposed MBS item descriptor for transcatheter closure of PDA, presented in Table 1, does not refer to any associated imaging or cardiac catheterisation that may be performed at the same time of the procedure. Therefore, consideration is needed as to whether the item descriptor as proposed actually reflects the complete medical service including the associated procedures such as imaging.

Table 1 Proposed MBS item descriptor for transcatheter closure of PDA

Category 3 – Cardio-Thoracic
PATENT DUCTUS ARTERIOSUS, Transcatheter closure of (Anaes.) (Assist.) **Fee**: $912.30 **Benefit**: 75% = $684.25

Current MBS funding

MBS funding for open heart surgery for congenital heart disease can be found on the 1974 Schedule. The original generic MBS item covered operations for congenital PDA.

Two specific MBS items for division or ligation of PDA for congenital heart disease were introduced on the Schedule on 1 November 1992. The current MBS item descriptors for surgical closure of PDA are presented in Table 2.

Table 2 MBS item descriptors for 38700 and 38703 as at 1 November 2012

Category 3 – Cardio-Thoracic
38700 PATENT DUCTUS ARTERIOSUS, shunt, collateral or other single large vessel, division or ligation of, without cardiopulmonary bypass, for congenital heart disease (Anaes.) (Assist.) **Fee**: $1,067.40 **Benefit**: 75% = $800.55
38703 PATENT DUCTUS ARTERIOSUS, shunt, collateral or other single large vessel, division or ligation of, with cardiopulmonary bypass, for congenital heart disease (Anaes.) (Assist.) **Fee**: $1,924.10 **Benefit**: 75% = $1,443.10

In 2011-12, there were 41 services for item 38700 with benefits paid of $19,839, and 95 services for item 38703 with benefits paid of $41,038. It should be noted that transcatheter closure of PDA is proposed as a direct substitute for surgical closure of PDA *without* cardiopulmonary bypass (item 38700).

Therapeutic Goods Administration

The Therapeutic Goods Administration (TGA) has provided regulatory approval for a range of trademarked PDA closure devices. Details regarding the listings on the Australian Register of Therapeutic Goods (ARTG) are provided in Table 3. The devices currently listed on the ARTG include the Flipper coil (FC), the Amplatzer Duct Occluder (ADO), the ADO II, and the ADO II-Additional Sizes (AS).

The listing for the Nit-Occlud Prosthesis (number 148233), as noted in the DAP, has recently been removed from the ARTG.

There are also devices for PDA closure currently not listed on the ARTG but which are referred to in the international literature. These include Gianturco coils, the Rashkind PDA occluder (both older technologies) and the Occlutech PDA occluder (an emerging technology currently undergoing phase I trials).

Table 3 ARTG listing of PDA Occluder Devices

ARTG number	Registered	ARTG label name
St Jude Medical Australia Pty Ltd		
162137	1 June 2009	AMPLATZER Cardiac Plug - Cardiac occluder
134070	20 Dec 2006	AMPLATZER Duct Occluder - Cardiac occluder
154956	5 Sept 2008	AMPLATZER Duct Occluder II - Cardiac occluder
191422	2 Nov 2011	AMPLATZER Duct Occluder II Additional Sizes - Cardiac occluder
162140	1 June 2009	AMPLATZER TorqVue 45 X 45 degree Delivery Sheath - Cardiac occluder delivery kit
134074	20 Dec 2006	AMPLATZER TorqVue Delivery System - Cardiac occluder delivery kit
134076	20 Dec 2006	AMPLATZER TorqVue Delivery System with Pusher Catheter - Cardiac occluder delivery kit
134075	20 Dec 2006	AMPLATZER TorqVue Exchange System - Cardiac occluder delivery kit
191136	27 Oct 2011	AMPLATZER TorqVue LP Catheter - Cardiac occluder delivery kit
William A Cook Australia Pty Ltd		
188074	18 Aug 2011	Flipper 35 PDA Closure Detachable Coil Delivery System – Embolisation implant inserter
194131	24 Jan 2012	MReye Flipper PDA Closure Detachable Coil - Embolisation implant, non-neurovascular

Current listing on the Prostheses List

Private health insurers are required to pay mandatory benefits for a range of medical devices that are listed on the Prostheses List.

In 2010-11 private health insurance benefits were paid for 12 PDA devices listed on the Prostheses List. It may be reasonable to assume that MBS benefits were claimed for these procedures even though there is no current MBS item specifically for this procedure. The current listing of devices for the closure of PDA is outlined in Table 4.

Table 4 Devices for the closure of PDA - Prostheses List as at February 2013

Code	Date	Product	Sponsor	Benefit
SJ260	Bef 2005	Amplatzer Duct Occluder	St Jude Medical Australia Pty Ltd	$10,200
SJ267	Bef 2005	Amplatzer Duct Occluder II	St Jude Medical Australia Pty Ltd	$10,200
SJ280	Feb 2013	Amplatzer Duct Occluder II Additional Sizes	St Jude Medical Australia Pty Ltd	$10,200
WC294	Feb 2013	Flipper PDA Closure Detachable Coil Delivery System and Mreye Flipper PDA Detachable Embolisation Coil	Cook Medical Australia Pty Ltd	$600
WC295	Feb 2013	Mreye Flipper PDA Detachable Embolisation Coil	Cook Medical Australia Pty Ltd	$250

The two listings for the Nit-Occlud PDA Occlusion System were deleted from the Prostheses List in February 2013.

Comparator for transcatheter closure of PDA

Transcatheter closure of PDA is proposed as a direct substitute for surgical closure of PDA *without* cardiopulmonary bypass. Surgical division or ligation of PDA, without cardiopulmonary bypass, for congenital heart disease is currently funded under MBS item 38700 (see Table 2 on Page 3).

Some patients may have medication with the aim to close their ductus while other patients may immediately proceed to transcatheter or surgical intervention if there is evidence of haemodynamic overload.

Identifying patients suitable for transcatheter closure of PDA involves transthoracic echocardiography to determine whether the patent duct is suitable to be closed with a device. Additionally, the determination of suitability will depend on various clinical and echocardiographic characteristics of the patient.

According to the applicant, patients weighing less than six (6) kilograms are usually considered unsuitable for the procedure in Australia. However, parental preference for surgery versus device closure, or cardiologist preference where the duct is large and the baby is small may factor into the decision making.

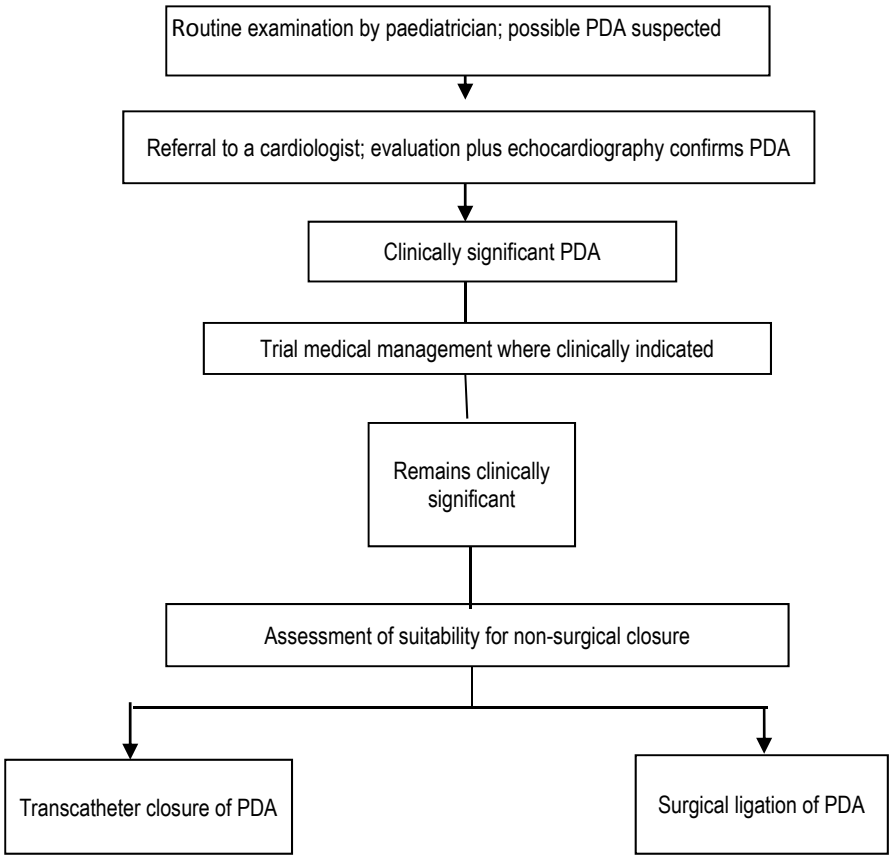
Consumer impact

Transcatheter closure of PDA is already available through the public healthcare system. It is anticipated that there will be no potential advantages (or disadvantages) to consumers should the procedure be explicitly funded under the MBS given it is a procedure that requires the proximity of cardiothoracic surgical backup in the event of complications.

Clinical need

The proposed clinical management algorithm is outlined in Figure 1.

Figure 1 Broad representation of the clinical management algorithm for diagnosis and treatment of PDA currently in Australia



Primary evidence

A systematic method has been undertaken to identify the best available evidence for the assessment of the safety, effectiveness and cost-effectiveness of transcatheter closure of PDA compared to surgical closure of PDA. No randomised controlled trials (RCTs) comparing transcatheter closure of PDA with surgical closure (without cardiopulmonary bypass) were identified for inclusion into this review. A systematic review (including a meta-analysis) of well-designed prospective RCTs would have been preferable as they are more likely to provide less biased information than other study designs about the true comparative benefits and harms of the alternative form of treatment being considered.

The quality of the evidence derived from the literature search has been limited by a number of factors. For example, the medical devices and services for transcatheter closure of PDA have been available for decades with incremental improvements to the established devices creating little incentives for large scale clinical trials. Additionally, the devices are used for a limited population i.e. those patients with clinically significant PDA who are suitable for transcatheter closure of the congenital defect.

Three non-randomised studies comparing transcatheter closure with surgical closure (all published in 2009) were identified for inclusion in this report (see Table 14 on Page 27). Two of the articles were based on studies at the Union Hospital in China:

- A prospective non-randomised study reported by Chen et al (Chin Med J 2009); and
- A retrospective study reported by Chen et al (Pediatr Cardiol 2009).

Chen et al (Chin Med J 2009) reported on a non-randomised study of 255 patients having isolated PDA with a minimal diameter of ≥4 mm. The patients were assigned to either the device or surgical closure group according to the patients' and/or their parents' preference with post procedural follow up of at least five years. The study concluded that transcatheter Amplatzer occlusion was less invasive and associated with fewer complications and residual shunt, and as effective in the regression of pulmonary hypertension and left ventricular dilation.

Chen et al (Pediatr Cardiol 2009) reported on a retrospective study of 181 patients aged ≥6 months with a PDA of 4-16 mm. A total of 130 patients underwent surgical closure for PDA, whereas 51 patients underwent Amplatzer occlusion. There were no deaths and no residual left-to-right shunting in either group at last follow-up. The study concluded that, although transcatheter Amplatzer device occlusion is as effective as and less invasive than surgical closure for PDA, surgical closure is less costly.

The third article was based on a retrospective study at the Veterans General Hospital in Taiwan. Lin et al (2009) reported on 20 infants born full-term and aged ≤3 months with a PDA ≥3 mm. The data were compared with a historical control group of young infants with large, symptomatic PDA in whom surgical ligation was performed previously at the hospital i.e. a non concurrent group of patients who historically received surgery during a different time period. The study reported that transcatheter implantation of the ADO is more cost effective than surgery for young infants, with significantly less length of stay in the hospital, length of intensive care, and hospital charges. However, the report notes that the implantation of the ADO is more expensive than coils.

