



Australian Government

Medical Services Advisory Committee

## Public Summary Document

### ***Application No. 1605 – Trans-radial delivery of a dual-filter cerebral embolic protection system during Transcatheter Aortic Valve Implantation (TAVI)***

**Applicant: Boston Scientific**

**Date of MSAC consideration: MSAC 80<sup>th</sup> Meeting, 26-27 November 2020**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

#### **1. Purpose of application**

An application requesting Medicare Benefits Schedule (MBS) listing the transcatheter insertion of a dual-filter cerebral embolic protection (CEP) device, or more broadly a ‘multi-filter’ CEP device during transcatheter aortic valve implantation (TAVI) in patients with aortic stenosis was received from Boston Scientific by the Department of Health.

#### **2. MSAC’s advice to the Minister**

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported the creation of a new Medicare Benefits Schedule (MBS) item for a dual-filter cerebral embolic protection (CEP) device, during transcatheter aortic valve implantation (TAVI) in patients with symptomatic severe aortic stenosis who meet MBS eligibility criteria for TAVI (high risk/inoperable and intermediate risk for surgery). MSAC accepted the evidence of non-inferior safety and superior effectiveness for CEP plus TAVI compared with TAVI alone, but recommended that the continued MBS listing would be subject to a rigorous review of the results from the large randomised controlled trial (PROTECTED TAVR) available in 2023. MSAC also considered that the best estimate of the incremental cost-effectiveness ratio (ICER) was informed by model inputs accepted by MSAC in other TAVI applications (MSAC applications 1361.2 and 1603) and recommended to the Prostheses List Advisory Committee (PLAC) that a reduction in the proposed Prostheses List benefit for the device would be required for the cost-effectiveness of CEP to be considered acceptable.

## Consumer summary

This application is from Boston Scientific and seeks to create a new Medicare Benefits Schedule (MBS) item for listing the transcatheter insertion of a dual-filter cerebral embolic protection (CEP) device.

TAVI is a procedure that helps to improve a damaged aortic valve. During a TAVI procedure, a catheter is placed in the femoral artery (in the groin) and guided into the heart. The CEP system captures and removes material (debris) that may enter the blood supply to the brain during the TAVI procedure and cause a stroke. This debris includes calcium that has been dislodged from the artery, tissue from the valve and artery, catheter coating material and other items.

The CEP system consists of two different filters, with sizes suitable for the arteries that provide the main blood supply to the brain. At the end of the procedure, the filters and any captured debris are retrieved into the catheter and removed from the patient.

MSAC accepted that CEP plus TAVI is safe and more effective than TAVI alone. However, MSAC considered that the price of the CEP device would need to be lower to make it acceptable for listing on the MBS.

### **MSAC's advice to the Commonwealth Minister for Health**

MSAC considered the CEP device to be effective, safe and cost-effective, and supported the creation of a new MBS item for a dual-filter cerebral embolic protection (CEP) device that can be used during TAVI. However, MSAC recommended a rigorous review of new data that will be available in 2023 from a clinical trial that is currently underway.

### **3. Summary of consideration and rationale for MSAC's advice**

MSAC noted that this application was for MBS listing of a dual-filter CEP device during TAVI in patients with aortic stenosis.

MSAC noted that the device is listed on the Prostheses List (BS364), with the same benefit as single-filter CEPs being \$1,955. This application requested a proposed benefit for dual-filter CEP of \$redacted.

MSAC noted that the CEP filter use during TAVI will be performed by accredited TAVI Practitioners in TAVI Hospitals. MSAC noted that training for the use of CEP consists of a 30-45 minute didactic session with demonstration. A TAVI Practitioner is deemed independent after performing 10 cases with clinical support from a field specialist rather than a proctor. MSAC agreed with the ESC and the applicant's pre-MSAC response that TAVI practitioners should be required to gain accreditation for CEP, managed by the TAVI Accreditation Committee.

MSAC acknowledged that there is a clinical need for this device, to reduce the risk of subclinical stroke in TAVI patients. MSAC considered there was reasonable biological plausibility that CEP would reduce stroke during TAVI and noted that the SENTINEL IDE trial reported significant collection of embolic material in the CEP filter with debris collected in almost all patients undergoing TAVI. MSAC noted that episodes of silent cerebral ischemia and micro-infarcts are common and have the potential to accelerate cognitive decline.

MSAC accepted the claim of non-inferior safety on the basis of similar rates of major vascular complications, acute kidney injury (AKI) and adverse event profiles.

MSAC noted that the individual randomised clinical trials (RCTs) and the meta-analysis of the RCTs did not show a statistically significant reduction in stroke and that the RCTs were not statistically powered to show a reduction in stroke. However, the cohort studies presented demonstrated a reduction in stroke as did the meta-analyses of the RCTs and cohort studies. MSAC noted that the point estimates from the RCTs generally reported a smaller stroke reduction than the cohort studies. MSAC also accepted the claim of superior clinical effectiveness and noted that the inclusion of cohort studies was justified on the basis of the individual RCTs not being powered to show differences in peri-procedural stroke.

MSAC noted that caution should be used when interpreting and disseminating information about the number needed to treat, since there is still uncertainty with that figure due to the low baseline of stroke and small absolute risk reductions. MSAC noted that this uncertainty could be conveyed by including the confidence intervals. MSAC noted that, in terms of stroke rates, ESC 'queried the relevance of [30-day stroke] as the CEP device is removed following the TAVI procedure'. In its pre-MSAC response, the applicant stated that the economic evaluation applied 30-day stroke rates in the model rather than earlier peri-procedural rates (within 7 days) because the timing of assessment was consistent across all studies, thereby reducing uncertainty in the estimate, while capturing the cumulative effect of TAVI+CEP within the peri-procedural duration, 30 days.

MSAC noted the cost-utility analyses presented in the ADAR assessing the cost-effectiveness of CEP in the high surgical risk and intermediate surgical risk populations undergoing TAVI. MSAC noted that the base cases considered that CEP was cost-effective in both populations at the proposed Prostheses List benefit. However, MSAC noted the economic models were sensitive to the time horizon. MSAC also considered the magnitude of the increase in long term mortality was uncertain but considered the assumption of higher mortality after stroke was not unreasonable. MSAC considered these factors and uncertainty in the magnitude of the clinical benefit due to the use of cohort studies contributed to the uncertainty in the incremental cost-effectiveness ratio (ICER) in the base case.

MSAC agreed with PASC that the TAVI procedure (the comparator arm in this assessment) should closely replicate/be guided by that used in the original TAVI listing to avoid overvaluing TAVI ([1605 Ratified PICO](#)). MSAC considered that the best estimate of the ICER was informed by model inputs accepted by MSAC in other TAVI applications (MSAC [Application 1361.2](#) and [1603](#)) that were presented in sensitivity analyses. These analyses report much higher ICERs, increasing **redacted%** and **redacted%** for the inoperable/high risk and intermediate risk populations, respectively. MSAC noted further analyses investigating the weighted CEP benefit at various willingness-to-pay thresholds. MSAC recommended to the Prostheses List Advisory Committee (PLAC) that a reduction in the proposed Prostheses List benefit for the device to be approximately **\$redacted** would be required for the cost-effectiveness of CEP to be considered acceptable at an ICER of \$50,000 per quality-adjusted-life year, which is considered to be an acceptable ICER for this level of high use and level of uncertainty around the clinical effectiveness and utilisation.

MSAC noted that there is uncertainty in the likely utilisation of CEP and the associated financial implications as the proportion of patients eligible for CEP and its likely uptake in Australian practice increases.

MSAC noted that investigation of cognitive outcomes following aortic valve replacement could be referred to the Medical Research Future Fund (MRFF).

MSAC considered the item descriptor should be limited to dual-filter devices and should not be restricted to patients with a particular surgical risk. MSAC noted that a time-based approach, based on the current TAVI fee (MBS item 38495 = \$1,455.10) was used to estimate an appropriate fee for the insertion and retraction of the dual-filter CEP device during the TAVI procedure (Fee = \$260.37, which is 17.9% of the current TAVI fee).

MSAC noted the evidence presented was weak relative to the hierarchy of evidence which considers systematic reviews of RCTs to be the most convincing evidence to assess the effectiveness of clinical interventions. MSAC noted that the applicant referred to a pending RCT (PROTECTED TAVR) in its pre-MSAC response, which will look at TAVI + CEP vs. TAVI alone measuring stroke rates at 72 hours (n = 3,000). Thus, MSAC recommended that this MBS item should be rigorously reviewed after 3 years in light of the findings of this pending RCT (available in 2023).

MSAC supported the following item descriptor:

*Percutaneous transcatheter delivery of dual-filter cerebral embolic protection (CEP) system during transcatheter aortic valve implantation (TAVI), for the reduction of postoperative embolic ischaemic strokes*

Fee: \$260.37                  Benefit 75% = \$195.28                  Benefit 85% = 221.31

#### **4. Background**

MSAC has not previously considered CEP.

