South Australian Policy Advisory Committee on Technology (SAPACT)

Health Technology Assessment (HTA) Decision Summary Update

Government of South Australia

SA Health

MitraClip® and PASCAL™ Transcatheter Mitral Valve Repair (TMVR) Systems for the Percutaneous Treatment of Mitral Regurgitation (MR)

SAPACT MEETING DATES	23rd, 24th and 25th SAPACT meetings (4 September, 20 November 2020, 19 February 2021)
APPLICATION #	2015 (refer to 1506 for previous MitraClip decision)
TECHNOLOGY	MitraClip® delivery system (Abbott Vascular, CA, USA) PASCAL™ transcatheter valve repair system (Edwards Lifesciences, CA, USA)
TECHNOLOGY CLASSIFICATION	TGA class III high-risk
PATIENT INDICATION (Therapeutic Goods Administration (TGA))	MitraClip: The MitraClip System is intended for reconstruction of the insufficient mitral valve through tissue approximation.
	Pascal: The Edwards PASCAL valve repair system is indicated for the percutaneous reconstruction of an insufficient mitral valve through tissue approximation.

SAPACT DECISION

☒ Restricted recommendation for clinical use with financial/operational restrictions and under audit conditions.

SAPACT recommendations for Percutaneous Treatment of Mitral Regurgitation within SA Health

The use of MitraClip TMVR in SA Health will result in additional cost but is likely to provide functional improvements to patients. SAPACT recommends the use of this technology under the following conditions:

- *Patient eligibility for FMR and DMR*
  - MR >= grade 3+. This should be confirmed with transthoracic echo within 6 months of the planned procedure.
  - Symptomatic, New York Heart Association (NYHA) Class II – ambulatory IV despite optimal medical therapy (including cardiac resynchronisation therapy, if appropriate)
  - Adequate treatment of cardiac / cardiovascular co-morbidities (HR, MR, CAD, LV dysfunction)
  - Ineligible for surgical intervention
  - Mitral valve leaflets are anatomically suitable for the procedure
- Exclusion criteria will be those deemed with the multidisciplinary team to be intermediate or low risk, those with unsuitable anatomy or prognosis despite intervention of less than 2 years.
- Based on the above criteria, patients are to be selected by a multidisciplinary structural heart team. The ideal composition of this team should include a cardiac surgeon with expertise in mitral valve surgery, an interventional cardiologist, an expert in transoesophageal echocardiography, an expert in heart failure, a cardiac anaesthetist/perioperative physician/geriatrician, and a specialist cardiac nurse. However, at minimum the team should include a cardiac surgeon, a structural heart disease interventional cardiologist who undertakes MitraClip insertions, and a heart failure specialist.
- *Reporting requirements*
  - Service providers are requested to submit annual patient outcome reports to their local health network's new technology committee. Outcomes prospectively collected to the database should include:
    a. Pre-procedure (age, comorbidities, STS, EuroScore III, NYHA class, Kansas City Cardiomyopathy Questionnaire (KCCQ) and EQ-5D-5L
    b. Procedure (duration, number of clips used, radiation dose, intraprocedural mitral regurgitation
    c. Post-procedure, at 30 days, 1 year and 2 years (death, stroke, bleeding, myocardial infarction, hospital readmission, NYHA class (symptoms), echocardiogram, KCCQ and EQ-5D-5L)
  - Providers are encouraged to contribute patient outcomes to the Australasian Cardiac Outcomes Registry (ACOR)
  - SAPACT encourages the sharing of experiences related to the percutaneous treatment of mitral regurgitation across local health networks. SAPACT notes that in the future, the Cardiac Network's Structural Heart Disease Subcommittee may be able to provide a valuable forum for statewide care discussions related to this technology.

Background

This is a re-application for MitraClip and another similar TMVR system, the PASCAL. SAPACT previously evaluated the SALHN MitraClip application in 2015 and did not recommend for use in SA Health (refer to SAPACT HTA Decision Summary #1506). The current application proposed that both CALHN and SALHN Cardiology Departments should aim to treat a total of 30 patients with moderate - severe (≥ grade 3+) inoperable MR per year.