In addition to the three studies identified in the literature search, the applicant also provided an article for consideration by the MSAC titled "Transcatheter Closure of the Patent Ductus Arteriosus: An Intention to Treat Analysis" which has been published in 2013 on behalf of ANZSCTS and the CSANZ. The Queensland Paediatric Cardiac Service, at the Mater Children's Hospital in Brisbane, established a cardiac catheterisation registry in 2003 which provided the dataset for analysis of all patients undergoing cardiac catheterisation with the intent to perform transcatheter closure of a PDA.

The registry included the analysis of 228 children with an isolated PDA who were admitted to the catheter laboratory at a single institution from January 2003 to December 2011. Sheridan et al (2013) reported successful occlusion in 96.2% of 208 patients (with the device of first choice) when transcatheter closure was intended. Of the 208 patients selected for transcatheter closure, all were followed through in the analysis. However there was differential follow up periods between the two devices. The study reported the use of FC and ADO with device selection evolving to ADO exclusively in 2011.

Sheridan et al (2013) concluded that transcatheter closure of the PDA has a high degree of safety and efficacy. It should be noted that this registry compared the relative merits of the two commercially available devices predominantly used in Australia for transcatheter closure of PDA. The relative merits of transcatheter closure of PDA versus surgery (in those patients who were potentially candidates for either approach) was not considered.

What are the economic considerations?

The review of literature has identified that transcatheter closure of PDA is likely to be non-inferior in terms of comparative safety and effectiveness despite both internal and external validity issues with the limited evidence base. Therefore a cost minimisation analysis is presented for the service relative to that of surgical closure of PDA. (see Table 21 on Page 33).

The cost-minimisation analysis takes into account that the service is currently provided for a small numbers of patients, and therefore the total government expenditure on the service is likely to be small. In the private setting, there is an estimate of 55 procedures for transcatheter closure of PDA in 2012-13 (see Table 33 on Page 45).

The report has considered the extent to which the analysis is limited by the quality of the underlying data and the extent of uncertainties in the clinical evidence. Transcatheter closure of PDA aims to successfully deliver the device with no residual shunt and complete regression of signs of volume overload. The outcomes generated by the economic evaluation represent the final outcomes of treatment.

The analysis did not restrict the service by the age of the patient or the type of the defect. Taking into account that the most commonly reported length of follow-up visits following transcatheter or surgical closure of PDA is periodic appointments over the next year, the follow-up period has not been factored in to the analysis. The potential for use of the service in a wider population or setting than the target population and setting is unlikely (see Table 25 on Page 38).

The comparison of the cost per patient for transcatheter versus surgical closure of PDA is summarised in Table 31 on Page 43. The procedure generates cost offsets from reduced use of health care resources. However, the cost of the ADO device ($10,200) significantly adds to the overall cost of the procedure.

In terms of cost-effectiveness of health resources (excluding the device cost), transcatheter closure of PDA provides relative benefit, for example shorter recovery time with a significantly decreased length of hospital stay, at lower costs (See Table 5).

The overall conclusion from the analysis is that transcatheter closure is currently undertaken as a safe and effective treatment for patients with PDA.

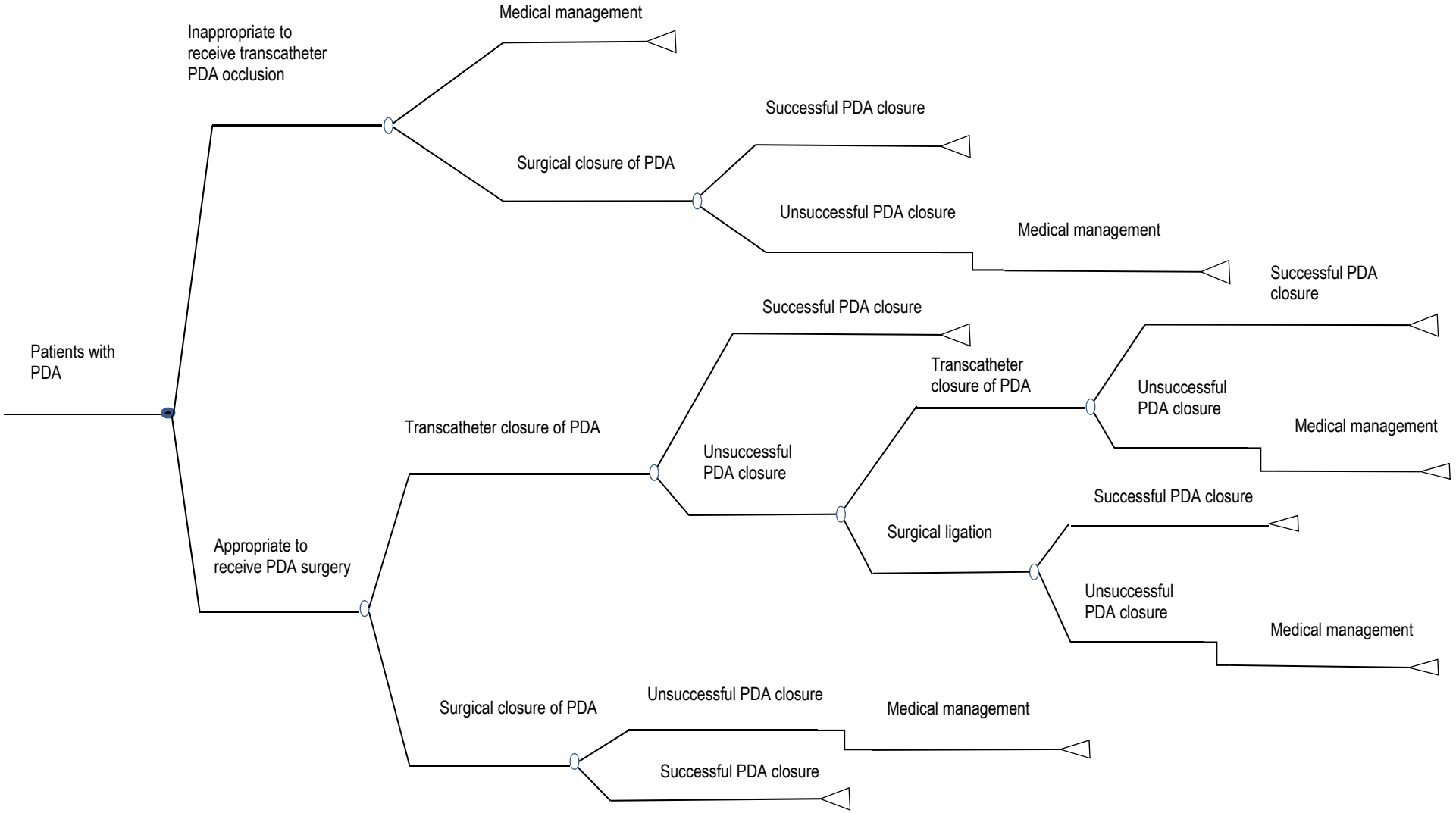
Table 5 Summary of parameters used in the analysis

Parameter	Transcatheter	Surgery
MBS	$2,210	$2,772
Device (ADO)	$10,200	-
ICU, laboratory/theatre & ward	$5,189	$13,061
Hospital stay	2 days	9 days

Rationale for cost-effectiveness

The decision tree for patients requiring closure of PDA is presented in Figure 2.

Figure 2 Decision analytic pathway for patients suitable for transcatheter closure of PDA



What are the financial considerations?

The procedure for transcatheter or surgical closure of PDA is mainly performed on young infants in major public hospitals. Currently there are a small number of procedures performed in the private sector. It is anticipated that the volume of services will remain constant should MBS funding be made available for transcatheter closure of PDA.

AIHW data for 2010-11 indicate that for closure of PDA, of a total of 559 hospital separations, there were 66 admissions to a private hospital and 493 admissions to a public hospital of which 119 were for private patients. The data also indicate that there were 60 same day patient separations for the public hospital admissions. There were no same day patient separations for the private hospital admissions.

A large proportion of the cost of transcatheter closure of PDA is the cost of the device itself. Devices currently listed on the Prostheses List include the ADO and FC. For the purposes of the financial analysis, the cost of the ADO ($10,200) has been used for the financial analysis. The cost for the ADO accounted for 58% of the total cost of the procedure in the financial analysis. This percentage is consistent with the study by Chen et al (Pediatr Cardiol 2009), who reported that the chief difference in costs between the transcatheter and surgical groups was the cost of the Amplatzer device, which accounted for 61.5% of the total cost of the device group.

Complication rates reported for closure of PDA are similar for both transcatheter and surgical groups and have not been factored into the financial analysis. Chen et al (Chin Med J 2009) reported that more acute procedure-related complications were recorded in the surgical group as compared with the transcatheter group. There were no early or late deaths, systemic infection or infectious endocarditis in either group of patients, and no thrombosis, thrombo-embolism, haemolysis and ADO dislodge in the transcatheter group. Atrial fibrillation was observed in one patient from the transcatheter group in the catheterisation laboratory, and it was converted by amiodarone. Lin (2009) reported that various minor, procedure-related complications occurred in both groups.

Overall, the cost of transcatheter closure of PDA is more expensive compared with surgery ($17,599 and $15,833 respectively) (see Table 36 on Page 47). The length of hospital stay is decreased for transcatheter closure of PDA compared with surgery. The difference in Intensive Care Unit (ICU) stay is associated with lower MBS costs ($2,210 and $2,772 respectively) due to the associated medical management for the surgical patients following admission to an ICU unit.

The comparison of the estimated annual MBS cost over the four years from 2013-14 for transcatheter versus surgical closure of PDA is shown in Table 6.

Table 6 Comparison of annual MBS cost – surgery vs transcatheter

	2013-14	2014-15	2015-16	2016-17
Surgery without cardiopulmonary bypass	$155,598	$158,415	$161,283	$164,203
Transcatheter closure	$124,020	$126,265	$128,551	$130,878
Difference in total cost	$31,578	$32,150	$32,732	$33,324

Based on 75% benefit of the Schedule fee as at 1 November 2012

Discussion

Surgical ligation for a PDA was first reported by Gross and Hubbard in 1938 and for many decades has remained the gold standard by which the efficacy and safety of newer therapies should be measured. Transcatheter closure of PDA, first described in 1967, has become the preferred method of treatment for children beyond the neonatal period (Sheridan et al 2013).

A systematic method has been undertaken to identify the best available evidence for the assessment of the safety, effectiveness and cost-effectiveness of transcatheter closure of PDA relative to surgical closure of PDA. However, the quality of the evidence derived from the literature search has been limited by a number of factors including that transcatheter closure of PDA has been available for decades with incremental improvements to the established devices.

Is it safe?

Recent studies indicate that closure of PDA can be achieved safely by transcatheter techniques.

Sheridan et al (2013) concluded that ADO I is the current device of choice, resulting in complete closure of all patients with no significant complications. The article also indicated that the development of devices with different design characteristics is likely to result in improved outcomes, particularly in the patient group weighing <6 kg with clinically significant PDA.

In the comparative study of long-term clinical outcome between ADO and surgical closure of PDA (Chen et al Chin Med J 2009), there were no cardiac deaths or significant complications in the transcatheter closure group. Acute major complications such as obstruction of the aorta and left pulmonary artery, embolisation, and haemolysis were not encountered in the study. The surgical group recorded more acute procedure-related complications as compared with the transcatheter closure group. Other complications associated with ADO, such as infective endocarditis, device integrity problems and deformations, were not reported in the 5 year follow-up period of the study.

Is it effective?

The available information and evidence for the effectiveness of transcatheter occlusion of PDA indicate that the procedure is effective with a high degree of successful closure.

Sheridan et al (2013) reported successful occlusion in 96.2% of 208 patients (with the device of first choice) when transcatheter closure was attempted. The study reported the use of FC and ADO with device selection evolving to ADO exclusively in 2011. It should be noted that this study looked at ‘single arm’ registry data – within that arm was simply a device comparison. There was no aggregate comparison of the transcatheter closure technique generically with surgical closure.