MSAC previously considered the MBS listing of TAVI for use in patients who are symptomatic severe AS at high risk (or inoperable) for SAVR or non-operable at its March 2016, October 2015 (Stakeholder meeting) July 2015, and April 2015 meetings. At its March 2016 meeting, MSAC supported MBS listing of the TAVI procedure for the aforementioned patient population (Public Summary Document [PSD] Application No. 1361.2). TAVI was listed on the MBS (MBS item 38495, and case conference items 6080, 6081) for this population on 1 November 2017. Application 1603 requesting MBS listing of TAVI using a balloon-expandable valve (BEV) system for patients with symptomatic severe aortic stenosis (AS) at intermediate risk for surgery will also be considered at the November 2020 MSAC meeting.

In the Ratified PICO (1605 Ratified PICO), PASC advised that the TAVI procedure (confirmed as the comparator arm in this assessment) should closely replicate/be guided by that used in the original TAVI listing. This will avoid overvaluing TAVI.

Table 1 presents a comparison of the TAVI economic evaluations. The Department investigated the economic impact of TAVI+CEP using key modelling inputs from other TAVI applications (see Table 12). The Department also investigated the financial impact of TAVI+CEP using utilisation estimates from other TAVI applications (see Table 12).

Table 1: Redacted

#### **5. Prerequisites to implementation of any funding advice**

The Sentinel Cerebral Protection System is registered on the Australian Register of Therapeutic Goods (ARTG) as a Class III medical device. It has an intended use as an embolic protection device, to capture and remove embolic material (thrombus/debris) that

may enter the cerebral vascular system during endovascular procedures (Table 2). The SENTINEL Cerebral Protection System is also listed on the Prostheses List.

**Table 2 Dual-filter CEP system listed on ARTG**

ARTG no.	Product no./ product category	Product description	Intended use	Sponsor
319101	44841 / Medical Device Class III	The SENTINEL Cerebral Protection System is a percutaneously delivered embolic protection device, designed to capture and remove debris dislodged during endovascular procedures. The device presents two independent deployable filters that act at the brachiocephalic and left common carotid arteries and presents a minimal profile in the aortic arch. At the completion of the procedure, the filters and debris are recaptured into the catheter and removed from the patient	Indicated for use as an embolic protection device to capture and remove embolic material (thrombus/debris) that may enter the cerebral vascular system during endovascular procedures. The diameters of the arteries at the sites of filter placement should be measured and the filters sized to the proximal and distal target vessels	Boston Scientific Pty Ltd

Source: Therapeutic Goods Administration, accessed 1 July 2020 [Link to TGA.gov.au](http://Link to TGA.gov.au)  
 ARTG = Australian Register of Therapeutic Goods; CEP = cerebral embolic protection

## 6. Proposal for public funding

The proposed MBS item descriptor is summarised in Table 3.

**Table 3 Proposed MBS item descriptor**

Category 3 – Therapeutic procedures
MBS item ##### Percutaneous transcatheter delivery of dual-filter cerebral embolic protection (CEP) system during transcatheter aortic valve implantation (TAVI), for the reduction of postoperative embolic ischaemic strokes
Fee: \$260.37*

Source: Table 11, p8 of the ADAR

*\*Note: The fee presented in the ratified PICO for application 1605 was \$277.92 which is 19.1% of the current TAVI fee (MBS item 38495 = \$1,455.10). The MBS fee presented above (\$260.37) is 17.9% of the current TAVI fee. The derivation of this fee is presented in Section D.5 of the ADAR and the assessment of the ADAR's fee justification is presented on Section D.4 under 'Medical service costs' in the second paragraph of this assessment report critique.*

The ADAR proposed that MSAC may consider 'future proofing' this MBS item, by altering the item descriptor to include 'multi-filter' CEP systems during TAVI. Currently there are no multi-filter CEP systems available in Australia, however, these are expected to enter the market in the future. The Commentary considered that this was considered appropriate.

The ADAR used a time-based approach to estimate the proposed fee for the insertion and removal of the CEP device. The SENTINEL IDE trial that compared TAVI with and without CEP reported an average procedure duration of 74.2 minutes for the TAVI arm and 87.5 minutes for the two CEP arms. Therefore, the ADAR concluded CEP required an additional 13.3 minutes – equating to 17.9% of the TAVI procedure time. This resulted in a proposed fee of \$260.37. This was lower than the fee in the ratified PICO (refer to Table 3).

As noted by PASC ([1605 Ratified PICO](#), p4), TAVI+CEP will have the same accreditation requirements for operators and institutions as applied for TAVI procedure which is the by PASC confirmed comparator [p9 Ratified PICO]). The PASC confirmed that the procedure is subject to the multiple operation rule, which reduces the fee payable by 50%.

### Prosthesis

The ADAR proposed a higher prosthesis benefit of \$redacted for the dual-filter CEP than the July 2020 Prostheses List benefit of \$1,895. This is a benefit equivalent to single-filter devices. However, the single-filter devices are not used in the proposed population.

The ADAR stated that \$redacted reflects the current sales price of the dual-filter CEP device. Currently, hospitals and patients are paying the difference between reimbursement and the price of the CEP device, resulting in inequity in access to the CEP device. An increase in the level of benefit of the dual-filter CEP device on the Prostheses List will provide adequate funding for the device. This would also provide equity of access for the proposed patient population in Australia. The ADAR considered the higher proposed benefit was supported by the cost-effectiveness of the TAVI + CEP procedure.

## **7. Summary of public consultation feedback/consumer Issues**

No consumer feedback/consumer comments were received for this application.

## **8. Proposed intervention's place in clinical management**

### **Description of Proposed Intervention**

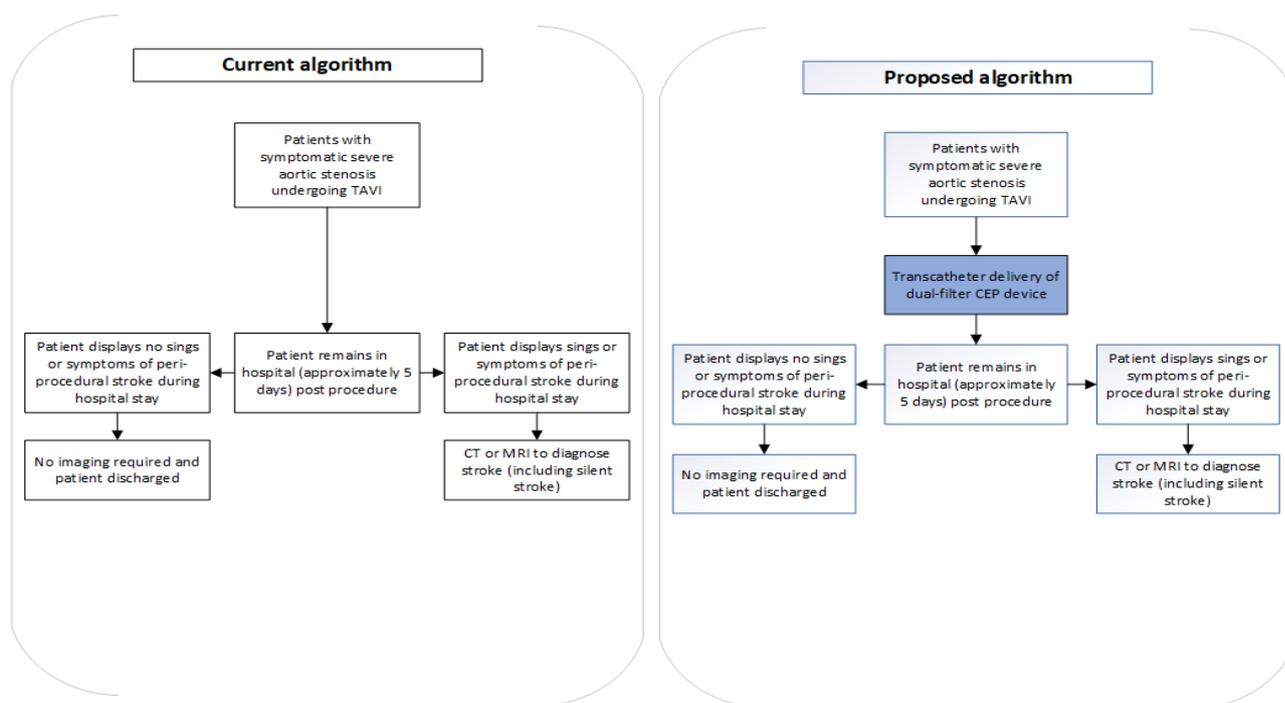
Percutaneous transcatheter delivery of a dual-filter CEP system, is intended to capture and remove debris that may enter the cerebral vascular system during the transcatheter aortic valve implantation procedure. The CEP system is comprised of two independent deployable filters, with sizes suitable for the arteries that provide the main blood supply to the brain. The CEP system is inserted via the radial artery, delivering an intra-luminal filter in the common trunk of the branchiocephalic artery (proximal filter), with a second filter delivered in the proximal section of the left common carotid artery (distal filter), filtering approximately 90% of the blood flow to the brain. At completion of the procedure, the filters and any captured debris are retrieved into the catheter and removed from the patient.