Summary of international evidence

PASCAL TMVR system

SAPACT noted the limited clinical evidence on the safety and clinical-effectiveness of the PASCAL system. Due to the lack of evidence the PASCAL transcatheter mitral valve repair (TMVR) system should not be used for routine clinical use in SA Health.

MitraClip TMVR system

Overall, the international HTA reports advise that the MitraClip TMVR system may be considered for patients with severe or moderate-to-severe (Grade 3+, 4+) degenerative mitral regurgitation (DMR) and functional mitral regurgitation (FMR) who are contraindicated for open heart surgery. The multi-disciplinary heart team (minimum three physicians, including a heart failure (HF) specialist) will have a key role in determining which patients are ineligible for surgical intervention that would benefit from the MitraClip procedure.

Clinical evidence from two pivotal open-label randomised controlled trials (COAPT trial of high quality and Mitra-FR trial of moderate quality) found non-inferior safety and likely superior clinical-effectiveness of the MitraClip procedure in the FMR population.

Lower quality evidence from three non-randomised comparative studies (EVEREST II HRR: Whitlow 2012, Velazquez 2015 and Swaans 2014) and the large transcatheter valve therapy single arm registry (Sorajja 2017) found uncertain comparative safety and clinical-effectiveness of the MitraClip procedure in the DMR population.

REGULATORY APPROVALS

1. MitraClip® delivery system

☒ **ARTG**: 26/09/2018 MitraClip NTR/XTR; 19/05/2017 MitraClip NT.
ARTG 309701 MitraClip NTR/XTR Clip Delivery System - Mitral valve clip
ARTG 309700 MitraClip NTR/XTR System - Mitral valve tissue repair system
ARTG 289168 MitraClip NT Clip Delivery System - Mitral valve clip
ARTG 289167 MitraClip NT System

☒ **US FDA**: 14/03/2019 MitraClip NTR/XTR and MitraClip NT (Expanded approval to heart failure patients with significant secondary mitral regurgitation, who have failed to get symptom relief from other therapies)

☒ **EU CE mark**: 04/2020 MitraClip for tricuspid regurgitation (TR)
25/03/2008 MitraClip for mitral regurgitation

2. PASCAL™ TMVR system

☒ **ARTG**: 25/08/2020
ARTG 342270 PASCAL Transcatheter Valve Repair System - Implant System – Mitral valve clip
ARTG 342271 PASCAL Transcatheter Valve Repair System - Guide Sheath - Catheter, intravascular, guiding

☐ **US FDA**: Not approved – PASCAL (under CLASP trial, NCT03170349).
The CLASP RCT evaluates the safety and effectiveness of the Edwards PASCAL system compared with the Abbott MitraClip device, for the treatment of moderate-to-severe (3+) or severe (4+) FMR in symptomatic heart failure patients. The study planned to enrol in late 2019. Edwards already has underway the CLASP IID U.S. pivotal trial, which is currently enrolling patients with symptomatic DMR.