Chen et al (Chin Med J 2009) reported recovery time in the ADO group was much shorter than in the surgical group, which was mainly due to fewer general anaesthesia and no surgical-related issues and complications. Additionally, unlike the residual PDA after surgical ligation which persisted if untreated, residual shunt detected soon after ADO disappeared automatically during the follow-up, which may be partially attributed to the self-expanding design of ADO or clot formation. The conclusion was that ADO was less invasive and associated with fewer complications and residual shunt, and as effective in the regression of pulmonary hypertension and left ventricular dilation. The article indicated that surgical closure should be reserved for those in whom the PDA is too large for device closure or at centres without access to device closure.

This review of the literature has not chosen to synthesize the results of the selected studies to statistically test the assertion around the clinical claim of non-inferiority. Ideally a more complicated analysis characterising both the heterogeneity across the included studies and the residual uncertainty around the comparative claim would have been preferable but this would have been challenging given the mix of prospective and retrospective non randomised studies.

The prospective study by Chen et al (Chin Med J 2009), the highest quality study identified for analysis, found that there was no statistically significant difference between the baseline characteristics of the transcatheter group and the surgical group (noting that the ratio of patients in the surgical group versus the transcatheter group in this study was 2.5:1). During long term post-procedural follow up, this study has suggested that that the rate of persistent residual shunt (PRS) free survival was slightly lower in the surgical group (91.3%) compared to the transcatheter group (98.6%) (overall P = 0.037). On the other metrics of treatment success (both in the short and long term) both treatment choices were by and large indistinguishable.

However, given the potential for systematic error (bias) inherent with the methodology used in the study reported by Chen et al (Chin Med J 2009), the conclusion from this study, as well as the other comparative studies needs to be interpreted with caution. Saying this, across the clinical parameters measured in the three comparative studies it is reasonable to infer that transcatheter closure is likely to be non-inferior (in terms of clinical effectiveness) to surgical closure of PDA.

Is it cost-effective?

The procedure for transcatheter or surgical closure of PDA is mainly performed on young infants in major public hospitals. Currently there are a small number of procedures performed in the private sector. It is anticipated that the volume of services will remain constant should MBS funding be made available for transcatheter closure of PDA.

The study reported by Sheridan et al (2013) did not include a cost analysis. The article noted that while the ADO is more expensive, the financial and patient emotional cost related to FC complications is likely to support the use of ADO. Sheridan et al (2013) also reported that it has been their practice to observe patients overnight following PDA occlusion, but with a demonstrably low complication rate, it may be appropriate to move to same day discharge, which would further mitigate the cost difference.

Conclusion

Transcatheter closure of PDA is reported to have a high degree of safety and efficacy. The evolution of devices utilised has included the Raskind PDA Occluder, Gianturco and Flipper coils, Nit-occlud coils and the ADOs. In the current era FC and the ADO are the devices which are predominantly used (Sheridan et al 2013).

The cost of the ADO is substantially more expensive than coils. However, the study provided by the applicant (Sheridan et al 2013) indicates that the ADO may be the device of first choice in the current era.

Overall, the cost of transcatheter closure of PDA is more expensive compared with surgery ($17,599 and $15,833 respectively). A large proportion of the cost for transcatheter closure of PDA is the cost of the device itself ($10,200 for the ADO).

The length of hospital stay is decreased for transcatheter closure of PDA compared with surgery. The difference in ICU stay is associated with lower MBS costs ($2,210 and $2,772 respectively) due to the associated medical management for the surgical patients following admission to an ICU unit.

In summary, both treatment choices appear to be the main stay of curative treatment for PDA. One is not intending to entirely substitute the other at a global level, rather decision on treatment is heavily dependent on individual factors and whether the anatomical and physiological characteristics of the patent ductus is amenable to transcatheter closure.

CONTEXT

Background

During foetal life, the ductus arteriosus is a normal structure that allows most of the blood leaving the right ventricle to bypass the pulmonary circulation and pass into the aortic arch. From the sixth week of foetal life onwards, the ductus is responsible for most of the right ventricular outflow, and it contributes to 60% of the total cardiac output throughout the foetal life. Only about 5-10% of its outflow passes through the lungs (Kim et al 2011).

Normally, functional closure of the ductus arteriosus occurs by about 15 hours of life in healthy infants born at term. This occurs by abrupt contraction of the muscular wall of the ductus arteriosus, which is associated with increases in the partial pressure of oxygen coincident with the first breath (Kim et al 2011).

Although functional closure usually occurs in the first few hours of life, true anatomic closure, in which the ductus loses the ability to reopen, may take several weeks. Spontaneous closure after 5 months is rare in the full-term infants (Kim et al 2011).

The failure of the ductus arteriosus to close is a congenital disorder referred to as PDA and is either an isolated lesion or may be present in association with other congenital defects. When the PDA fails to close there is a persistent shunt from the aorta to the pulmonary artery which results in increased pulmonary blood flow and volume loading of the left atrium and left ventricle.

What is congenital heart disease?

Congenital heart disease is any disorder of the heart or central blood vessels that is present at birth. It can take many forms and includes abnormalities of the heart or heart valves, such as holes between the pumping chambers of the heart, or valves that do not open or close properly; defects, such as the narrowing of major blood vessels, like the aorta and pulmonary artery; or combinations of disorders. Symptoms may appear at birth, or sometime thereafter, and can include breathlessness or a failure to attain normal growth and development. Most children with congenital heart disease are treated with surgery or catheter-based techniques, usually in infancy or early childhood (Hurst et al 2001).

Congenital heart disease constitutes one of the leading causes of death in the first year of life. Among babies born in Australia in 2003, ventricular septal defect (VSD) was the most commonly reported congenital heart condition, with 630 cases recorded, followed by PDA (406), atrial septal defect (ASD) (402) and pulmonary stenosis (134) (AIHW 2011).

Incidence of PDA

According to the applicant, the prevalence of congenital heart disease in Australia is about 1 in 100 and PDAs would represent 10% of the disease burden (incidence 1 in 1000).

On average in the United States, PDA occurs in about 8 out of every 1,000 premature babies, compared with 2 out of every 1,000 full-term babies. Premature babies also are more vulnerable to the effects of PDA (National Heart Lung and Blood Institute 2011). European statistics indicate an incidence of 1 in 2000 full term infants. A higher prevalence is found in low birth weight premature babies (Orphanet 2009).

Hospitalisations

In 2007–08, there were 5,802 hospitalisations in Australia with congenital heart disease as a principal diagnosis. The highest rate of hospitalisation was for ASD (6 hospitalisations per 100,000 persons), followed by VSD (2 per 100,000), Tetralogy of Fallot (1.3 per 100,000) and PDA (1.2 per 100,000). The lowest hospitalisation rate was for pulmonary stenosis, with 0.3 hospitalisations per 100,000 people. Note that hospitalisations data in this report are based on 'episodes of care' rather than the number of people hospitalised with a condition (AIHW 2011).

The applicant indicates that there are 200-300 patients with PDAs that require closure in Australia each year. However, AIHW procedures data for 2009-10 indicate that there were 550 procedures performed for closure of PDA of which 29% (160 procedures) were performed percutaneously (see Table 7).

In 2009-10, AIHW data indicate that children under 15 years of age accounted for 82% (453 procedures) of the total 550 procedures for closure of PDA.

Table 7 AIHW procedures data for closure of PDA

AIHW data	2008/09	2009/10
Percutaneous closure		
Under 5 years	76	91
5 to 14 years	19	13
15 years and over	48	56
Total	**143**	**160**
Surgical closure		
Under 5 years	372	340
5 to 14 years	9	9
15 years and over	40	41
Total	**421**	**390**
Total procedures	**564**	**550**

A procedure is defined as a clinical intervention that is surgical in nature, carries a procedural risk, carries an anaesthetic risk, requires specialised training, and/or requires special facilities or equipment only available in an acute care setting.

Clinical presentation of patients with a PDA

Patients can present at any age. Three-week to 6-week-old infants can present with tachypnoea, diaphoresis, inability or difficulty with feeding, and weight loss or no weight gain. A PDA with a moderate-to-large left-to-right shunt may be associated with a hoarse cry, cough, lower respiratory tract infections, atelectasis (collapse of the lung tissue), or pneumonia. With large defects, the patient may have a history of feeding difficulties and poor growth during infancy, described as failure to thrive. However, frank symptoms of congestive heart failure are rare.

The typical child with a PDA is asymptomatic. At times, the patient may report decreased exercise tolerance or pulmonary congestion in conjunction with a murmur.

Adults with a PDA that has gone undiagnosed may present with signs and symptoms of heart failure, atrial arrhythmia, or even differential cyanosis limited to the lower extremities (Medscape 2011).

Left untreated, patients with a large PDA are at risk to develop Eisenmenger Syndrome, in which the pulmonary vascular resistance (PVR) can exceed systemic vascular resistance, and the usual left-to-right shunting reverses to a right-to-left direction. At this stage, the PVR is irreversible, closure of the PDA is contraindicated, and lung transplantation may be the only hope for long-term survival (Medscape 2011).

Indications for percutaneous closure

The vast majority of PDAs are detected and closed in early childhood. Indications for transcatheter closure of a PDA in infancy include symptoms of congestive heart failure, failure to thrive, and evidence of left ventricular volume overload (Dimas 2010).

The Amplatzer Duct Occluders (ADOs) come in a range of sizes: five sizes for the ADO I, eight sizes for the ADO II, and nine sizes for the ADO II Additional Sizes (AS). The use of the ADO I is more convenient for moderate- and large-sized defects, and deployment of the ADO II is much easier than that of the ADO II AS. Potential complications of the left pulmonary artery and occlusion of the descending aorta can be avoided by deploying the new, miniaturised ADO II AS device inside the duct. Transcatheter treatment of PDA in premature newborns and smaller infants will be performed more easily with the ADO II AS (Baspinar 2012).

Occasionally PDAs present in later life with an asymptomatic cardiac murmur, breathlessness, endarteritis, or rarely with impaired cardiac function or pulmonary hypertension. Adult duct anatomy differs frequently from the common childhood pattern making transcatheter closure technically much more complex (Bentham 2012).

Technique for transcatheter closure of PDA

The use of the Portsmann plug and the original Rashkind device to close patent ducts prompted the development of both coils and dedicated ductal closure plugs.

The technique for closure depends on whether one uses coils or Amplatzer plugs. Coils are generally delivered retrograde from the femoral artery, with two thirds of the first coil loop delivered in the pulmonary artery, and the other 2.5 to 3.5 loops of coil delivered in the aortic ductal ampulla. Larger ducts may require two coils, or the use

of a snare or bioptome to hold the first coil in place while a second coil is delivered. The multiple coil technique has become less necessary with the development of Amplatzer PDA plugs.

When using an Amplatzer PDA plug, the ductus is crossed from the pulmonary artery side, the distal end of the catheter is positioned in the descending aorta, and the Amplatzer plug, with its larger aortic cap, is deployed in the aorta, pulled back against the aortic ampulla, and the rest of the body of the plug is deployed within the ductus so that a small part of the plug extrudes toward the pulmonary end of the ductus. Both the lateral tension of the nitinol mesh and aortic pressure keeps the Amplatzer plug in place, and the same thing is true for coils (Lock 2006).

Proposed MBS listing

The applicant has indicated that the technique involved in the procedure and the devices utilised most closely resemble those of MBS item 38272 which covers transcatheter closure of ASD. MBS item 38272 has a schedule fee of $912.30 as of 1 November 2012.

However, the applicant has also provided a draft item descriptor including a proposed Schedule fee of $963.90. For the purposes of this report, the proposed fee for transcatheter closure of ASD will be used for the financial evaluation of transcatheter closure of PDA. Additionally, clinical advice indicates the proposed MBS listing should only attract a 75% (in-hospital) benefit.