### **Description of Medical Condition(s)**

Embolic ischaemic strokes can occur in patients undergoing endovascular procedures such as TAVI. The origin of these embolic cerebrovascular events is variable and can include dislodged calcium particles, atherosclerotic plaque material, thrombus, valve and arterial wall tissue, and sheared interventional catheter coating material. Thrombus/debris lodges in an artery and blocks the flow of blood, this leads to a type of ischaemic stroke. This can lead to serious debilitation or death.

Many endovascular procedures associated with structural interventions are known to be cardioembolic, including transcatheter aortic valve implantation/replacement, mitral valve repair/replacement, left atrial appendage closure, valve in valve, and thoracic endovascular aortic repair. Given that the largest body of clinical evidence is from studies conducted in patients with severe, symptomatic aortic stenosis undergoing TAVI, this application focuses on the use of the percutaneous trans-radial delivery of a dual-filter CEP system as an adjunctive therapy for TAVI.

The current and proposed clinical management algorithms of patients with symptomatic severe aortic stenosis undergoing TAVI is provided in Figure 1. The only proposed change to the current clinical management algorithm is the use of the dual-filter CEP system adjunct to the TAVI procedure in all patients.



**Figure 1 Current and proposed clinical management algorithms with introduction of dual-filter CEP**

Source: Figure 5, p12 of the Commentary

CEP = cerebral embolic protection; CT = computed tomography; MRI = magnetic resonance imaging; TAVI = transcatheter aortic valve implantation

## 9. Comparator

The nominated comparator was the TAVI procedure without the use of a dual-filter CEP system (i.e. standard of care [SoC]). This was consistent with the ratified PICO.

The ADAR considered that single-filter CEP systems are not comparable to the dual-filter CEP as they only have a single-filter and are sized for the internal carotid artery (i.e. are sized too small to be used in either the left common carotid, or the brachiocephalic artery, or present a double-occlusion balloon system for use in small diameter carotid arteries).

The ADAR considered embolic deflection devices were not appropriate comparators as no embolic deflection devices are registered on the ARTG and deflection devices do not capture and remove embolic material, which can lead to this material causing potential harm elsewhere downstream in the circulatory system.

## 10. Comparative safety

The ADAR presented three randomised controlled trials (RCTs) and three observational studies to support its clinical claim (Table 3). The ADAR presented three RCTs (SENTINEL

IDE<sup>1</sup>, CLEAN TAVI<sup>2</sup>, and MISTRAL-C<sup>3</sup>) that compared TAVI + CEP with TAVI alone.

The primary efficacy outcomes were magnetic resonance imaging (MRI) outcomes:

- SENTINEL IDE measured the reduction in median total new lesion volume in protected territories between the Imaging Cohort Arms (Test and Control) as assessed by diffusion-weighted (DW)-MRI at Day 2-7 post-TAVI;
- CLEAN-TAVI measured numerical difference in new positive DW-MRI brain lesions at 2 days after TAVI; and
- MISTRAL-C measured new cerebral lesions by brain DW-MRI 5-7 days after TAVI.

The ADAR also presented three non-randomised studies (SENTINEL-Ulm<sup>4</sup>, Kroon 2009<sup>5</sup>, and Seeger 2019<sup>6</sup>). Seeger 2019 was a pooled propensity score matched analysis of patients from SENTINEL IDE trial, CLEAN TAVI trial and SENTINEL-Ulm study.

The ADAR noted that there is an ongoing RCT, PROTECTED TAVR<sup>7</sup>, comparing TAVI+CEP and TAVI alone in patients with aortic stenosis, with an estimated sample size of 3,000 patients. The primary endpoint in this study is stroke at 72 hours. The PROTECTED TAVR RCT is currently recruiting hence no data is available. The estimated completion date, noted as July 2022, is expected to be significantly delayed given the COVID-19 pandemic. The pre-MSAC response stated that results are not expected to be available until late 2022 at earliest.

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<sup>1</sup> Kapadia, SR, Kodali, S, Makkar, R, Mehran, R, Lazar, RM, Zivadinov, R, Dwyer, MG, Jilaihawi, H, Virmani, R, Anwaruddin, S & Thourani, VH 2017, Protection against cerebral embolism during transcatheter aortic valve replacement, *Journal of the American College of Cardiology*, vol. 69, no. 4, pp.367-377

<sup>2</sup> Haussig, S, Mangner, N, Dwyer, MG, Lehmkühl, L, Lücke, C, Woitek, F, Holzhey, DM, Mohr, FW, Gutberlet, M, Zivadinov, R & Schuler, G 2016, Effect of a cerebral protection device on brain lesions following transcatheter aortic valve implantation in patients with severe aortic stenosis: the CLEAN-TAVI randomized clinical trial, *Jama*, vol. 316, no.6, pp.592-601.

<sup>3</sup> Van Mieghem, NM, Schipper, ME, Ladich, E, Faqiri, E, Van Der Boon, R, Randjgari, A, Schultz, C, Moelker, A, van Geuns, RJ, Otsuka, F & Serruys, PW 2013, Histopathology of embolic debris captured during transcatheter aortic valve replacement, *Circulation*, vol. 127, no. 22, pp.2194-2201.

<sup>4</sup> Seeger, J, Gonska, B, Otto, M, Rottbauer, W & Wöhrle, J 2017, Cerebral embolic protection during transcatheter aortic valve replacement significantly reduces death and stroke compared with unprotected procedures, *JACC: Cardiovascular Interventions*, vol. 10, no. 22, pp.2297-2303.

<sup>5</sup> Kroon, H, van der Werf, H, Hoeks, S, van Gils, L, van den Berge, F, El Faquir, N, Rahhab, Z, Daemen, J, Poelman, J, Schurer, R & van den Heuvel, A 2019, Early Clinical Impact of Cerebral Embolic Protection in Patients Undergoing Transcatheter Aortic Valve Replacement: A Two-Center Registry in the Netherlands, *Circulation: Cardiovascular Interventions*, vol. 12, no. 6, e007605

<sup>6</sup> Seeger, J, Kapadia, SR, Kodali, S, Linke, A, Wöhrle, J, Haussig, S, Makkar, R, Mehran, R, Rottbauer, W & Leon, M 2019, Rate of peri-procedural stroke observed with cerebral embolic protection during transcatheter aortic valve replacement: a patient-level propensity-matched analysis, *European heart journal*, vol. 40, no. 17, pp.1334-1340

<sup>7</sup> Boston Scientific Corporation. Stroke PROTECTION With SEntinel During Transcatheter Aortic Valve Replacement (PROTECTED TAVR). Available from: <https://clinicaltrials.gov/ct2/show/NCT04149535>. NLM identifier: NCT04149535.

**Table 3 Summary of study characteristics**

Trial/Study	N; TAVI device	Design/ duration/ follow up	Risk of bias	Patient population	Key outcome(s)	Result used in economic model
<b>RCTs</b>						
SENTINEL IDE (Kapadia 2017, NCT02214277)	TAVI+CEP= 121 TAVI alone= 123  TAVI next gen: 78.3%	RCT, PG, SB, MC; U.S. and Germany 90 days	Low	Severe AS, <u>high risk</u> SAVR as per HT • 82.3±8.3 yrs • STS score <sup>^</sup> 6.7±3.79 <i>Low &lt;4%: 14%<sup>a</sup></i> <i>Int. 4-7% ~55%</i> <i>High &gt;7% 30%</i> • Previous AF 31.7% • Previous stroke 5.8%	Primary endpoint: MRI outcomes. Procedural complications: AKI, vascular Mortality Reduction in stroke Neurocognitive dysfunction post- procedure HRQoL	Yes – in meta-analysis (see <i>bottom row in Table</i> )
CLEAN TAVI (Haussig 2016, NCT01833052)	TAVI+CEP= 50 TAVI alone= 50  TAVI 1 <sup>st</sup> gen: 100%	RCT, SC, SB Germany; 1 month	Low	Symptomatic severe AS increased risk for SAVR as per HT. Baseline: • 80 yrs • STS score <sup>^</sup> 5.5 <i>Low &lt;4%: 40%<sup>a</sup></i> <i>Int. 4-7% ~50%</i> <i>High &gt;7% ~10%</i> • Previous AF 34% • Previous stroke ~ 4%.	Primary endpoint: MRI outcomes. Procedural complications: AKI, vascular Mortality Reduction in stroke Reduction in TIA Neurocognitive dysfunction post- procedure HRQoL (no results)	Yes – in meta-analysis (see <i>bottom row in Table</i> )
MISTRAL-C (Van Mieghem 2016)	TAVI+CEP= 32 TAVI alone= 33  TAVI next gen: 55%	RCT, MC, SB; Netherlands 6-months	Low (clinical) =; high (MRI outcomes <sup>†</sup> )	High risk for SAVR as per HT. Baseline: <sup>b</sup> • 81 yrs • STS score <sup>^</sup> 4.8; • Previous AF 28% • Previous stroke 19%.	Primary endpoint: MRI outcomes. Procedural complications, AKI, vascular Mortality Reduction in stroke Neurocognitive dysfunction post- procedure	Yes – in meta-analysis (see <i>bottom row in Table</i> )
<b>Non-randomised</b>						
SENTINEL-Ulm (Seeger 2017a, Seeger 2017b, Seeger 2017c)	TAVI+CEP= 280 TAVI alone= 280 (PSM cohort)  TAVI next gen: 100%	SC, pro. Germany; 1-month	Low	<i>All-comers TAVI population.</i> HT assessed Baseline: • 80 yrs • STS score <sup>^</sup> ~6.5% • Previous AF 35% • Previous stroke ~10%.	Procedural complications, AKI, vascular Mortality Reduction in stroke	Yes, in sensitivity analysis. No data available at 30 days, hence not included in base-case.