☒ **EU CE mark**: 19/02/2019 PASCAL for MR; 19/05/2020 PASCAL for TR

QUALITY OF EVIDENCE

Quality of Evidence	Comprehensive systematic searches were conducted in 8 published scientific databases and 25 grey literature sources. Three HTA Reports on MitraClip: (1) Commonwealth Medical Services Advisory Committee (MSAC) Public Decision Summary (April 2020), (2) Scottish Health Technologies Group (SHTG) (August 2019) and (3) National Institute for Health and Care Excellence (NICE), as well as local SA Health Finance, Economics, Cardiac and HTA consultations informed the SAPACT Recommendations. Note that the clinical evidence found was for MitraClip only, none for PASCAL. Degnerative/Primary Mitral Regurgitation (DMR) • The MSAC assessment took into account 3 non-randomised comparative studies (EVEREST II HRR: Whitlow 2012, Velazquez 2015 and Swaans 2014) and the large transcatheter valve therapy single arm registry (n=2952 and 85.9% DMR) (Sorajja 2017). Key concerns with the Sorajja 2017 study are that it was not comparative, and there was a high rate of censoring within the 12-month follow up. • The SHRG Report found that the evidence on using MitraClip® in patients with DMR was of lower quality than evidence for patients with FMR. Functional/Secondary Mitral Regurgitation (FMR) Two pivotal open-label RCTs were published comparing MitraClip plus medication with medication alone in patients with severe FMR: (1) Mitra-FR trial (Obadia 2018; French study; 2-year follow-up) - neutral results and (2) COAPT trial (Stone 2018; US and Canada; 3-year follow-up) - highly positive on efficacy of MitraClip. Proposed explanations for differing trial results related to differences in: patient selection (the COAPT enrolled a subset of patients who had a more severe MR and less advanced LV disease compared with Mitra-FR patients); differing normal care in the USA and France; how experienced the staff doing the procedure were; and the different lengths of time patients were followed after the procedure. The MSAC assessment found that GRADE assessment tool suggested the COAPT is of high quality whereas MITRA-FR is of moderate quality given the significant amount of missing data for key secondary outcomes.

CLINICAL NEED

Burden of Illness	Prevalence: about 300,000 MR patients; Incidence: about 20,000 new patients/year Aging population - 12% of those ≥ 75 years old Untreated severe MR, 30% mortality within 6 years

	Australian mitral valve surgery (2009-10): Mitral valve repairs ≈1200; Mitral valve replacements ≈1300
Need	MR may be degenerative (DMR) or functional (FMR). DMR is caused by wear and tear to the chords and leaflets in the valve. In FMR, the chords and leaflets are structurally normal but there is geometrical distortion of the subvalvular apparatus caused by idiopathic cardiomyopathy, or weakening of the cardiac walls caused by coronary artery disease (ischaemic MR). DMR is currently treated by surgery to repair or replace the mitral valve. FMR can be conservatively managed using drugs for treating heart failure but this is not curative, and surgical options such as undersized annuloplasty may be an option. However, people with MR of either cause are usually older (typically over 70 years) and frail, with multiple comorbidities. This increases the perioperative risks of morbidity and mortality for open heart surgery. For these patients, TMVR may be an appropriate management option. Surgery is the standard and accepted treatment for severe MR; optimal medical management for mild/moderate MR or severe MR unsuitable for surgery. There is a potential unmet need for a safe and effective approach to repair in adult patients who are ineligible for surgery.