It should be noted that the proposed MBS item descriptor for transcatheter closure of PDA, presented in Table 1 on Page 3, does not refer to any associated imaging or cardiac catheterisation that may be performed at the same time of the procedure. Therefore, consideration is needed as to whether the item descriptor as proposed actually reflects the complete medical service including the associated procedures such as imaging.

Current MBS listing

MBS funding for open heart surgery for congenital heart disease can be found on the 1974 Schedule. The original generic MBS item covered operations for congenital PDA.

Two specific MBS items for division or ligation of PDA for congenital heart disease were introduced on the Schedule on 1 November 1992. The current MBS item descriptors for surgical closure of PDA are presented in Table 2 on Page 3.

The number of services claimed for these items is listed in Table 8. It should be noted that transcatheter closure of PDA is proposed as a direct substitute for surgical closure of PDA *without* cardiopulmonary bypass (item 38700).

Table 8 MBS items 38700 and 38703 – Usage 2007/08 – 2011/12

MBS data	2007/08	2008/09	2009/10	2010/11	2011/12
38700					
Under 5 years	41	39	30	46	34
Total	52	49	38	49	41
38703					
Under 5 years	74	38	43	76	86
Total	82	42	55	91	95

In 2011-12, there were benefits paid of $19,839 for item 38700, and benefits paid of $41,038 for item 38703.

Therapeutic Goods Administration

The Therapeutic Goods Administration has provided regulatory approval for a range of trademarked PDA closure devices. Details regarding the listings on the Australian Register of Therapeutic Goods (ARTG) are provided in Table 3 on Page 4. The devices currently listed on the ARTG include the Flipper coil (FC), ADO, ADO II and ADO II-AS. The listing for the Nit-Occlud Prosthesis (148233), as noted in the DAP, has recently been removed from the ARTG.

There are also a couple of devices for PDA closure currently not listed on the ARTG but which are referred to in the international literature. These include Gianturco coils, the Rashkind PDA occluder (both older technologies) and the Occlutech PDA occluder (an emerging technology currently undergoing phase I trials) (Clinicaltrials.gov identifier NCT01479218).

According to the applicant, FC and ADO are the devices most commonly used in the current era.

Prostheses List

Private health insurers are required to pay mandatory benefits for a range of medical devices that are listed on the Prostheses List.

In 2010-11 private health insurance benefits were paid for 12 PDA devices listed on the Prostheses List. It may be reasonable to assume that MBS benefits were claimed for these procedures even though there is no MBS item currently specifically for this procedure. The current listing of devices for the closure of PDA is outlined in Table 4 on Page 5.

Comparator for transcatheter closure of PDA

Surgical ligation of PDA *without* cardiopulmonary bypass (MBS item 38700) has been identified as the appropriate comparator for transcatheter closure of PDA, in particular an isolated PDA that is not associated with co-existent congenital cardiac abnormalities. Surgical ligation of PDA with cardiopulmonary bypass (MBS item 38703) is a more complex procedure usually performed with other cardiac procedure in association with co-existent congenital cardiac abnormalities.

The Schedule fee for item 38700 as of 1 November 2012 is $1,067.40 (see Table 2 on Page 3). The associated explanatory note for item 38700 is presented in Table 9.

Table 9 Current Explanatory Note associated with item 38700

T.8.69 Cardiac and Thoracic Surgical Items Items 38470 to 38766 must be performed using open exposure or minimally invasive surgery which excludes percutaneous and transcatheter techniques unless otherwise stated in the item.

The utilisation rate for MBS item 38700 for surgical closure of PDA, without cardiopulmonary bypass, is low. In 2011-12 there were only 41 procedures in total performed (see Table 8 on Page 19).

Consumer impact

Transcatheter closure of PDA is already available through the public healthcare system. It is anticipated that there will be no potential advantages (or disadvantages) to consumers should the procedure be explicitly funded under the MBS given it is a procedure that requires the proximity of cardiothoracic surgical backup in the event of complications.

Clinical management algorithm

The current clinical management algorithm for diagnosing and treating patients with PDA is illustrated in Figure 1 on Page 6. Given transcatheter closure has been established for some time in the Australian health care setting, only one clinical management algorithm is presented.

It should be noted that the clinical assessment in which patients are selected for either transcatheter or surgical closure of their PDA may be occurring during their initial presentation. The diagram illustrates this as sequential but in clinical reality many clinicians are ascertaining the characteristics of the PDA immediately on referral.

Differences between transcatheter and surgical closure of PDA

Indications

Management of PDA currently varies. Asymptomatic neonates may be monitored as outpatients, while symptomatic patients, depending on the onset and severity of the symptoms, PDA can be treated medically or surgically subject to the severity of the opening. Paediatric patients generally present with tachycardia, breathlessness and/or respiratory problems and poor feeding. Diagnosis is by echocardiogram and in most neonatal intensive care units in Australia the first line medical therapy for symptomatic PDA is usually ‘long courses’ of indomethacin (Hoellering et al 2009). Surgery is considered if the PDA fails to close or reopens following the medical therapy. Traditionally, surgical ligation of the PDA involves a thoracotomy and dissection and ligation of the PDA. The PDA may also be clamped, oversewn or clipped.

Another emerging minimally invasive option is video assisted thoracoscopic surgery (VATS). It is not clear if thoracoscopy provides shorter hospital stays or decreases costs. Additionally, thoracoscopy is contraindicated for adults with calcified PDA. Because of the limited control and visualisation available, thoracoscopy in

neonates is not widely advocated; it appears to have no definite advantage, given that the open procedure uses such a small incision. Clinical advice indicates that in Australia, the video assisted thoracoscopic approach is not used for paediatric patients.

Contraindications

There is considerable debate in the literature over when a PDA should be treated; there have been trials of treatment approaches involving pre-symptomatic, symptomatic and prophylactic treatment (to reduce the risk of bacterial endocarditis). At present, the therapeutic options in Australia for PDA are medication (indomethacin or ibuprofen), surgery by open approach or minimally invasive video assisted surgery and transcatheter closure. It is unclear how many of these patients may be managed with medication alone.

At present medical devices used in transcatheter closure of PDA are unsuited to closure of very small or very large PDAs as well as of PDA with certain morphology as per the Krichenko classification. The Krichenko classification is based upon angiographic appearance and includes Type A (conical), Type B (window), Type C (tubular), Type D (complex) and Type E (elongated) (Krichenko et al 1989).

In relation to size, PDA with a minimal ductal diameter of <2 mm are generally regarded as small PDA and ducts with a minimal ductal diameter of 2-4 mm are regarded as medium size PDA and those >4mm classified as large PDA. However the cut off between what is regarded as small, medium to large varies across the literature. Further ductal length is sometimes measured to guide device selection.

The various devices available are designed to accommodate a variation of PDA size and morphology but generally speaking PDAs that are too small or too large in diameter or oddly shaped (non-conical or window like) tend to be unsuited for closure by transcatheter approach. For some of these patients surgical ligation may be the only alternative. There is no strict upper limit on ductal diameter over which transcatheter is no longer suitable as some larger PDAs may be shaped in a way that still make them amendable to transcatheter intervention. Vice versa, some smaller PDAs may not be suitable for transcatheter closure because neither a coil or occluding device are likely to neatly fit into the lumen of the ductus running the risk of protrusion into the pulmonary artery or the aorta. Therefore the target population for transcatheter closure of PDA is a sub-group of the total number of patients with PDAs requiring closure.

Complications

Recent studies indicate that closure of PDA can be achieved safely by transcatheter techniques. Sheridan et al (2013) concluded that ADO I is the current device of choice, resulting in complete closure of all patients with no significant complications. The article also indicated that the development of devices with different design characteristics is likely to result in improved outcomes, particularly in the patient group weighing <6 kg with clinically significant PDA.

In the prospective non randomised study of long-term clinical outcome comparing between ADO and surgical closure of PDA (Chen et al Chin Med J 2009), there were no cardiac deaths or significant complications in the transcatheter closure group. Acute major complications such as obstruction of the aorta and left pulmonary artery, embolisation, and haemolysis were not encountered in the study. The surgical group

recorded more acute procedure-related complications as compared with the transcatheter closure group. Other complications associated with ADO, such as infective endocarditis, device integrity problems and deformations, were not reported in the 5 year follow-up period of the study.

Clinical claim

As the medical devices to close the PDA are deployed via transcatheter approach, it is possible to avoid a thoracotomy and dissection of friable ductus tissue. As such, it is proposed that treatment via transcatheter closure of PDA may have an arguably lower complication rate, less patient discomfort and shorter patient hospital stays and thus a more favourable safety profile.

The overall clinical claim in terms of clinical effectiveness is that transcatheter closure of PDA will achieve the same long term patient outcome as achieved by surgical ligation with an overall net claim of non-inferiority.

Primary elements

The PICO criteria for the evaluation are provided in Table 10.

Table 10 Summary of PICO to define research questions

Patients	Patients with clinically significant PDA (identified by transthoracic echocardiography)
Intervention	Transcatheter closure of PDA
Comparator	Surgical closure of PDA
Outcomes	Effectiveness including but not limited to: • successful duct closure • no residual shunt detected • equivalent long term outcome to surgical ligation • resolution of disease process (absence of cardiac failure) • vascular occlusion • patient mortality • procedure time • duration of hospitalisation post-procedure • recovery time post-procedure Safety including but not limited to: • patient mortality • infection • bleeding at catheterisation site • re-operation for failed transcatheter deployment of device • incidence of device complications including but not limited to: - unable to achieve stable position - migration/dislodgement/protrusion of device - obstruction of aorta or pulmonary artery by device - device embolisation - inappropriate deployment of device

EVIDENCE

Introduction

A systematic method has been undertaken to identify the best available evidence for the assessment of the safety, effectiveness and cost-effectiveness of transcatheter closure of PDA relative to surgical closure of PDA. The quality of the evidence derived from the literature search has been limited by a number of factors. For example, the medical devices and services for transcatheter closure of PDA have been available for decades with incremental improvements to the established devices. Additionally, the devices are used for a limited population i.e. those patients with clinically significant PDA who are suitable for transcatheter closure of the congenital defect.

PDA is present in up to 70% of preterm infants born before 28 weeks' gestation. Left-to-right PDA shunts have been associated with neonatal morbidities, including bronchopulmonary dysplasia, necrotising enterocolitis, and increased mortality; however, to date, no randomised controlled trial has addressed the potential causative role of persistent PDA in any of these morbidities (Wickremasinghe et al 2012).

In regard to prophylactic medical treatment, although randomised controlled trials have shown that prophylactic indomethacin treatment decreases certain short-term morbidities, such as symptomatic PDA and pulmonary and/or intracranial haemorrhage, long-term benefits from prophylactic indomethacin have yet to be demonstrated (Wickremasinghe et al 2012).

There is even less information available for guidance when indomethacin therapy fails to close a PDA. However, recent studies using near-infrared spectroscopy have raised new concerns about the potential for long-term neurodevelopmental problems following prolonged PDA exposure because of decreased cerebral oxygenation in the presence of a persistent PDA (Wickremasinghe et al 2012).

Although a moderate-size PDA needs to be closed by the time a child is 1-2 years old, there is great uncertainty about whether it needs to be closed during the neonatal period. While 95% of neonatologists believe that a moderate-size PDA should be closed if it persists in infants (born before 28 weeks) who still require mechanical ventilation, the number that treat a PDA when it occurs in infants that do not require mechanical ventilation varies widely (Clyman et al 2012).

Under the assumption that closure of a PDA is beneficial, most clinical trials have focused on the most expeditious way in which to close a PDA without looking at whether closing the PDA improves outcome. Those trials that have included control groups treated with a placebo have permitted treatment of PDA that persisted after reaching a defined study endpoint, often just days after enrolment. This study design has resulted in high rates of treatment in the "placebo" group (usually in the range of 40%). Additionally, the detection of adverse effects is equally compromised (Bose 2007).