Trial/Study	N; TAVI device	Design/ duration/ follow up	Risk of bias	Patient population	Key outcome(s)	Result used in economic model
Kroon 2019	TAVI +CEP= 333 TAVI alone= 333  (PSM cohort <sup>d</sup> resulted in 333 pairs, out of a total of 831 consecutive patients)  TAVI next gen: estimated 50.5%	MC retro., Netherlands 1-month 2006-2017	Low	Severe AS assessed by HT. Baseline: 50%: • median 81 yrs, • STS score <sup>a</sup> 4.3% (3.1%–6.6%).	Procedural complications, AKI, vascular Mortality Reduction in stroke Reduction in TIA	Yes - in meta-analysis (see bottom row in Table)
<b>Pooled PSMA</b>						
Seeger 2019	TAVI +CEP= 533 TAVI alone= 533 (PSM cohort; was performed to adjust for possible confounders and resulted in 533 matched pairs (N=1066).  TAVI next gen: >50%*	Propensity score analysis (optimal matching)	Low	Patients from the SENTINEL IDE trial, CLEAN TAVI trial and SENTINEL-Ulm observational study in a patient level pooled PSM analysis (N= 1306). Baseline <sup>e</sup> : 50% • Men, mean age 81 yrs • STS score <sup>a</sup> of ~ 6.6%.	Mortality at 72 hours Reduction in clinical stroke at 72 hours	Yes, in sensitivity analysis.
<b>Meta-analysis</b>						
Meta-analysis SENTINEL IDE, CLEAN TAVI, Kroon (2019) and MISTRAL-C	As above	RCTs + cohort studies	As above	As above	30-day outcomes: Non-disabling stroke, Disabling stroke, Death	Yes – base case

Source: Table 3, pxii-xiv of the Commentary

AS = Aortic stenosis; AKI = acute kidney injury; HRQOL = health –related quality of life; HT = Heart Team; MC = multicentre; MRI = magnetic resonance imaging; PSMA = propensity score matching; SC = single centre; STS= Society of Thoracic Surgeons; TAVI= Transcatheter aortic valve implantation; TIA = transient ischaemic attack; pro = prospective; retro. = retrospective yrs = years

<sup>a</sup> STS scores reflect total (all groups)

\* The pooled PSMA by Seeger (2019) did not report individual devices used, however reported that 63% were balloon-expandable, 21% were self-expandable and 16% were mechanical-expandable. Given the distribution of TAVI devices in the source studies for this PSMA, it can be expected that the majority of patients received a next generation device.

<sup>‡</sup> In terms of clinical outcomes, 100% of patients were included in the assessment

<sup>a</sup> Low risk is not relevant to this current application

<sup>b</sup> Key exclusion criteria were the presence of a permanent pacemaker or automated internal cardiac defibrillator at baseline, a history of prior stroke with sequelae and dementia

<sup>c</sup> Patients with valve-in-valve procedures were excluded

<sup>d</sup> (n=168 excluded as treated before 2011 when CEP was not introduced in the practice, yet, n=1 excluded because of missing baseline data)

<sup>e</sup> In total, 717 patients underwent TAVI+CEP and 589 patients were treated with TAVI alone

<sup>‡</sup> given missing data

The SENTINEL IDE RCT did not report any statistically significant differences in the primary safety outcome, the incidence of major adverse cardiac and cerebrovascular events (MACCE) during the peri-procedural period or at 30-days. The SENTINEL-Ulm cohort study, and the meta-analysis of peri-procedural MACCE reported a significant reduction in peri-procedural MACCE.

There was no statistically significant difference in major vascular complications (excluding MACCE) at the peri-procedural or 30-day stage. The ADAR presented a second meta-analysis excluding the results of the MISTRAL-C trial as its results were contrary to the other trials. The commentary considered this analysis was most robust as it reduced the statistical heterogeneity of the meta-analysis. SENTINEL IDE reported that none of the vascular complications in the TAVI+CEP treatment arm was in the radial artery and only one brachial event was reported within 30 days of the index procedure.

The studies presented in the ADAR did not find statistically significant differences in acute kidney injury at 30-days (Table 4) or peri-procedurally.

**Table 4 Key safety outcomes**

Study ID (type)	Risk of bias	Timing	TAVI+CEP n/N (%)	TAVI alone n/N (%)	RD (95% CI)	OR (95% CI)
<b>MACCE (peri-procedural)</b>						
SENTINEL IDE (RCT)	Low	In-hospital	14/244 (5.7)	10/119 (8.4)	-0.03 [-0.08, 0.03]	0.66 [0.29, 1.54]
SENTINEL-Ulm <sup>a</sup> (cohort)	Low	7 days	7/280 (2.5)	22/280 (7.9)	<b>-0.05 [-0.09, -0.02]</b>	<b>0.30 [0.13, 0.72]</b>
Meta-analysis Heterogeneity (I <sup>2</sup> ); p-value	-	-	21/524 (4.01)	32/399 (8.02)	<b>-0.05 [-0.08, -0.02]</b> 0%; p=0.43	<b>0.45 [0.21, 0.98]</b> 40%; p=0.20
<b>MACCE (30-days)</b>						
SENTINEL IDE (RCT)	Low	30 days	7/117 (6.0%)	11/119 (9.2%)	-0.03 [-0.10, 0.03]	0.62 [0.23, 1.67]
<b>Major vascular complications</b>						
SENTINEL IDE (RCT)	Low	30 day	21/244 (8.6)	7/119 (5.9)	0.03 [-0.03, 0.08]	1.51 [0.62, 3.65]
MISTRAL-C (RCT)	Low	30 day	0/32 (0.0)	6/33 (18.2)	-0.18 [-0.32, -0.04]	0.07 [0.00, 1.21]
CLEAN TAVI (RCT)	Low	30 day	5/50 (10.0)	6/50 (12.0)	-0.02 [-0.14, 0.10]	0.81 [0.23, 2.87]
Meta-analysis (all RCTs) Heterogeneity (I <sup>2</sup> ); p-value	-	-	26/326 (7.98)	19/202 (9.41)	-0.05 [-0.16, 0.07] 74%; p=0.02	0.77 [0.22, 2.65] 56%; p=0.11
Meta-analysis (excluding MISTRAL-C) Heterogeneity (I <sup>2</sup> ); p-value	-	-	26/294 (8.84)	13/169 (7.69)	0.02 [-0.03, 0.07] 0%; p=0.48	1.23 [0.60, 2.53] 0%; p=0.43
<b>Acute kidney injury (30 days)</b>						
SENTINEL IDE (RCT)	Low	30 day	1/116 (0.9)	0/110 (0.0)	0.01 [-0.02, 0.03]	2.87 [0.12, 71.21]
MISTRAL-C (RCT)	Low	30 day	0/32 (0.0)	1/33 (3.0)	-0.03 [-0.11, 0.05]	0.33 [0.01, 8.49]
CLEAN TAVI (RCT)	Low	30 day	1/50 (2.0)	5/50 (10.0)	-0.08 [-0.17, 0.01]	0.18 [0.02, 1.63]
Meta-analysis (all RCTs) Heterogeneity (I <sup>2</sup> ); p-value	-	-	2/198 (1.01)	6/193 (3.11)	-0.03 [-0.10, 0.05] 73%; p=0.02	0.41 [0.08, 1.99] 0%; p=0.38

Source: Table 28, p52; Table 29, p53; Table 31, p55 and Table 34, p56 of the Commentary

Abbreviations: CEP, cerebral protection device; CI, confidence interval; MACCE = Major adverse cardiac and cerebrovascular events; RD, risk difference; OR, odds ratio; TAVI, during transcatheter aortic valve implantation

**Bold** = statistically significant

<sup>a</sup> Combination of all-cause mortality, all stroke, and acute kidney injury stage 3

## 11. Comparative effectiveness

Table 5 presents the key stroke outcomes from the RCTs and observational studies. The ADAR presented several analyses: meta-analysis of RCTs alone, the propensity score matched analysis of two RCTs and two cohort studies (Seeger 2019), and meta-analysis of all available studies.