CLINICAL BENEFIT DMR Overall, clinical evidence found uncertain comparative safety and clinical-effectiveness of the MitraClip procedure in the DMR population. FMR Overall, clinical evidence found non-inferior safety and likely superior clinical-effectiveness of the MitraClip procedure in the FMR population.	
Safety	DMR Compared to optimal medical management, TMVR with MitraClip has uncertain safety for the DMR population. Similar to older literature, the large TMVR registry reported similar rates of 30-day mortality and clinical adverse events (Sorajja 2017). Acute procedure success was reported to be 92% (residual MR grade ≤2, no cardiac surgery and no in hospital mortality). One year mortality was reported to be 25.8%. In two of the four observational studies that evaluated MitraClip in patients with DMR, an estimated 24% of patients died within 1 year of the MitraClip procedure. The most common complications in these studies related to bleeding and partial detachment of the clip used in the MitraClip procedure. FMR • The MITRA-FR trial showed no significant difference between the trial groups with respect to the rate of death from any cause or unplanned hospitalization for heart failure at 1 year (the composite primary outcome), whereas the COAPT trial showed a significantly lower rate (by an estimated 47%) of hospitalization for heart failure at 2 years (the primary outcome) and significantly lower (by 57%) all-cause mortality at 2 years (a secondary outcome) in the device group. • The most common complications in both trials were device implantation failure (4.2%) and the need for unplanned mitral valve surgery or MitraClip® implantation (3.2%). The COAPT trial supported the claim for non-inferior safety for MitraClip with a significant 38% reduction in the risk of mortality by 2 years in patients who received MitraClip vs medical therapy.
Effectiveness	DMR Based on the comparative evidence, the MSAC advised that TMVR has non-inferior clinical-effectiveness in the DMR population, relative to optimal medical management. Four observational studies evaluated MitraClip® in patients with DMR. In these studies there were reductions in the severity of MR, improvements in patient quality of life, and reductions in hospitalisations due to heart failure. FMR The Mitra-FR trial does not support the claim for superior clinical-effectiveness. The MITRA-FR trial showed no significant differences in clinical effectiveness outcomes of TMVR relative to optimal medical management. However, the COAPT trial supports the claim for superior clinical-effectiveness. The COAPT trial demonstrated that TMVR was statistically significantly superior to optimal medical management with respect to all primary and secondary effectiveness outcomes, including: • quality of life at 1 year compared with maximally tolerated guideline-directed medical therapy (GDMT) in patients with heart failure and 3 to 4+ FMR. • distance a patient could walk in 6 minutes at 1 year • reduction in NYHA functional class by 2 years • reduced HF hospitalisations by 2 years
SUITABILITY OF PATIENT GROUP	
Suitability of Patient Group	SA Health Proposed number of patients per year in SA Health (across CALHN and SALHN; regional LHNs patients are referred to SALHN and NALHN patients are referred to CALHN) = 30 • *Patient eligibility for FMR* o MR >= grade 3+. This should be confirmed with transthoracic echo within 6 months of the planned procedure. o Symptomatic, NYHA Class II – ambulatory IV despite optimal medical therapy o Adequate treatment of cardiac / cardiovascular co-morbidities (HR, MR, CAD, LV dysfunction) o Ineligible for surgical intervention • *Patient eligibility for DMR* o Similar to that for FMR, but with an explicit consideration that the mitral valve leaflets are suitable for the procedure. • Exclusion criteria will be those deemed with the multi-disciplinary team to be intermediate or low risk, those with unsuitable anatomy or prognosis despite intervention of less than 2 years.