Search strategy

The search for information on the treatment of PDA involved three approaches:

1. Search of the published literature, including reviews by the U.S. Food and Drug Administration (FDA) and the National Institute for Health and Clinical Excellence (NICE);
2. Search of registers of clinical trials, including the U.S. National Institutes of Health, the Cochrane Central Register of Controlled Trials and the Australian New Zealand Clinical Trials Registry (ANZCTR); and
3. Manual checking of the reference lists of all included articles.

The search of FDA literature retrieved a Summary of Safety and Effectiveness Data for the AMPLATZER® Duct Occluder (Premarket Approval Application Number: P020024, Date of Notice of Approval to Applicant: May 14, 2003). The conclusions drawn from the studies presented in the Summary were that the effectiveness of the ADO was demonstrated by successful closure of PDA at the 12-month follow-up. Complete closure by echocardiography was 98.6%. The total serious and major adverse event rate associated with the ADO of 1.3% demonstrated the device provided a reasonable assurance of safety in the closure of PDA in the intended population.

The Cochrane Library search retrieved the NICE issued guidance in October 2004 for the endovascular closure of PDA. The guidance indicated that the current evidence on the safety and efficacy of endovascular closure of PDA appeared adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance. The procedure should be performed in units where there are arrangements for cardiac surgical support in the event of complications.

There were no trials for surgical or transcatheter closure of PDA retrieved from the search of ANZCTR.

The search of the Medline, Embase and the Cinahl databases was conducted in March and April 2013. The complete search strategy is presented in Table 11.

Table 11 Complete search strategies

Database	Search strategy
MEDLINE	1. *Ductus Arteriosus, Patent/ 2. Septal occluder device/ 3. Cardiac catheterization/ 4. 2 or 3 5. 1 and 4 6. Limit 5 to (English language and humans and yr = 2002-current) 7. ("clinical trial" OR "Clinical Trial, Phase I" OR "Clinical Trial, Phase II" OR "Clinical Trial, Phase III" OR "Clinical Trial, Phase IV" OR "comparative study" OR "controlled clinical trial" OR "meta-analysis" OR "multicenter study" OR "practice guideline" OR "randomized controlled trial" OR review).pt 8. 6 and 7 9. Exp costs-and-cost-analysis/ 10. Ec.fs 11. 9 or 10 12. 6 and 11 13. 8 or 12 All terms followed by "/" are MeSH headings; * = subject is a major focus of the article; exp = term is exploded to include all narrower terms; ec = economics subheading; fs = floating subheading - meaning that the subheading may be attached to any of the subject headings
EMBASE	1. *Patent Ductus Arteriosus, Patent/ 2. Septal occluder/ 3. heart catheterization/ 4. transcatheter and closure 5. 2 or 3 or 4 6. 1 and 5 7. Limit 6 to (English language and humans and yr = 2002-current) 8. (clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or comparative study or major clinical study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial or meta analysis or review or systematic review).sh. 9. economic aspects/ or exp economic evaluation 10. 7 and (8 or 9) *Patent Ductus Arteriosus/ - asterisk means subject is a major focus of the article; / = term is subject heading; sh = subject heading; pt = publication type; exp = term is "exploded" to include narrower terms
CINAHL	1. *Ductus Arteriosus, Patent/ 2. Prostheses and implants/ 3. heart catheterization/ 4. transcatheter and closure 5. 2 or 3 or 4 6. 1 and 5 7. Limit 6 to (English language and humans and yr = 2002-current) 8. (clinical trial or meta analysis or practice guidelines or randomized controlled trial or review or systematic review).pt 9. ec.fs or exp costs and cost analysis 10. 8 or 9 11. 7 and 10 *Ductus Arteriosus, Patent/ - asterisk means subject is a major focus of the article; / = term is subject heading; pt = publication type; ec = economics subheading; exp = term is "exploded" to include narrower terms

Search results

The search of the published literature from the Medline, Embase and Cinahl databases retrieved 86 results with a total of 81 citations excluding duplicates from the Embase and Cinahl databases (See Table 12**)**. Three comparative studies were identified for inclusion in this report (see Table 14 on Page 27).

Table 12: Summary of retrieved articles from the database search

	MEDLINE	EMBASE; CINAHL
Number of citations retrieved by search	**49**	**37**
Duplicates		5
Number of excluded citations		
Not a trial/study	8	6
Trial/study does not include transcatheter and surgical closure of PDA in separate arms	35	24
Characteristics of the recruited participants do not overlap with the main indication	3	2
Number of included citations (duplicates removed)	3	0

Exclusion of studies

A total of 78 citations were excluded for the direct analysis of the evidence pertaining to the comparison of transcatheter and surgical closure of PDA. As previously mentioned, there is limited evidence for appropriate comparative studies. However, a number of retrieved articles were useful sources of information when assessing the safety, effectiveness and cost-effectiveness of transcatheter closure of PDA.

The main exclusion criterion was that the study did not include transcatheter closure of PDA and the main comparator of surgical closure of PDA in separate arms (59 citations). A further 5 citations were for studies that did not include the proposed patient population and 14 citations were not a study i.e. journal articles.

The reasons to exclude citations can be further defined by inappropriate population, intervention or comparator (see Table 13). Studies of a defined population group were excluded, for example studies of Marfan patients and patients with rubella syndrome. Studies on devices such as Gianturco coils were excluded, as well as studies for one device only or studies comparing devices with other devices or medical treatment.

It should be noted that in the comparative studies that were finally included, the description of the surgical closure undertaken did not explicitly mention whether it was conducted without cardiopulmonary bypass. However the surgical technique chosen in these studies (posterolateral thoracotomy) tends to be performed without bypass in isolated PDA lesions without co-existent congenital cardiac abnormalities. Surgical ligation of PDA with cardiopulmonary bypass tends to be reserved for those patients with co-existent cardiac abnormalities.

Table 13 Reasons to exclude citations from further detailed assessment

	MEDLINE	EMBASE; CINAHL
Population	4	2
Intervention	18	9
Comparator	16	12
Journal	8	6
Case study	0	3
Number of excluded citations	46	32

Comparative studies

Three comparative studies, all published in 2009, were identified for inclusion in this report (see Table 14). Two of the articles were based on studies at the Union Hospital in China:

- A prospective non-randomised study reported by Chen et al (Chin Med J 2009); and
- A retrospective study reported by Chen et al (Pediatr Cardiol 2009).

The third article was based on a retrospective study at the Veterans General Hospital in Taiwan.

Table 14 Comparative studies presented in the assessment report

Comparison of long-term clinical outcome between transcatheter Amplatzer occlusion and surgical closure of isolated patent ductus arteriosus	
Study date	2000 to 2003, follow up until July 2008
Location	Union Hospital, China
Study type	Non-randomised
Author	Chen Z, Wu L, Luo Y, Lin C, Peng Y, Zhen X and Chen L
Journal	Chinese Medical Journal 2009: 122(10):1123-1127
Transcatheter amplatzer occlusion and surgical closure of patent ductus arteriosus: comparison of effectiveness and costs in a low-income country	
Study date	2005 to 2007
Location	Union Hospital, China
Study type	Retrospective
Author	Chen Z, Chen L, Wu L
Journal	Pediatric Cardiology 2009: 30:781–785
Closure of large patent ductus arteriosus in infants	
Study date	2003 to 2006 (transcatheter) 1997 to 2002 (surgical)
Location	Veterans General Hospital, Taiwan
Study type	Retrospective
Author	Lin C, Hsieh K, Huang T, and Weng K
Journal	American Journal of Cardiology 2009: 103:857-861

Chen et al (Chin Med J 2009) reported on a non-randomised study of 255 patients having isolated PDA with a minimal diameter of ≥4 mm. The patients were assigned to either the device or surgical closure group according to the patients' and/or their patents' preference. Seventy-two patients accepted the transcatheter procedure and 183 underwent surgical operation.

The study reported that the successful closure rate was equal in the two groups. The operating and recovery times were significantly shorter in the transcatheter group. Chen et al (Chin Med J 2009) concluded that their study confirmed the long-term safety and efficacy of transcatheter Amplatzer occlusion which was less invasive and associated with fewer complications and residual shunt, and as effective in the regression of pulmonary hypertension and left ventricular dilation.

The second study reported by Chen et al (Pediatr Cardiol 2009) was a retrospective study of 181 patients aged ≥6 months with a PDA of 4-16 mm. A total of 130 patients underwent surgical closure for PDA, whereas 51 patients underwent Amplatzer occlusion. There were no deaths and no residual left-to-right shunting in either group at last follow-up. The study concluded that, although transcatheter Amplatzer device occlusion is as effective as and less invasive than surgical closure for PDA, surgical closure is less costly.

The third article was based on a retrospective study at the Veterans General Hospital in Taiwan. Lin et al (2009) reported on 20 infants born full-term and aged ≤3 months with a PDA ≥3 mm. The data were compared with a historical control group of young infants with large, symptomatic PDA in whom surgical ligation was performed previously at the hospital i.e. a non concurrent group of patients who historically received surgery during a different time period. This study design brings with a lot of issues around potential systematic error such as selection bias. The study reported that transcatheter implantation of the ADO is more cost effective than surgery for young infants, with significantly less length of stay in the hospital, length of intensive care, and hospital charges. However, the report notes that the implantation of the ADO is more expensive than coils.

Table 15 presents the outcome measure in the three comparative studies. It should be noted that these three studies were conducted in a health system other than Australia. This may limit the transferability of the results. A clearer understanding of the similarities and differences across health systems where the studies were conducted versus Australia (in terms of organisational structure, resources, clinical pathways etc) as well as an understanding of the relative frequency of PDA between the study and Australian population would better inform a discussion as the extent to which these studies are transferable. That said, at face value the study population broadly appears to be representative of what is seen in the Australian population and because the interventions described in the studies (both transcatheter closure and surgical closure) are similar to those provided in the Australian healthcare system, this review has concluded that the studies presented are likely to be externally valid. This is despite issues with their methodological quality and internal validity.

Table 15 Outcome measures in comparative studies

Chen et al (Chin Med J 2009)	
Population group	Isolated PDA ≥4 mm
Number of patients	255 patients: 72 ADO 183 surgery
Outcome	No residual shunt before discharge ADO=68/72 (94.4%) Surgery=173/183 (94.5%)
Complications	All complications (Major bleeding, pleural effusion, pneumothorax, pneumonia, blood transfusion, arrhythmia requiring medication) ADO 1.4% Surgery 13.7%

Chen et al (Pediatr Cardiol 2009)	
Population group	Age ≥6 months, minimum diameter 4-16 mm
Number of patients	181 patients: 51 ADO 130 surgery
Outcome	Residual shunting rate in the ADO group was low and comparable to that of the surgical group
Complications	Requiring management: 1 ADO 8 surgery

Lin (2009)	
Population group	Born full-term, age ≤3 months, minimum diameter ≥3 mm
Number of patients	38 patients: 20 ADO 18 surgery
Outcome	No significant difference in the rate of residual shunt, and pulmonary or aortic stenosis
Complications	Various minor, procedure-related complications occurred in both groups

Manual search of citations

Further articles were retrieved from the manual search of citations of the included studies and the article provided by the applicant (see Table 17). Some of the retrieved articles compared transcatheter and surgical closure of PDA. However, the majority of articles were pre 2000 and therefore the comparison was made for Rashkind or Gianturco coils. Table 16 lists the article with the appropriate intervention and comparator for inclusion in this report.