The meta-analyses of RCTs alone did not find any statistically significant differences for the reported stroke outcomes. The Commentary noted the trials were not powered to detect a difference in stroke. The point estimates from the meta-analysis of RCTs generally favoured CEP (with the exception of no difference reported for early disabling stroke).

The ADAR considered that the propensity score matched analysis (Seeger 2019) demonstrated that use of a CEP results in a reduction in early peri-procedural strokes (all strokes and disabling strokes). Seeger 2019 used an optimal matching attempt that matched patients on several factors but not on history of stroke or transient ischaemic attack (TIA). In the matched cohorts 11.3% (60/533) of patients who had TAVI alone and 10.9% (58/533) of patients with CEP had a history of stroke or TIA. The Commentary considered that the outcomes from Seeger (2019) provided the best estimates for the peri-procedural stroke outcomes. The ADAR considered that the meta-analysis of all RCTs and cohort studies supported this conclusion. Observational studies and meta-analyses combining RCTs and observational studies may not produce reliable estimates of stroke reduction as observational studies may be affected by unobserved confounders. This had flow on effects to the economic evaluation.

The pre-ESC response considered the lack of power to detect a difference in peri-procedural stroke in the RCTs is overcome by meta-analysing the totality of comparative data, by increasing the total sample size and thus reducing uncertainty. It highlighted that both cohort studies were propensity score matched, meaning patients were well balanced on important patient characteristics, thus mitigating the risk of confounding. Given the patient populations were well matched across RCTs and cohort studies, the device utilisation across trials was comparable and applicable, and outcomes were defined the same way across both sets of data further supports the meta-analysis of the included RCTs and cohort studies. The exchangeability was further supported by lack of heterogeneity consistently across outcomes when meta-analysing the totality of the evidence.

The meta-analysis of all studies (RCT and observational) demonstrated CEP resulted in a statistically significant reduction in all strokes and disabling strokes at 30 days. The ADAR considered these results support those from the early peri-procedural analyses, demonstrating superiority of the CEP device used adjunct to TAVI compared with TAVI alone. The Commentary noted that for non-disabling stroke at 30 days, the meta-analysis of the three RCTs and one cohort study found no significant difference between TAVI+CEP and TAVI alone, with the risk differences of the individual studies and the meta-analysis being zero or close to zero. The 30-day meta-analyses results for disabling and non-disabling stroke were used in the economic model.

The ADAR considered that the reduction in stroke was clinically meaningful as any reduction in stroke is considered clinically relevant.

**Table 5 Summary of key outcomes**

Outcomes	Participants (studies)	Quality of evidence (GRADE) <sup>a</sup>	TAVI+CEP n/N (%)	TAVI alone n/N (%)	OR (95%CI)	RD (95% CI) NNT (95% CI) <sup>a</sup>
<b>Stroke - any</b>						
Early peri-procedural: 72 hours	Seeger 2019 k=3 (2 RCTs, 1 cohort); N=1,066	⊕⊕⊖⊖ LOW	TAVI+CEP: 10/533 (1.88)	TAVI alone: 29/533 (5.44)	<b>0.33</b> [0.16, 0.69]	<b>-0.04</b> [-0.06, -0.01] NNT: 25 [17, 100]
Early peri-procedural (24h - 7 days)	k=2 RCT; k=2 cohort; N=1,689 (all studies)	⊕⊕⊖⊖ LOW	TAVI+CEP: 24/907 (2.7)	TAVI alone: 37/782 (4.7)	<b>0.49</b> [0.28, 0.85]	<b>-0.02</b> [-0.04, -0.01] NNT: 50 [25, 100]
Early peri-procedural (24h - 7 days) RCTs only	k=2 N=463	⊕⊕⊖⊖ LOW	17/294 (5.8)	15/169 (8.9)	<b>0.67</b> [0.33, 1.39]	-0.03 [-0.08, 0.02] NNT: 33 [13, -50]
30 day	k=4 (RCT; k=3 cohort k=1); N=1,056	⊕⊕⊕⊖ MODERATE	TAVI+CEP: 15/531 (2.8)	TAVI alone: 33/526 (6.3)	<b>0.45</b> [0.24, 0.84]	<b>-0.04</b> [-0.06, -0.01] NNT: 25 [17, 100]
30 day RCTs only	k=3 N= 391	⊕⊕⊕⊕ HIGH	TAVI+CEP 9/198 (4.6)	TAVI alone: 16/193 (8.3)	0.56 [0.24, 1.29]	-0.04 [-0.09, 0.01] NNT: 25 [11, -100]
<b>Stroke - disabling</b>						
Early peri-procedural: 72 hours	PSMA of k=3 (2 RCTs, 1 cohort); N=1066	⊕⊕⊖⊖ LOW	TAVI+CEP: 2/533 (0.38)	TAVI alone: 29/533 (5.44)	<b>0.15</b> [0.03, 0.67]	-0.02 [-0.03, -0.01] NNT: 50 [33, 100]
Early peri-procedural (24h - 7 days)	k=2 RCT; k=2 cohort; N=1689	⊕⊕⊖⊖ LOW	TAVI+CEP: 5/907 (0.55)	TAVI alone: 16/782 (2.05)	<b>0.30</b> [0.10, 0.92]	-0.01 [-0.02, 0.00] NNT: 100 [50, NC]
Early peri-procedural (24h - 7 days) RCTs only	k=2 N=463	⊕⊕⊖⊖ LOW	2/294 (0.68)	1/169 (0.59)	0.98 [0.09, 10.86]	-0.00 [-0.02, 0.02] NNT: NC [50, -50]
30 days	k=4 (RCT; k=3 cohort k=1); N=1056	⊕⊕⊕⊖ MODERATE	TAVI+CEP: 3/531 (0.56)	TAVI alone: 17/525 (3.24)	<b>0.22</b> [0.07, 0.64]	-0.02 [-0.04, 0.00] NNT: 50 [25, NC]
30 day RCTs only	k=3 N= 390	⊕⊕⊕⊕ HIGH	TAVI+CEP 0/198 (0)	TAVI alone: 3/192 (1.56)	0.24 [0.03, 2.24];	-0.01 [-0.03, 0.01] NNT: 100 [33, -100]
<b>Mortality</b>						
Early peri-procedural (1-7 days)	K=4 (RCT k=2, cohort k=2); N=1,654	⊕⊕⊖⊖ LOW	TAVI+CEP: 12/889 (1.35)	TAVI alone: 17/765 (2.22)	0.71 [0.27, 1.88]	-0.01 [-0.02, 0.01] NNT: 100 [50, -100]
30 day	k=4 (RCT k=3 cohort k=1); N=1,059	⊕⊕⊕⊖ MODERATE	TAVI+CEP: 20/532 (3.76)	TAVI alone: 19/527 (3.61)	1.09 [0.56, 2.09]	-0.00 [-0.02, 0.02] NNT: NC [25, -25]

Outcomes	Participants (studies)	Quality of evidence (GRADE) <sup>a</sup>	TAVI+CEP n/N (%)	TAVI alone n/N (%)	OR (95%CI)	RD (95% CI) NNT (95% CI) <sup>a</sup>
30 day RCTs only	k=3 N= 393	⊕⊕⊕⊕ HIGH	TAVI+CEP: 2/199 (1.01)	TAVI alone: 6/194 (3.09)	0.37 [0.08, 1.65]	-0.01 [-0.04, 0.01] NNT: 100 [25, -100]

Source: Table 4, pp xvi-xvii; Table 40, p62 of the Commentary

AKI=acute kidney injury; CEP=cerebral embolic protection; NNT=number needed to treat; CI=confidence interval; NC = not calculable; RCT=randomised controlled trial; RD=risk difference; OR=odds ratio; PSMA=propensity score matched analysis; MA=meta-analysis k=number of studies; N=number of participants; TAVI=transcatheter aortic valve implantation. <sup>a</sup> GRADE Working Group grades of evidence (Guyatt et al., 2013); ⊕⊕⊕⊕ **High quality**: We are very confident that the true effect lies close to that of the estimate of effect. ⊕⊕⊕⊖ **Moderate quality**: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. ⊕⊕⊖⊖ **Low quality**: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. ⊕⊖⊖⊖ **Very low quality**: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

**Bold** = statistically significant

<sup>a</sup> NNT values are negative where the point estimate for 95% confidence interval estimated that stroke or mortality could occur more frequently with CEP. NNT values not calculable when the point estimate for 95% confidence interval estimated no difference in the incidence of stroke or mortality.