	• Patient selection will be done by a multidisciplinary structural heart team, typically including a cardiac surgeon with expertise in mitral valve surgery, an interventional cardiologist, an expert in transoesophageal echocardiography, an expert in heart failure, a cardiac anaesthetist/perioperative physician/geriatrician, and a specialist cardiac nurse. International literature The MSAC, SHTG and NICE advised that TMVR using the MitraClip may be considered for patients with severe or moderate-to-severe DMR and FMR (Grade 3+, 4+) who are contraindicated for open heart surgery. Two thirds of patients who receive the MitraClip are expected to have DMR and the other one third, FMR. The multi-disciplinary health team (minimum three physicians, including a heart failure (HF) specialist) will have a key role in determining which patients are ineligible for surgical intervention that would benefit from the MitraClip procedure (MSAC).
FINANCIAL	
Device costs	*A key concern at SAPACT was the lack of accurate costing of the MitraClip procedure and associated casemix funding and cost offsets.* Local cost for MitraClip were estimated as follows: • Cost per MitraClip device kit = AUD [*redacted*] (compared to AUD [*redacted*] in 2015). *1-3 clips per patient may be used (average 1.7 clips); SA Health pays for [redacted] clip(s)/patient/procedure.* • The approximate average cost per MitraClip procedure (device, other supplies, laboratory items, labour, bed stay) is likely to be AUD [*redacted*]. o *Clinical costs are estimated by the MSAC to be approximately $13,663.22, excluding cost of the device and catheter.* o *The average cost per separation for patients with a primary diagnosis of I340 Mitral (Valve) insufficiency is over $37,000 (IHPA, nationwide), which is likely to relate to MitraClip procedures (based on about 90 cases, and likely to be driven by the use of MitraClip in Eastern states).* • ABF Funding DRG F19A (Trans-Vascular Percutaneous Cardiac Intervention, Major Complexity): 5.4581 = AUD 29,041
Value for Money	SA Health A costing analysis was undertaken to estimate the budget impact of MitraClip TMVR on SA Health. • *Based on estimates from MSAC and cost per separation for I340 from IHPA, the cost of the procedure (excluding the MitraClip kit) is likely to be between AUD 13,500 and 19,000. See comments above.* • *The difference in number of hospitalisations in the first two years following the procedure are approximately 0.64 HF inpatient separations based on the COAPT trial; and* • *The average cost of patients with a primary diagnosis of either 'Heart Failure, unspecified' or 'congestive heart failure' in South Australian Hospitals is AUD 11,005 (2018-2019).* • *Based on the total cost of procedure of AUD [redacted]; less the Commonwealth contribution (45% or AUD -13,068); offset by a reduction in hospitalisations over 2 years (AUD -7,043):* o *The additional cost to SA Health per patient is approximately AUD 20,543* o *The budget impact to SA Health based on 30 patients per year is AUD 616,287* MSAC MSAC did not consider the MSAC applicant's requested price to be value for money, hence recommended a lower price (specifically to reduce price of MitraClip device to maintain the same incremental cost-effectiveness ratio (ICER) per quality-adjusted life-year (QALY) for the MitraClip procedure). *MSAC proposed MBS item descriptors for MitraClip: MBS fee: $1,455.10 Benefit 75% = $1,091.35* The MSAC application requested an MBS fee of $1,748.45 for the MitraClip insertion procedure and $[*redacted*] for the MitraClip device. The total cost of the MitraClip procedure (Pre-procedural heart team assessment, MBS insertion fee, hospitalisation fees, Post-procedural/Pre-discharge TTE) was estimated by the application as $13,663.22 (without device) or $[*redacted*] (with device)). MSAC recommended the same price be paid for the MitraClip device irrespective of the number of devices used in a single procedure. MSAC considered that the difference in the requested fees for TMVR compared with TAVI ($1,748.45) was not well justified, and recommended the fee for TMVR be consistent with the fee for TAVI ($1455.10). TMVR has acceptable economic value according to current US thresholds Note that the COAPT trial and economic substudy (Baron 2019) were funded by Abbott. Baron 2019 paper on *Cost-effectiveness of TMVR vs medical therapy in patients with heart failure and FMR* using results from the COAPT trial concluded that TMVR has acceptable economic value according to current US thresholds: • For symptomatic patients with heart failure and 3 to 4+ FMR, TMVR increases life expectancy and quality adjusted life expectancy compared with optimal medical management at an incremental cost per QALY gained that represents acceptable economic value according to current US thresholds. • TMVR was projected to increase life expectancy by 1.13 years and QALYs by 0.82 years at a cost of USD 45,648, yielding a lifetime ICER of USD 40,361 per life-year gained and USD 55,600 per QALY gained. • Although follow-up costs were significantly lower with TMVR compared with optimal medical management, cumulative 2-year costs remained higher with TMVR because of the upfront cost of the index procedure.