Table 16 Summary of information from the manual search of citations

Left ventricular remodeling and change of systolic function after closure of patent ductus arteriosus in adults: device and surgical closure	
Location	South Korea
Study type	Clinical outcomes: 28 device closure, 17 surgical closure
Author	Young-Hoon Jeong, MD, et al
Journal	American Heart Journal
Year	2007
Vol(No):pages	154:436-440

Jeong et al (2007) reported the study of 45 adult patients (28 ADO 17 surgery) with PDA with 2-dimensional echocardiographies performed before closure and 1 day (ADO) or within 7 days (surgery) after closure, and then repeated at ≥6 months. There were no differences in basic patterns of left ventricular (LV) remodelling and changes of systolic function between ADO and surgical groups, but immediate deterioration of LV systolic function was less prominent in the ADO group than in the surgical group. The cause of this phenomenon could not be clearly demonstrated in the study, but might result from perioperative intravascular volume change, bleeding, physical and emotional stress, and/or myocardial depressive effect of general anaesthesia and inflammatory reaction in the surgical wound.

Jeong et al (2007) concluded the LV ejection fraction remained low in both groups late after PDA closure compared with the preclosure state in adults.

Registry

The applicant provided an article "Transcatheter Closure of the Patent Ductus Arteriosus: An Intention to Treat Analysis" which has been published in 2013 on behalf of ANZSCTS and the CSANZ. The registry included the analysis of all children with an isolated PDA who were admitted to the catheter laboratory at a single institution from January 2003 to December 2011. Details of the registry data are listed in Table 17.

Table 17 Details of registry data presented in the report

Transcatheter Closure of the Patent Ductus Arteriosus: An Intention to Treat Analysis	
Trial date	January 2003 to December 2011
Location	Queensland Australia
Study type	Registry
Author	Sheridan et al
Journal	Heart, Lung and Circulation
Year	2013
Vol(No):pages	1284:1-5

Two hundred and twenty eight children with a median age of 3.0 years and weight 14.2 kg underwent cardiac catheterisation to occlude a PDA. Sheridan et al (2013) reported successful occlusion in 96.2% of 208 patients (with the device of first

choice) when transcatheter closure was intended. Of the 208 patients selected for transcatheter closure, all were followed through in the analysis. However there was differential follow up periods between the two devices. The study reported the use of FC and ADO with device selection evolving to ADO exclusively in 2011.

Sheridan et al (2013) concluded that ADO I is the current device of choice, resulting in complete closure of all patients with no significant complications. The article also indicated that the development of devices with different design characteristics is likely to result in improved outcomes, particularly in the patient group weighing <6 kg with clinically significant PDA.

The study reported by Sheridan et al (2013) did not include a cost analysis. The article noted that while the ADO is more expensive, the financial and patient emotional cost related to FC complications is likely to support the use of ADO. Sheridan et al (2013) also reported that it has been their practice to observe patients overnight following PDA occlusion, but with a demonstrably low complication rate, it may be appropriate to move to same day discharge, which would further mitigate the cost difference.

It should be noted that this analysis of registry data primarily compared the relative merits of the two commercially available devices currently used in Australia for transcatheter closure of PDA. The relative merits of transcatheter closure of PDA versus surgery (in those patients who were potentially candidates for either approach) was not considered in this data sets.

Clinical trials

The literature search retrieved a citation for the Multicenter USA Amplatzer Patent Ductus Arteriosus Occlusion (ADO) Device Trial (see Table 18). This trial was conducted from September 1999 to June 2002, with 484 patients enrolled in 25 centres. Forty-five (9%) of 484 patients did not have ADO implantation, because the PDA was too small or because of elevated pulmonary resistance. The median age of the patients at catheterisation was 1.8 years (range 0.2 to 70.7 years), and weight was 11 kg (range 4.5 to 164.5 kg) (Pass et al 2004).

The ADO was implanted successfully in 435 (99%) of 439 patients. At the last evaluation, PDA closure was documented in 428 (98%) of patients. There have been two cases of partial left pulmonary artery occlusion after ADO implantation and no cases of significant aortic obstruction. Conclusions were that moderate to large PDAs can be effectively and safely closed using the ADO device, with excellent initial and one-year results. This device should obviate the need for multiple coils or surgical intervention for these defects. Given this was simply a device efficacy trial (without comparison to surgery) the relevance of this trial is limited.

Table 18 Multicenter USA Amplatzer PDA Occlusion Device Trial

Multicenter USA Amplatzer Patent Ductus Arteriosus Occlusion (ADO) Device Trial	
Trial date	September 1999 to June 2002
Location	25 centres in 18 states in the U.S.
Study type	Non-randomised
Author	Pass et al 2004
Journal	Pediatric Cardiology

Table 19 presents the outcome measures in the clinical trial.

Table 19 Outcome measures in the clinical trial

Population group	Weight ≥5 kg
Number of patients	484 patients
Outcome	ADO safely and effectively closed moderate to large PDAs
Complications	Serious procedural complications were rare

The clinical trials website was searched for the term "patent ductus arteriosus" on 15 March 2013, returning 72 results. The type of studies included 15 observational, 55 interventional and 1 expanded access (NCT00583583 Emergency/Compassionate Use - AMPLATZER Duct Occluder). Table 20 presents a list of the relevant clinical trials identified in the search.

Table 20 Other clinical trials

Trial
NCT01479218 *Phase 1 Study for Safety and Effectiveness of the New Occlutech PDA Occluder, for Non Surgical Closure of Patent Ductus Arteriosus*
NCT00713700 *Closure of Patent Ductus Arteriosus With the AMPLATZER DUCT Occluder II*
NCT00583596 *Closure of Patent Ductus Arteriosus With the AMPLATZER Duct Occluder the AMPLATZER® Duct Occluder*
NCT01063712 *Safety and Effectiveness of the Device "Nit-Occlud® PDA-R"*

Interpretation

The review of literature has identified that transcatheter closure of PDA is likely to be non-inferior in terms of comparative safety and effectiveness despite both internal and external validity issues with the limited evidence base. Therefore a cost minimisation analysis will be undertaken for the service relative to that of surgical closure of PDA.

Table 21 Cost-minimisation analysis to be used for the economic evaluation

Comparative safety	**Comparative effectiveness**			
	Inferior	**Uncertain**	**Non-inferior**	**Superior**
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Non-inferior	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

CEA = cost-effectiveness analysis; CMA = cost-minimisation analysis; CUA = cost-utility analysis
? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis
a 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations
b An adequate assessment of 'non-inferiority' is the preferred basis for demonstrating equivalence

ECONOMIC EVALUATION

Overview of the economic evaluation

Transcatheter closure of PDA has been identified to be non-inferior to surgical closure of PDA (see Table 21 on Page 33). A cost-minimisation analysis is presented taking into account that the service is currently provided for a small numbers of patients, and therefore the total government expenditure on the service is likely to be small.

The review of literature has provided limited information on which to base a judgement about the clinical and economic performance of transcatheter closure of PDA relative to that of surgical closure. Therefore, the economic evaluation includes the following information:

- the intended population;
- the circumstances of use; and
- the variables used in the economic evaluation.

The analysis did not restrict the service by the age of the patient or the type of the defect. Taking into account that the most commonly reported length of follow-up visits following transcatheter or surgical closure of PDA is periodic appointments over the next year, the follow-up period has not been factored in to the analysis. The potential for use of the service in a wider population or setting than the target population and setting is unlikely (see Table 25 on Page 38).

The costs and benefits of transcatheter or surgical closure of PDA are assumed to be similar post discharge from hospital. Therefore, discounting has not been applied to the cost-minimisation analysis.

Type of economic evaluation

The cost analysis of transcatheter versus surgical closure of PDA compares costs only. This analysis is presented as transcatheter technique is current practice and is proposed to be non-inferior to surgical ligation in terms of efficacy and safety, and may generate cost offsets from reduced use of health care resources.

The method used for the determination of a cost-minimisation analysis for transcatheter closure of PDA is presented in Table 22.

Table 22 Method used to identify the type of analysis

<table>
<tr><td colspan="2" rowspan="2"></td><td colspan="4">Comparative effectiveness versus comparator</td></tr>
<tr><td colspan="2">Superior</td><td>Non-inferior</td><td colspan="2">Inferior</td></tr>
<tr><td rowspan="5">Comparative safety versus comparator</td><td rowspan="3">Superior</td><td colspan="2" rowspan="3">CEA/CUA</td><td rowspan="3">CEA/CUA</td><td>Net clinical benefit</td><td>CEA/CUA</td></tr>
<tr><td>Neutral benefit</td><td>CEA/CUA*</td></tr>
<tr><td>Net harms</td><td>None^</td></tr>
<tr><td>Non-inferior</td><td colspan="2">CEA/CUA</td><td>CEA/CUA*</td><td colspan="2">None^</td></tr>
<tr><td rowspan="3">Inferior</td><td>Net clinical benefit</td><td>CEA/CUA</td><td rowspan="3">None^</td><td colspan="2" rowspan="3">None^</td></tr>
<tr><td>Neutral benefit</td><td>CEA/CUA*</td></tr>
<tr><td>Net harms</td><td>None^</td></tr>
</table>

Abbreviations: CEA = cost-effectiveness analysis; CUA = cost-utility analysis

* May be reduced to cost-minimisation analysis. Cost-minimisation analysis should only be presented when the proposed service has been indisputably demonstrated to be no worse than its main comparator(s) in terms of both effectiveness and safety, so the difference between the service and the appropriate comparator can be reduced to a comparison of costs. In most cases, there will be some uncertainty around such a conclusion (i.e., the conclusion is often not indisputable). Therefore, when an assessment concludes that an intervention was no worse than a comparator, an assessment of the uncertainty around this conclusion should be provided by presentation of cost-effectiveness and/or cost-utility analyses.

^ No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this intervention

Population

Identifying patients suitable for transcatheter closure of PDA involves transthoracic echocardiography to determine whether the patent duct is suitable to be closed with a coil or occluding device. According to the applicant, there are broad clinical and echocardiographic features which support closure of the PDA with transcatheter techniques:

- Clinical signs of cardiac failure (failure to thrive, tachypnoea, hepatomegaly)
- The presence of typical a continuous murmur
- Echocardiographic evidence of left atrial and left ventricular dilatation
- Echocardiographic evidence of elevation of pulmonary artery pressures

Some of these patients may have previously trialled medication to close their ductus without success or were unable to receive medication due to a contraindication but medication has a limited role in PDA management. Some patients at the point of diagnosis may immediately proceed to transcatheter or surgical intervention if there is evidence of haemodynamic overload. Expert clinical advice is that the minimal indication for PDA closure is the presence of a continuous murmur. The presence of a continual murmur in the absence of heart failure does not preclude PDA closure, as there is an increased risk of sub acute bacterial endocarditis by leaving the ductus patent.

Circumstances of use

The diagnostic workup for a patient with a suspected PDA is directed at defining the presence and size of the PDA, the functional effect of the shunt on the left atrium and left ventricle, the pulmonary circulation, and any associated lesions. According to the applicant, patients weighing less than six (6) kilograms are usually considered unsuitable for the procedure in Australia.

The various devices available are designed to accommodate a variation of PDA size and morphology but generally speaking PDAs that are too small or too large in diameter or oddly shaped (non-conical or window like) tend to be unsuited for closure by transcatheter approach.

Surgical closure of PDA in the adult may pose some problems due to the friability and/or calcification of the ductus, atherosclerosis, and aneurysm formation, as well as the presence of other unrelated comorbid conditions, such as coronary atherosclerosis or renal disease, that may adversely affect the perioperative risk. Adults with PDA are better suited for percutaneous closure with either the occlusion device or coils because of its high success and few complications. If the PDA is associated with other conditions that require surgical correction, the ductus may be closed during the same operation, although percutaneous closure of the PDA before other cardiac surgery may decrease the risk of cardiopulmonary bypass (Warnes et al 2008).