The clinical evidence presented in the ADAR did not show significant differences in mortality between TAVI with CEP and TAVI alone. The Commentary noted that there were very few deaths among patients either group.

Data was available from three RCTs for neurocognitive outcomes, but there were many limitations. This included assessments at different time points across the, the range of outcome measurement methods implemented, lack of statistical power (SENTINEL IDE), large amounts of missing data (CLEAN TAVI) and missing data being unbalanced between the treatment arms (MISTRAL-C).

The available data from the three RCTs indicated that TAVI+CEP was associated with numerically fewer new lesions and lower volume of lesions on DW-MRI in all or in protected territories compared to TAVI alone. The Commentary noted that one of the trials had a large amount of missing data and that the assessments were made up to 7 days after the procedure. In the case of protected territories, adjusting for valve type resulted in a significantly lower mean volume in TAVI+CEP patients than in TAVI alone in the SENTINEL IDE trial.

## Clinical claim

The ADAR claimed that transcatheter delivery of the dual-filter CEP device during TAVI is superior in terms of comparative effectiveness, based on a statistically significant reduction in the rate of peri-procedural strokes demonstrated in the propensity score matched analysis (Seeger 2019). The Commentary considered the clinical claim may be supported when solely considering the results of the meta-analyses that combine RCTs and cohort studies and noted that the ADAR did not provide a rationale for including cohort studies in their meta-analysis.

The ADAR claimed that transcatheter delivery of the dual-filter CEP device during TAVI is non-inferior in terms of comparative safety when compared to the TAVI procedure without the delivery of a dual-filter CEP device. The Commentary considered this clinical claim was appropriate.

## 12. Economic evaluation

The ADAR performed a modelled cost-utility analysis to evaluate the cost-effectiveness of TAVI+CEP vs. TAVI alone (Table 6), including two TAVI risk populations separately: the MBS funded inoperative/high risk population; and the intermediate surgical risk population

(as per application 1603). The ADARs model included an acute phase (within 30-days post-surgery) and a non-acute phase (beyond 30 days). The Commentary considered that the model presented in the ADAR was appropriate and reflected the eligible population.

**Table 6 Summary of the economic evaluation**

<b>Perspective</b>	Healthcare system
<b>Comparator</b>	No CEP
<b>Type of economic evaluation</b>	Cost-utility and cost-effectiveness analysis
<b>Sources of evidence</b>	Meta-analysis of 30-day stroke and mortality rates from; SENTINEL IDE, CLEAN TAVI, Kroon (2019) and MISTRAL-C
<b>Time horizon</b>	Lifetime
<b>Outcomes</b>	Quality-adjusted life years
<b>Methods used to generate results</b>	A decision tree analysis with Markov chain
<b>Health states</b>	No stroke Non-disabling stroke Disabling stroke Dead
<b>Cycle length</b>	The decision tree analysis to 30-days post-procedure, then annual cycles
<b>Discount rate</b>	5%
<b>Software packages used</b>	Excel

Source: MSAC 1605 ADAR Table 86, p144

Key structural assumptions of the ADARs model included:

- No possibility of stroke recurrence is incorporated. The ADAR considered this to be conservative, biasing against the TAVI+CEP arm of the model because history of stroke is a key risk factor of having another stroke.
- Patients' disability level does not change over time. Given the age and medical history of the modelled patient population, the ADAR considered this was likely a conservative assumption (i.e. the impairment experienced by stroke sufferers is more likely to deteriorate than improve over time).

Point estimates for disabling and non-disabling strokes were sourced from a meta-analysis of all available studies (including cohort studies) of TAVI + CEP vs. TAVI only. However, the difference in non-disabling stroke was not statistically significant. The Commentary considered the superior effectiveness of TAVI+CEP vs. TAVI only for 30-day stroke outcomes was appropriate. If point estimates for RCTs only were used, this would have resulted in a greater incremental increase of strokes for the TAVI only arm (increase from 6.3% to 8.3% [increase of 2%]) compared to TAVI + CEP and (2.8% to 4.6% [1.8%]). This would have slightly favoured TAVI+CEP. However, the RCTs did not report a statistically significant reduction in stroke. The Commentary considered that given the limitations of long-term TAVI + CEP survival and Australian data, the assumptions were reasonable and conservative as they biased against TAVI + CEP.

The stepped economic evaluations below for inoperable/high (Table 7) and intermediate (Table 8) risk patients. In the ADAR, the base case ICER for the inoperable/high and intermediate risk populations were \$redacted/QALY and \$redacted/QALY, respectively. The ADAR modelled intermediate risk patients from a baseline age of 81 years instead of 82 years. Corrected values have been italicised in Table 8 to provide a corrected base case of \$redacted/QALY.

**Table 7 Stepped economic evaluation: Inoperable/high risk population**

Step #	Step description	Duration	Effectiveness	Costs included	Incremental cost	Incremental effectiveness	ICER
1	Trial-based economic evaluation	30-day	Strokes*	Screening and index procedure	\$redacted	3.46%	\$redacted per stroke avoided
2	Extrapolation of patient survival	Lifetime	Life years	Screening, index procedure and stroke-related healthcare costs	\$redacted	\$redacted	\$redacted per life year
3	Incorporation of stroke-related healthcare costs	Lifetime	Life years	Screening, index procedure and stroke-related healthcare costs	\$redacted	\$redacted	\$redacted per life year
4	Translation of life years to QALYs	Lifetime	QALYs	Screening, index procedure and stroke-related healthcare costs	\$redacted	\$redacted	\$redacted per QALY

Source: Table 7, pxx of the Commentary

Abbreviations: CEP, cerebral embolic protection; ICER, Incremental cost effectiveness ratio; QALYs, Quality adjusted life years.

Note: As calculated from the meta-analysis of SENTINEL IDE, MISTRAL-C, CLEAN TAVI and Kroon 2019

TAVI+CEP: non-disabling stroke=2.26%, disabling stroke =0.56%

TAVI alone: non-disabling stroke =3.04%, disabling stroke =3.24%

**Table 8 Stepped economic evaluation: Intermediate risk population**

Step #	Step description	Duration	Effectiveness	Costs included	Incremental cost	Incremental effectiveness	ICER
1	Trial-based economic evaluation	30-day	Strokes*	Screening and index procedure	\$redacted	3.46%	\$redacted per stroke avoided
2	Extrapolation of patient survival	Lifetime	Life years	Screening, index procedure and stroke-related healthcare costs	\$redacted	redacted redacted <sup>a</sup>	\$redacted per life year \$redacted per life year <sup>a</sup>
3	Incorporation of stroke-related healthcare costs	Lifetime	Life years	Screening, index procedure and stroke-related healthcare costs	\$redacted	redacted redacted <sup>a</sup>	\$redacted per life year \$redacted per life year <sup>a</sup>
4	Translation of life years to QALYs	Lifetime	QALYs	Screening, index procedure and stroke-related healthcare costs	\$redacted	redacted redacted <sup>a</sup>	\$redacted per QALY \$redacted per QALY <sup>a</sup>

Source: Table 8, pxxi of the Commentary

Abbreviations: CEP, cerebral embolic protection; ICER, Incremental cost effectiveness ratio; QALYs, Quality adjusted life years.

Note: As calculated from the meta-analysis of SENTINEL IDE, MISTRAL-C, CLEAN TAVI and Kroon 2019.

TAVI+CEP: non-disabling stroke=2.26%, disabling stroke =0.56%

TAVI alone: non-disabling stroke =3.04%, disabling stroke =3.24%

<sup>a</sup> Corrected values using a baseline age of 82

In both populations, TAVI+CEP had an ICER of less than \$50,000/QALY. The Commentary considered the comparative incremental utility gained by TAVI+CEP vs. TAVI may be lower than estimated in the model; particularly due to no stroke recurrence and increased disability over time due to stroke. As the TAVI only arm had greater rates of stroke, incremental utilities calculated were likely higher than if decline in utility for stroke related disabilities were modelled.

The modelled results were most sensitive to applied stroke rates and the time horizon. It was also sensitive to utility values and health state costs. The Commentary considered that there is uncertainty concerning the appropriate time horizon and health state values to use in the economic evaluation. Any increase in the time horizon would decrease the ICER as the bulk of costs in the model are incurred in the first year whereas health state costs are gained for the duration of the model. The Commentary considered that these areas of uncertainty were addressed and the base case values might be justified (Table 9).