Australian Funding Approvals	MSAC Decisions - Approved At the 78th Commonwealth MSAC Meeting on 3 April 2020, after considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported the public funding of reduction of MR through tissue approximation, using transvenous/transeptal techniques. Specifically, MSAC supported TMVR with MitraClip for patients with MR due to FMR and DMR who cannot have open heart surgery. MSAC felt that the procedure was effective and safe and – at a reduced price – cost-effective. MSAC recommended that the Commonwealth Department further negotiate with the applicant regarding pricing as a condition of listing (not finalised as of August 2020, email correspondence). Funding was supported on a cost-minimisation basis against optimised medical management in patients with DMR. For patients with FMR, funding was supported on a cost-effectiveness basis against optimised medical management, but with the time-horizon adjusted to 7 years (instead of 10 years) in the economic model. MSAC recommended that a compulsory TMVR registry be established to ensure quality control, as a condition of listing. MSAC Decisions - Rejected The MSAC noted that it had rejected a similar application three times previously (2012, 2014 and 2016 for Applications 1192, 1192.1 and 1192.2) due to uncertain clinical effectiveness, comparative safety and cost-effectiveness. MSAC noted that the three previous submissions sought listing in the DMR population only. • 2016 (1192.2) In patients with severe DMR (grade 3+ or 4+) who are considered high risk for surgery | MSAC did not support funding due to continued uncertainty about clinical effectiveness and cost effectiveness. However, MSAC noted that there is a clinical need in a small group of patients with severe degenerative mitral regurgitation who are unsuitable for surgery. • 2014 1192.1 In patients with severe MR considered to be at high risk for surgery and currently treated by medical management | MSAC considered that it was difficult to define the patient population who would clinically benefit from the intervention. MSAC did not support public funding for the reduction of MR through TMVR because of uncertain comparative safety, effectiveness and cost-effectiveness due to limited direct comparative data. • 2012 1192 MitraClip procedure as an alternative treatment to mitral valve surgery or medical management (high-risk patients not suitable for surgery) | MSAC did not support public funding as there is no evidence to suggest that the procedure is more effective than surgery, and lack of comparative data compared to medical management. International approvals • Scottish Health Technology Assessment Group (SHTG) Advice (August 2019) - Approved The SHTG advises the introduction of new technologies into the National Health Service in Scotland (NHS Scotland). o Minimally invasive valve repair using the MitraClip® device should be considered for patients with severe or moderate-to-severe MR who are not eligible for surgery. Treatment decisions should be made by a team of healthcare professionals with different expertise and who have experience of performing this procedure. This team should take into account individual patients' level of risk, other existing conditions, preferences and quality of life. o Annual MitraClip® procedure volume per centre should be maximised to support optimal patient outcomes and ensure clinical experience with this complex procedure is achieved and retained. o More research is needed to clarify whether MitraClip® is effective for reducing both types of MR compared with medication. Studies that assess the value for money of MitraClip® from a UK perspective are also desirable. • NICE Recommendations (May 2019) – Approved The NICE advises implementation of new technologies within the NHS in England. o Current evidence on the safety and efficacy of percutaneous mitral valve leaflet repair for MR is adequate to support the use of this procedure, in patients for whom open surgery is contraindicated following risk assessment, provided that standard arrangements are in place for clinical governance, consent and audit. o Patient selection should be done by a multidisciplinary structural heart team, typically including an interventional cardiologist, an expert in transoesophageal echocardiography, an expert in heart failure, a cardiac anaesthetist, a cardiac surgeon and a specialist nurse. o Percutaneous mitral valve leaflet repair for MR should only be done in specialised centres with access to both cardiac surgical and vascular surgical support in case emergency treatment of complications is needed. o This procedure should only be done by clinicians with specialist training and supervision by an experienced mentor for at least the first 20 procedures. o Clinicians should enter details about all patients having percutaneous mitral valve leaflet repair for MR onto the National Institute for Cardiovascular Outcomes Research database.
FEASIBILITY OF ADOPTION	
Organizational Feasibility	This procedure may be used provided that standard arrangements are in place for funding, clinical governance, consent and audit by the LHN(s).
Credentialing and Competency	The application detailed that the SALHN team has some previous experience with this procedure. Training program/ implementation will be with either therapy specialist from Abbott or a proctor. The MitraClip procedure should only be done by clinicians with specific training and accreditation in the procedure. The clinician(s) should be appropriately credentialed and approved by the SA Health Credentialing and Scope of Practice Committee to implant the MitraClip (refer to paragraph 3.4.3 New Clinical Procedures, Technologies and Treatments of the SA Health Credentialing Policy Directive).

CONSISTENCY WITH EXPECTED SOCIETAL/ ETHICAL/ LEGAL VALUES	
Values	Consistent with expected societal, ethical and legal values at this time. SA Health
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