Table 23 Population and circumstance of use

Term	Description
Target population and circumstances of use	Patients ≥6 kilograms in the Australian setting with an isolated congenital defect suitable for transcatheter closure of the defect
Study population and circumstances of use	Patients in an international setting with a lesion suitable for transcatheter closure of the defect
Wider population and circumstances of use	Patients in the Australian setting with a PDA suitable for transcatheter closure of the defect

Consistency across characteristics

The comparison of characteristics of the population and setting identified in selected literature is presented in Table 24.

Table 24 Comparison of characteristics for selected literature

Trial ID	Chen (Chin Med J 2009)	Sheridan (2013)
Data period	Jan 2000-Jul 2003	Jan 2003-Dec 2011
Trial location	China	QLD, Australia
Target Population	Patients who underwent ADO or surgical closure Union Hospital	All patients with an isolated PDA Paediatric lab
Medical condition	Patients with moderate to large Isolated PDA (4-16mm)	Isolated PDA
Treatment	ADO	FC and ADO I, II and II AS devices
Total number of patients	n=72	n=208 (device closure not attempted for 21 patients)
Initial successful closure	ADO=68/72 (94.4%) Surgery=173/183 (94.5%) No residual shunt before discharge	FC =70/76 (92.1%) ADO =130/132 (98.6%) No residual shunt post discharge follow up
Number of patients with successful long term closure	Follow-up of at least 5 year Persistent residual shunt free survival Surgery 91.3% ADO 98.6%	Complete closure FC 73.4% at 1-76mth follow up (medium 8 mths) ADO 100% at 1-75mths follow up (median 3 mths)
Age of the population	At least 6 months	Median = 3yrs Range= 0.4-16.4yrs
Weight of the population	23.8±13.1kg Range = 5.2-65.1kg	Median wt = 14.2kg Range = 5.5-68kg
Complications	Major bleeding, pleural effusion, pneumothorax, pneumonia, blood transfusion Surgery 25/183 (13.7%) Arrhythmia requiring medication ADO 1/72 (1.4%)	FC n=6 (5 embolisation, 1 coil unstable) ADO n=2 (aortic obstruction)
Restriction criteria	Cardiac comorbidities Shunting due to severe pulmonary hypertension Type of PDA Patients <6mths	Data analysis only on patients with isolated PDA

Justifying restrictions

The analysis does not restrict the service by the age of the patient or the type of the defect. The medical condition following transcatheter closure of PDA does not progress. The potential for use of the service in a wider population or setting than the target population and setting is unlikely (see Table 25).

Table 25 Population groups – target, study and wider

Population	Target	Study	Wider
Clinical condition	Isolated PDA due to congenital heart disease	Congenital heart disease not specified	Both isolated lesion and with other cardiac conditions
Comment	The analysis does not restrict by the severity of the patient's condition		
Age	Not restricted by age	Varied	Not restricted by age
Comment	The analysis does not restrict the service by the age of the patient		
Gender	Both	Not identified	Not restricted by gender
Comment	PDA affects both males and females		
Initiation criteria	Clinically significant PDA	Varied	Not restricted by type/size of the defect
Comment	The analysis does not restrict the service by the type of the defect		
Position in management algorithm	Second line but some first-line use	Varied	Second line but some first-line use
Comment	Medical management may be clinically indicated		

Outcomes

Transcatheter closure of PDA aims to successfully deliver the device with no residual shunt and complete regression of signs of volume overload. The outcomes generated by the economic evaluation represent the final outcomes of treatment.

Time horizon

The most commonly reported length of follow-up visits following closure of PDA is periodic appointments over the next year. For the purposes of the analysis, the assumption is made that the follow-up would be of a similar nature for both transcatheter and surgical closure of PDA. Therefore the follow-up period has not been factored in to the cost-minimisation analysis.

Discounting

The costs and benefits of transcatheter or surgical closure of PDA are assumed to be similar post discharge from hospital. Therefore, discounting has not been applied to the cost-minimisation analysis.

Dealing with uncertainty

The report has considered the extent to which the analysis is limited by the extent of uncertainties in the clinical evidence. As outlined earlier, the quality of the evidence has been limited by a number of factors. For example, the medical devices and services for transcatheter closure of PDA have been available for decades with incremental improvements to the established devices. Additionally, the devices are used for a limited population i.e. those patients with clinically significant PDA who are suitable for transcatheter closure of the congenital defect.

However, there is a certain level of data available for transcatheter and surgical closure of PDA in the Australian setting. The information available from the AIHW has been valuable in identifying the number of patients undergoing these procedures, as well as the overall hospital treatment in the public and private sectors.

Variables in the economic evaluation

Variables used in the economic evaluation include MBS items, the prosthetic item and health care resources.

Direct health care resources

The health care resource items for which there would be a change in use associated with providing transcatheter closure of PDA include diagnostic and hospital services. The list of health care resources included in the economic evaluation is presented in Table 26.

Table 26 Summary of health care resources

Resource	Type
Diagnostic imaging	MBS
Anaesthesia	MBS
Procedure	MBS
Device	Private Health Insurer
Theatre	Private Health Insurer / Government
ICU	Private Health Insurer / Government
Hospital stay	Private Health Insurer / Government

Outcomes

The available information and evidence for the effectiveness of transcatheter occlusion of PDA indicate that the procedure is effective with a high degree of successful closure.

Sheridan et al (2013) reported successful occlusion in 96.2% of 208 patients (with the device of first choice) when transcatheter closure was attempted. The study reported the use of FC and ADO with device selection evolving to ADO exclusively in 2011.

Chen et al (Chin Med J 2009) reported recovery time in the ADO group was much shorter than in the surgical group, which was mainly due to fewer general anaesthesia and no surgical-related issues and complications. Additionally, unlike the residual PDA after surgical ligation which persisted if untreated, residual shunt detected soon after ADO disappeared automatically during the follow-up, which may be partially attributed to the self-expanding design of ADO or clot formation. The conclusion was that ADO was less invasive and associated with fewer complications and residual shunt, and as effective in the regression of pulmonary hypertension and left ventricular dilation. The article indicated that surgical closure should be reserved for those in whom the PDA is too large for device closure or at centres without access to device closure.

Present value of health outcomes

The following series of tables identify health care resource items that may be associated with patients undergoing transcatheter or surgical closure of PDA. The outcome that is considered to best reflect the clinical management algorithm performance of transcatheter or surgical closure of PDA is the successful closure of the defect.

Specialist consultation and diagnostic services have been included in the analysis for all patients undergoing closure of PDA by either surgical or transcatheter technique. However, it should be noted that the follow-up period has not been factored in to the analysis i.e. the most commonly reported length of follow-up visits for both transcatheter or surgical closure of PDA is periodic appointments over the next year. The estimated utilisation of these items is presented in Table 31. The MBS item for the initial specialist consultation is item 104. Diagnostic services include electrocardiogram (ECG), chest x-ray and echocardiographic examination. For the purposes of the analysis, the 75% (in-hospital) benefit has been used in the model.

Table 27 Specialist Consultation and Diagnostic Services

	MBS item	Schedule fee	75% benefit
Initial specialist consultation	**104**	$85.55	$64.20
ECG	**11700**	$31.25	$23.45
Chest x-ray	**58503**	$47.15	$35.40
Transthoracic echocardiography	**55115**	$230.65	$173.00
Anaesthesia for echocardiography	**21936**	$118.80	$89.10

Schedule fee as at 1 November 2012

MBS items associated with transcatheter closure of PDA include the specialist services, cardiac catheterisation and the procedure (see Table 28).

Table 28 Procedural services and associated MBS items

	MBS item	Schedule fee	75% benefit
Both surgery & transcatheter			
Anaesthesia for patients <12 months	**25015**	$19.80	$14.85
Assistant	**51303**	20% of fee	
Transcatheter			
Anaesthesia (cardiac catheterisation)	**21941**	$138.60	$103.95
Anaesthesia (55 minutes)	**23042**	$79.20	$59.40
Cardiac catheterisation	**38206**	$642.45	$482.00
Transcatheter closure of PDA	**New**	$912.30	$684.25
Surgery			
Anaesthesia (open heart)	**20560**	$396.00	$297.00
Anaesthesia (1.21 minutes)	**23062**	$118.80	$89.10
Surgical closure of PDA	**38700**	$1,067.40	$800.55
ICU initial management	**13870**	$362.10	$271.60
ICU subsequent management	**13873**	$268.60	$201.45

Schedule fee as at 1 November 2012

The estimated hospital costs and length of stays used in the analysis are presented in Table 29 and Table 30. For the purposes of the analysis, the total length of hospital stay has been estimated at 2 days for transcatheter closure of PDA and 9 days for surgical closure of PDA.

Table 29 Theatre and hospital costs used in the analysis

	Estimated cost
Theatre	
Catheter laboratory	$3,641
Theatre	$1,790
Device	$10,200 (ADO)
Hospital stay	
ICU	$2,209 (per day)
Ward	$774 (per day)

ICU and ward costs sourced from the Victorian Government guide to fees for admitted patients 2012/13

Table 30 Length of ICU stay and recovery time used in the analysis

Parameter	Transcatheter	Surgery	Source
ICU stay (days)	0.9 ± 1.3	3.4 ± 2.1	Lin (2009)
Hospital stay (days)*	1.3 ± 0.5	8.7 ± 2.3	Chen (Chin Med J 2009)

** Recovery time*

Results of the economic evaluation

Transcatheter closure of PDA has been identified to be non-inferior to surgical closure of PDA (see Table 21 on Page 33). A cost-minimisation analysis is presented taking into account that the service is currently provided for a small numbers of patients, and therefore the total government expenditure on the service is likely to be small.

The report has considered the extent to which the analysis is limited by the quality of the underlying data and the extent of uncertainties in the clinical evidence. Transcatheter closure of PDA aims to successfully deliver the device with no residual shunt and complete regression of signs of volume overload. The outcomes generated by the economic evaluation represent the final outcomes of treatment.

The analysis did not restrict the service by the age of the patient or the type of the defect. Taking into account that the most commonly reported length of follow-up visits following transcatheter or surgical closure of PDA is periodic appointments over the next year, the follow-up period has not been factored in to the analysis. The potential for use of the service in a wider population or setting than the target population and setting is unlikely (see Table 25 on Page 38).

The comparison of the cost per patient for transcatheter versus surgical closure of PDA is summarised in Table 31. Overall, the estimated cost of transcatheter closure of PDA is more expensive relative to its comparator, surgical ligation ($17,599 and $15,833 respectively for 2012-13). However, the cost of the ADO device ($10,200) significantly adds to the overall cost of the procedure.

In terms of cost-effectiveness of health resources (excluding the device cost), transcatheter closure of PDA provides relative benefit, for example shorter recovery time with a significantly decreased length of hospital stay, at lower costs.

Table 31 Comparison of cost per patient

	Transcatheter		Surgery	
	Units	**Total**	**Unit**	**Total**
Consultation and diagnostic				
Specialist consultation	1	$64.20	1	$64.20
Chest x-ray	2	$70.80	2	$70.80
ECG	1	$23.45	1	$23.45
Transthoracic echocardiography	2	$346.00	2	$346.00
Anaesthesia for echocardiography	2	$178.20	2	$178.20
Both surgery and transcatheter				
Anaesthesia for patient less than 12 months	1	$14.75	1	$14.85
Ward stay	2	$1,548.00	6	$4,644.00
Transcatheter closure of PDA				
Catheter laboratory	1	$3,641.00		
Device	1	$10,200.00		
Initiation anaesthesia (cardiac catheterisation)	1	$103.95		
Anaesthesia (55 mins)	1	$59.40		
Cardiac catheterisation	1	$482.00		
Transcatheter closure of PDA	1	$684.25		
Assistant	1	$182.46		
Surgical closure of PDA				
Theatre			1	$1,790.00
Initiation anaesthesia (open heart)			1	$297.00
Anaesthesia (1.21 mins)			1	$89.10
Surgical closure of PDA			1	$800.55
Assistant			1	$213.48
ICU stay			3	$6,627.00
ICU initial attendance			1	$271.60
ICU followup attendance			2	$402.90
TOTAL		**$17,598.56**		**$15,833.13**

MBS costs based on 75% benefit of the Schedule fee as at 1 November 2012

FINANCIAL IMPLICATIONS

Overview of the financial analysis

Transcatheter closure of PDA is proposed as a direct substitute for surgical closure of PDA *without* cardiopulmonary bypass (MBS item 38700). There are two specific MBS items for division or ligation of PDA for congenital heart disease (see Table 2 on Page 3). However, surgical ligation of PDA with cardiopulmonary bypass (MBS item 38703) is a more complex procedure usually performed with other cardiac procedures.