**Table 9 Key drivers of the economic model**

Description	Method/Value	Impact
Time horizon	Time horizon was 17-18 years (life time) in the base case but was varied from 5 to 20 years in sensitivity analyses	High; favoured intervention
Stroke rates	Lower disabling and non-disabling stroke rates were used for TAVI+CEP against TAVI from meta-analysed results in Section B.6 for both the intermediate and inoperable/high risk populations. Refer to Section C.2.1 for values.	High, favoured intervention
Utility values	Baseline and 12 month post-procedure values for intermediate and inoperable/high risk groups were sourced from Baron (2018) <sup>8</sup> and Reynolds (2012) <sup>9</sup> , respectively. Disutility values of -0.248 for non-disabling stroke and -0.608 for disabling stroke from Wu 2014 <sup>10</sup> calculated and used.	High, favoured intervention
Health state costs	Australian values were used and inflated to 2020 values using the health price index. Costs of \$2,114 and \$16,341 per annum, used for non-disabling and disabling stroke, respectively. TAVI+CEP vs TAVI only had a far lower rate of disabling stroke (0.56% vs 3.24%), resulting in lower health state costs.	High, favoured intervention

Source: Table 10, pxxii and Table 77, p105

CEP = cerebral embolic protection; TAVI = transcatheter aortic valve implantation

Table 10 presents univariate and multivariate sensitivity analyses using the inputs from MSAC applications for TAVI for inoperable and high risk patients ([1361.2 Public Summary Document](#)) and the TAVI for intermediate risk patients ([1603 Application](#)) to be considered at the November 2020 MSAC meeting. The ICER for TAVI+CEP vs. TAVI is much higher (inoperable high risk ICER = **redacted%**; intermediate risk ICER = **redacted%**) if the model inputs from previous applications are used.

**Table 10 Redacted**

Additional analyses were performed by the Department to estimate the weighted CEP benefit at various willingness-to-pay thresholds using inputs from previous TAVI models. The ICER was weighted using the estimated utilisation.

**Table 11 Redacted**

<sup>8</sup> Baron SJ, Thourani VH, Kodali S, et al. Effect of SAPIEN 3 Transcatheter Valve Implantation on Health Status in Patients With Severe Aortic Stenosis at Intermediate Surgical Risk: Results From the PARTNER S3i Trial. *JACC Cardiovasc Interv.* 2018;11(12):1188-1198.

<sup>9</sup> Reynolds MR, Magnuson EA, Wang K, Thourani VH, Williams M, Zajarias A, Rihal CS, Brown DL, Smith CR, Leon MB, Cohen DJ. Health-related quality of life after transcatheter or surgical aortic valve replacement in high-risk patients with severe aortic stenosis: results from the PARTNER (Placement of AoRTic TraNscatheter Valve) Trial (Cohort A). *Journal of the American College of Cardiology.* 2012 Aug 7;60(6):548-58.

<sup>10</sup> Wu B, Kun L, Liu X, He B. Cost-effectiveness of different strategies for stroke prevention in patients with atrial fibrillation in a health resource-limited setting. *Cardiovasc Drugs Ther.* 2014;28(1):87-98.

### 13. Financial/budgetary impacts

A market share approach was used to estimate the financial implications of listing the transcatheter delivery of dual-filter CEP system during TAVI on the MBS (Table 12). The ADAR stated that the inoperable/high risk market is estimated based on current utilisation of MBS item 38495, TAVI. The intermediate risk market is estimated based on current utilisation of MBS item 38488 for SAVR. The ADAR estimated that 14.8% of SAVR patients would be intermediate risk based on published estimates of risk stratification for patients undergoing SAVR and the assumption that no high-risk patients currently receive SAVR. Given that yearly MBS usage for SAVR up to the end of 2019 were utilised in this section, the commentary considered the slight decrease projected is justifiable.

The ADAR estimated that 61.5% of TAVI patients are anatomically suitable for CEP (Voss 2020)<sup>11</sup>. The ADAR also assumes high uptake as it is an adjunct service which reduces the risk of peri-procedural stroke without any adverse safety or effectiveness implications; the uptake rates increases linearly from **redacted**% in Year 1 to **redacted**% in Year 5 in both populations. The Commentary noted that if eligibility rates of 94.7% from the SENTINEL IDE study were used, this would result in a total of 825 – 2,237 inoperable/high risk patients, and 92 – 169 intermediate risk patients from Year 1 to Year 5. The pre-ESC response noted that this is not an accurate reflection of anatomical suitability as it only includes patients post randomisation. Prior to randomisation patients underwent study baseline evaluation and CT assessment, where 11% of patients failed screening due to anatomical criteria and 17% failed screening due to other reasons.

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<sup>11</sup> Voss S, Schechtel J, Nöbauer C, Bleiziffer S, Lange R. Patient eligibility for application of a two-filter cerebral embolic protection device during transcatheter aortic valve implantation: does one size fit all?. *Interact Cardiovasc Thorac Surg.* 2020;30(4):605-612.

**Table 12 Total costs to the MBS associated with CEP use during TAVI procedures**

Year	Year 1	Year 2	Year 3	Year 4	Year 5
	2021	2022	2023	2024	2025
<b>Current MBS population (Inoperable/high risk patient)</b>					
Projected TAVI services	2,177	2,418	2,622	2,798	2,953
Eligible population (61.5%; Voss 2020)	1,339	1,487	1,612	1,721	1,816
CEP services (uptake rate redacted%-redacted%)	Redacted	Redacted	Redacted	Redacted	Redacted
Net impact	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
- cost to MBS	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
- cost to patients	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
<b>Intermediate risk population</b>					
Projected SAVR services	2,401	2,351	2,300	2,250	2,199
Patients at intermediate risk (14.8%; Thourani 2015) <sup>12</sup>	356	349	342	334	327
Use of TAVI (68.2%; De Backer 2016) <sup>13</sup>	243	238	233	228	223
Eligible population (61.5%; Voss 2020)	150	146	143	140	137
CEP services (uptake rate redacted%-redacted%)	Redacted	Redacted	Redacted	Redacted	Redacted
<b>Expanded MBS population (Inoperable/high risk and intermediate risk patient)</b>					
CEP services	Redacted	Redacted	Redacted	Redacted	Redacted
Net impact	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
- cost to MBS	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
- cost to patients	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted
<b>Cost to private health insurance</b>					
Total prostheses costs (inoperable/high risk patients)	\$Redacted	\$Redacted	\$Redacted	Redacted	\$Redacted
Total prostheses costs (Inoperable/high risk and intermediate risk patient)	\$Redacted	\$Redacted	\$Redacted	\$Redacted	\$Redacted

Source: Table 11, pxxiii and Table 12, pxxiv of the Commentary

<sup>a</sup> For MBS items incurred outside of hospital the 85% MBS rebate was applied (MBS item 104 and 105). For MBS items incurred in hospital the 75% was applied (MBS items 20803 and 23083).

Note some differences due to rounding

The ADAR estimated CEP utilisation in the high risk and inoperable population by forecasting current use of TAVI on the MBS. In 2019, there were 1,503 TAVI services processed on the MBS; from January to June 2020, there were 870 TAVI services processed [Source: Medicare Item Reports data for 38495]. However, the utilisation of TAVI has been higher than predicted for this population. The predicted use of TAVI for high risk and inoperable patients ranged from 768 for 2017-18 (Year 1 of TAVI listing) to 843 in 2020-21 (Year 4); the actual use in Year 1 [2017-18] of listing was 1,035 services (Source Predicted vs. Actual [PVA] TAVI snapshot, 1361.2). The financial impact of CEP may be higher if

<sup>12</sup> Thourani VH, Suri RM, Gunter RL, Sheng S, O'Brien SM, Ailawadi G, Szeto WY, Dewey TM, Guyton RA, Bavaria JE, Babaliaros V. Contemporary real-world outcomes of surgical aortic valve replacement in 141,905 low-risk, intermediate-risk, and high-risk patients. *The Annals of thoracic surgery*. 2015 Jan 1;99(1):55-61.

<sup>13</sup> De Backer O, Luk NH, Olsen NT, Olsen PS, Søndergaard L. Choice of treatment for aortic valve stenosis in the era of transcatheter aortic valve replacement in Eastern Denmark (2005 to 2015). *JACC: Cardiovascular Interventions*. 2016 Jun 13;9(11):1152-8.

growth of TAVI use in the high risk/inoperable population is higher than forecast by the ADAR.

Table 13 presents a comparison of the estimated utilisation of TAVI for intermediate risk patients in the ADAR and the ADAR for TAVI in intermediate risk patients (1603) that was also considered at the November 2020 MSAC meeting. The estimated use of TAVI for the intermediate risk population was **redacted** in application 1603 (TAVI intermediate risk) than the TAVI CEP ADAR (**redacted**). Using the estimated utilisation from application 1603 resulted in **redacted** MBS and prostheses costs. The financial impact of CEP may be **redacted** if the estimates in application 1603 better reflect the likely utilisation of TAVI in the intermediate risk population.