The surgical approach is generally 100% successful but requires general anaesthesia and either a lateral thoracotomy incision of multiple thorascopy sites. The attractiveness of transcatheter closure is a direct result of the technique being less invasive without the need for general anaesthesia. These attributes reduce potential morbidity relative to surgical closure, as well as avoiding the need for an extended hospital stay (Kramer et al 2000).

The procedure for transcatheter or surgical closure of PDA is mainly performed on young infants in major public hospitals. Currently there are a small number of procedures performed in the private sector. It is anticipated that the volume of services will remain constant should MBS funding be made available for transcatheter closure of PDA.

A large proportion of the cost of transcatheter closure of PDA is the cost of the device itself. Medical devices currently listed on the Prostheses List include the ADO and FC. For the purposes of the financial analysis, the cost of the ADO ($10,200) has been used for the financial analysis. The cost for the ADO accounted for 58% of the total cost of the procedure in the financial analysis. This percentage is consistent with the study by Chen et al (Pediatr Cardiol 2009), who reported that the chief difference in costs between the transcatheter and surgical groups was the cost of the Amplatzer device, which accounted for 61.5% of the total cost of the device group.

Complication rates reported for closure of PDA are similar for both transcatheter and surgical groups and have not been factored into the financial analysis. Chen et al (Chin Med J 2009) reported that more acute procedure-related complications were recorded in the surgical group as compared with the transcatheter group. There were no early or late deaths, systemic infection or infectious endocarditis in either group of patients, and no thrombosis, thrombo-embolism, haemolysis and ADO dislodge in the transcatheter group. Atrial fibrillation was observed in one patient from the transcatheter group in the catheterisation laboratory, and it was converted by amiodarone. Lin et al (2009) reported that various minor, procedure-related complications occurred in both groups.

Overall, the estimated cost of transcatheter closure of PDA is more expensive relative to its comparator, surgical ligation ($17,599 and $15,833 respectively for 2012-13). A breakdown of these costs per patient can be found in Table 36 on Page 47.

Number of patients

The estimated number of patients with PDA for 2011-12 was sourced from the AIHW Implanted Cardiac Device (ICD)-10: Q25. The data sources used in the estimation of the eligible population are shown in Table 32.

Table 32 Estimated number of patients with PDA for 2011-12 with data sources

Parameter	Value	Source
Births July 2011 to June-2012	297,811	Australian Bureau of Statistics (ABS) 3222.0 - Population Projections, Australia, 2006 to 2101, June 2012
Rate of PDA	19 per 10,000 (0.19%)	Based on AIHW ICD-10: Q25 and ABS 3101.0 June 2012
Cases of PDA	566	Estimated from above

Number of procedures

The estimated number of procedures for transcatheter closure of PDA is outlined in Table 33. As this procedure is already performed in the public setting, only private percutaneous treatment of PDA is relevant for the purposes of this analysis.

The rate of uptake used in the model is estimated at 1.8% per annum, in line with the average increase of births per year. Based on AIHW data, approximately 29% of all patients are treated percutaneously, a third of which are performed in a private setting.

Table 33 Estimated number of procedures

	2012-13	2013-14	2014-15	2015-16
Rate of PDA (19 per 10,000 births)	576	587	597	608
Transcatheter closure of PDA (total)	167	170	173	176
Transcatheter closure of PDA (private)	55	56	57	58

Frequency and duration of treatment

For the purposes of the financial analysis, transcatheter closure of PDA is a once-only procedure, i.e. successful insertion of the device will result in a resolution of the disease process. The procedure time reported in two studies is outline in Table 34. It should be noted that the study reported by Prieto et al (1998) was for coil occlusion. The procedural time was distributed less evenly for coil versus surgical patients because of the significantly longer duration (315 ± 45 minutes) for 2 patients, who experienced coil embolisation during the procedure. If these 2 patients are excluded, mean procedure time is 148 ± 36 minutes for the remaining 22 coil occlusion patients.

Table 34 Estimated duration of transcatheter and surgical procedures

	Transcatheter			Surgery		
	N=	Mean (mins)	Range (mins)	N=	Mean (mins)	Range (mins)
Prieto 1998	24	162	90-360	12	161	105-225
Chen 2009 Chin Med J	72	55.4	±19.7	183	80.9	±23.4

The length of hospital stay is decreased for transcatheter closure of PDA compared with surgery. Chen et al (Chin Med J 2009) reported that although the successful closure rate was equal in the transcatheter and surgical groups, the operating and recovery times were significantly shorter in the transcatheter group. All patients in the surgical group required general anaesthesia with intubation and mechanical ventilation while only 41.7% of patients in the transcatheter group, who were all small children under the age of 5 years, had such requirements.

Chen et al (Pediatr Cardiol 2009) reported that their study showed that the duration of hospital stay was significantly less for patients undergoing Amplatzer occlusion than for patients undergoing surgical closure. However, the length of hospital stay for the Amplatzer device and surgical groups was longer than that reported in other countries, which was due to their performing PDA closure on an in-patient instead of an out-patient basis.

Lin et al (2009) reported that compared with the patients who underwent surgical ligation of PDA, significantly less length of stay in the hospital, length of intensive car, and hospital charges were noted in patients treated with transcatheter closure of PDA. Further details of all three studies can be found at Table 35.

Table 35 Length of hospital stay from literature sources

Study	Transcatheter		Surgery	
	N=	Mean	N=	Mean
Chen (Chin Med J 2009)[1]	72	1.3 days	183	8.7 days
Chen (Pediatr Cardiol 2009)	51	3.6 days	130	8.8 days
Lin 2009	20	9.0 days (±6.3)	18	14.7 (±7.7)

[1]*Hospital stay referred to as "recovery time"*

Disaggregation of estimates

The financial analysis uses the ICU and ward costs sourced from the Victorian Government guide to fees for admitted patients 2012/13. The guide places a value of $2,209 per day in the ICU and $774 on an overnight ward stay. It should be noted that the fees will vary between hospitals, and are determined on either a Diagnosis Related Group (DRG) or bed day basis.

Catheterisation laboratory and theatre costs are derived from figures in Kramer et al (2000) and Gray et al (1993), the only literature which provides a breakdown of these expenses. These costs were then adjusted to reflect modern dollar amounts.

The model used in the financial analysis assumes a stay of 2 days in a ward for transcatheter patients, and for surgical patients, 3 days in the ICU and 6 in a ward, for a total stay of 9 days. This figure correlates with 2010-11 AIHW average length of stay of 10.5 days for closure of PDA.

Table 36 Total cost per patient for 2012-13

	Transcatheter	Surgery
Pre-procedure		
MBS	$385	$385
Procedure		
MBS	$1,562	$1,415
Theatre	$3,641	$1,790
Device	$10,200	$-
Total l	**$15,403**	**$3,205**
Post-procedure		
MBS	$262	$972
Ward	$1,548	$4,644
ICU	$-	$6,627
Total	**$1,810**	**$12,243**
Total MBS cost	**$2,210**	**$2,772**
Total costs	**$17,599**	**$15,833**

Based on 75% benefit of the Schedule fee as at 1 November 2012
Totals have been calculated using unrounded estimates

MBS cost

The MBS cost is based on the 75% benefit of the MBS items as outlined in the economic evaluation (see Table 27 on Page 40 and Table 28 on Page 41). The estimated total MBS cost over 4 years for transcatheter closure of PDA is presented in Table 37.

Table 37 Total MBS cost for transcatheter closure of PDA: 2013-14 to 2016-17

	2013-14	2014-15	2015-16	2016-17
Pre-procedure				
Initial specialist consultation (104)	$3,604	$3,669	$3,735	$3,803
Electrocardiogram (11700)	$1,316	$1,340	$1,364	$1,389
Chest x-ray (58503)	$1,987	$2,023	$2,060	$2,097
Transthoracic echocardiography (55115)	$9,710	$9,886	$10,065	$10,247
Anaesthesia for echocardiography (21936)	$5,001	$5,092	$5,184	$5,278
Procedure				
New MBS item	$38,405	$39,100	$39,808	$40,529
Assistant (51303)	$10,241	$10,427	$10,616	$10,808
Cardiac catheterisation (38206)	$27,054	$27,544	$28,043	$28,550
Anaesthesia for patients <12 months (25015)	$834	$849	$864	$880
Anaesthesia - cardiac catheterisation (21941)	$5,835	$5,940	$6,048	$6,157
Anaesthesia - 55 minutes (23042)	$3,334	$3,394	$3,456	$3,518
Chest x-ray (58503)	$1,987	$2,023	$2,060	$2,097
Post-procedure				
Transthoracic echocardiography (55115)	$9,710	$9,886	$10,065	$10,247
Anaesthesia for echocardiography (21936)	$5,001	$5,092	$5,184	$5,278
Total	**$124,020**	**$126,265**	**128,551**	**$130,878**

Based on 75% benefit of the Schedule fee as at 1 November 2012

Results of the financial analysis

The estimated number of procedures for transcatheter closure of PDA is low. In the private setting, there is an estimate of 56 procedures in 2013-14. This takes into account that the procedure for transcatheter or surgical closure of PDA is mainly performed on young infants in major public hospitals. Therefore, it is anticipated that the volume of services will remain constant.

AIHW data for 2010-11 indicate that for closure of PDA, of a total of 559 hospital separations, there were 66 admissions to a private hospital and 493 admissions to a public hospital of which 119 were for private patients. The data also indicate that there were 60 same day patient separations for the public hospital admissions. There were no same day patient separations for the private hospital admissions.

Overall, the cost of transcatheter closure of PDA is more expensive compared with surgery ($17,599 and $15,833 per patient respectively). However, a large proportion of the cost for transcatheter closure of PDA is the cost of the device itself ($10,200 for the ADO).

The length of hospital stay is decreased for transcatheter closure of PDA compared with surgery. The difference in ICU stay is associated with lower MBS costs ($2,210 and $2,772 per patient respectively) due to the associated medical management for the surgical patients following admission to an ICU unit.

ABBREVIATIONS

ABS	Australian Bureau of Statistics
AIHW	Australian Institute of Health and Welfare
ADO	Amplatzer duct occlude
ANAES	Anaesthetic
ANZCTR	Australian New Zealand Clinical Trials Registry
ANZSCTS	Australian and New Zealand Society of Cardiac and Thoracic Surgeons
ARTG	Australian Register of Therapeutic Goods
ASD	Atrial septal defect
ASSIST	Assistant
CSANZ	Cardiac Society of Australia and New Zealand
DAP	Decision analytic protocol
DRG	Diagnosis Related Group
FC	Flipper coil
FDA	Food and Drug Administration
ICD	International Classification of Diseases
ICU	Intensive Care Unit
LV EF	Left ventricular ejection fraction
MBS	Medicare Benefits Schedule
MSAC	Medical Services Advisory Committee
NICE	National Institute for Health and Clinical Excellence
PASC	Protocol Advisory Sub-Committee
PICO	Patients; Intervention; Comparator; Outcomes
PDA	Patent ductus arteriosus
TGA	Therapeutic Goods Administration
VATS	Video assisted thoracoscopic surgery
VSD	Ventricular septal defect

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