Table 13 Redacted

#### 14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Safety	The ADAR's claim of non-inferior safety on the basis of similar rate of major vascular complications, AKI and adverse event profiles appears well justified.
Effectiveness	<p>The key clinical evidence supporting a reduction in peri-procedural stroke was a propensity score matched analysis that included patients from two randomised controlled trials (RCTs) and one observational study (Seeger 2019). This was supported by a meta-analysis of three RCTs and another cohort study. Inclusion of cohort studies in addition to the three RCTs was justified on the basis of the individual RCTs not being powered to show differences in peri-procedural stroke.</p> <p>Cohort studies were propensity score matched, but internal validity can still be affected through the influence of unreported confounders (known and unknown).</p> <p>A consistent effect in favour of TAVI+CEP was observed across all stroke outcomes.</p> <p>To note an ongoing RCT, PROTECTED TAVR<sup>14</sup>, comparing TAVI+CEP and TAVI alone in patients with aortic stenosis, with an estimated sample size of 3,000 patients and primary endpoint of stroke at 72 hours.</p>
MBS item descriptor	<p>If MSAC recommends this item for public funding, it could potentially be difficult to justify only allowing its use for the high-risk/inoperable population. ESC noted there are several cerebral embolic protection (CEP) systems and that it may be appropriate to fund the specific intervention (i.e. transcatheter delivery of a dual-filter CEP) until evidence emerges for safety and effectiveness of other devices.</p> <p>ESC advised that MSAC may wish to consider whether CEP should have similar accreditation requirements to the TAVI procedure.</p>
Proposed prosthesis benefit	The ADAR proposes a higher prosthesis benefit of <b>\$redacted</b> for dual-filter CEP (relative to the \$1,995 benefit for single or dual filter CEP on the Prostheses List) and justifies it as saying it is cost-effective at the proposed benefit. ESC noted that the key drivers of the economic model favoured CEP. ESC advised that the economic evaluation, if accepted by MSAC, is favourable at the higher CEP costs.

<sup>14</sup> Boston Scientific Corporation. Stroke PROTECTION With SEntinel During Transcatheter Aortic Valve Replacement (PROTECTED TAVR). Available from: <https://clinicaltrials.gov/ct2/show/NCT04149535>. NLM identifier: NCT04149535.

<b>ESC key issue</b>	<b>ESC advice to MSAC</b>
Uncertainty in the ICER	Model parameters are sensitive to change. The sensitivity analyses demonstrate robust outcomes. However, MSAC may wish to consider the use of other TAVI model inputs (1361.2 and 1603) and how this would impact the ICER.
Uncertainty in the financial estimates	There is uncertainty in the utilisation rates due to higher than expected use of TAVI in the high risk and inoperable populations and the potential for number of patients undergoing TAVI to increase if TAVI subsidy is expanded to intermediate and low surgical risk populations.  The estimated number of TAVI interventions used in this application (1605) should be consistent with other relevant TAVI applications (e.g. 1603). Moreover, there is a possibility CEP device utilisation may expand over time with new TAVI indications received by the Department.

## **ESC discussion**

ESC noted that this application was for Medicare Benefits Schedule (MBS) listing of a dual-filter cerebral embolic protection (CEP) device during transcatheter aortic valve implantation (TAVI) in patients with aortic stenosis.

ESC noted there was no consumer feedback.

ESC discussed whether CEP should be limited to the high-risk/inoperable populations that is currently funded on the MBS. However, ESC noted that if MSAC recommends this item for public funding, it could potentially be difficult for the Department to justify only allowing its use for the high-risk population, since there is no biological reason to limit its use in this way. ESC considered that it is possible that patients with an intermediate or low surgical risk may have a similar stroke risk to high risk/inoperable patients. ESC advised that MSAC may wish to consider whether CEP should have similar accreditation requirements to TAVI.

ESC noted that the item should be limited to dual-filter CEP, rather than be agnostic, until evidence emerges for safety and effectiveness of other devices.

ESC noted that the applicant-developed assessment report (ADAR) included three randomised controlled trials (RCTs) and two cohort studies. The inclusion of cohort studies was justified on the basis of the individual RCTs not being sufficiently powered to show differences in the key outcome of relevance – peri-procedural stroke.

In terms of safety, the applicant claimed non-inferior safety on the basis of similar rates of major vascular complications, acute kidney injury (AKI) and adverse event profiles. ESC noted that no differences were observed in AKI between TAVI+CEP and TAVI alone during peri-procedural period (based on the SENTINEL IDE trial and on a meta-analysis of two cohort studies) and no differences were observed in AKI between TAVI+CEP and TAVI alone at 30 days (based on a meta-analysis of three RCTs).

ESC noted that the rates of major vascular complications at 30 days do not differ between TAVI+CEP and when TAVI is performed alone, supporting the safety of the CEP procedure when used adjunct to TAVI (refer to Table 5). This is supported by the meta-analysis of the three RCTs; the risk difference and odds ratios are in favour of the TAVI+CEP intervention but there was no significant difference in the incidence of major vascular complications between TAVI+CEP and TAVI only at 30 days.

However, ESC noted the high statistical heterogeneity ( $I^2$ ) for the meta-analysis of the three RCTs, and noted the Commentary's statement, "The ADAR conducted a sensitivity analysis by removing MISTRAL-C from the meta-analysis, whereby the heterogeneity became low and non-significant. The rationale and justification for conducting a sensitivity analysis by removing MISTRAL-C was that its results were contrary to those of the other RCTs. However, the results of both meta-analyses show that there is no significant difference between treatment and control arms. The analysis that excluded MISTRAL-C was the more robust one, given that heterogeneity was lower."

ESC noted that both cohort studies (Seeger 2019 and Kroon 2019) were propensity score matched (PSM), meaning patients might be well balanced on important patient characteristics. ESC noted in the pre-ESC response that the applicant was reasonably confident that the observed effects, particularly those occurring during the early peri-procedural period, could be attributed to the protective effects of the CEP device, and not to patient characteristics. However, ESC noted that internal validity can still be affected by unreported confounders (both known and unknown). ESC also noted in the pre-ESC report that the applicant considers this the best evidence for the assessment of early peri-procedural stroke, given the large sample size ( $N = 1,066$ ) of patients matched on important baseline characteristics with consistent assessment of stroke 72 hours after the TAVI procedure. ESC agreed with the commentary that Seeger (2019) provided the best estimate in peri-procedural stroke reduction. The commentary concluded that this analysis significantly favoured TAVI+CEP over TAVI alone with respect to peri-procedural stroke (risk difference [RD] 95% confidence interval  $-0.04 [-0.06, -0.01]$ ,  $P = 0.002$ ).

ESC noted that the meta-analyses of RCTs alone did not find any statistically significant differences for the reported stroke outcomes (see Table 5). However, ESC noted that the RCTs were small and may have lacked statistical power to demonstrate a statistically significant difference in stroke outcomes. ESC agreed with the commentary's observation that a consistent effect in favour of TAVI+CEP was observed across all stroke outcomes. In terms of peri-procedural stroke and 30 day stroke, the incremental treatment effect in favour of TAVI+CEP was statistically significant and consistent, with a magnitude of treatment difference in favour of TAVI+CEP of 4-5%, meaning 20-25 patients would need to use dual-filter CEP device adjunct to the TAVI procedure to prevent one stroke event and 50-100 patients would need to be using the CEP device adjunct to the TAVI procedure to prevent one disabling stroke.

ESC noted that that the economic evaluation was based on 30-day stroke outcomes and queried the relevance of this outcome as the CEP device is removed following the TAVI procedure.

ESC noted that the economic modelling demonstrates that using a dual-filter CEP device is cost-effective for both intermediate (ICER: \$redacted/quality-adjusted life year [QALY]) and high risk/inoperable (ICER: \$redacted/QALY) patients. ESC noted that ICERs differed between the high risk/inoperable and the intermediate risk populations. This was mostly due to the assumption that the intermediate risk population has the same long-term mortality risk as the general population. The high risk/inoperable population were assumed to have a 1.9 times higher risk of death. ESC noted that the results are sensitive to model inputs and that the model generally is in favour of the intervention, but the (one-way) sensitivity analysis also demonstrated that the incremental cost-effectiveness ratios (ICERs) did not exceed the \$50,000/QALY threshold in any of the one-way sensitivity analyses. ESC considered there was uncertainty in the extrapolation of 30-day outcomes over the lifetime horizon in the model and noted that the assumption that there was no increased risk of recurrent stroke was

conservative. ESC noted that there may be uncertainty in the baseline risk of stroke in patients undergoing TAVI and noted that application 1361.2 modelled a different rate of stroke [see Table 10].

However, ESC noted that for the high/risk inoperable population, the ICER for TAVI+CEP exceeded the \$50,000/QALY threshold if model inputs for stroke utility values from previously MSAC-accepted applications were used (TAVI high/inoperable risk; 1361.2) [Table 10]. ESC advised that it may be reasonable for MSAC to consider these confidential results when assessing the cost-effectiveness of TAVI+CEP.

ESC noted the ADARs proposed benefit of \$**redacted** for CEP (which reflects the current sales price of the CEP device but is greater than the benefit of \$1,995 on the Prostheses List) but questioned whether this higher premium is justified in light of the bias towards the intervention in the modelling.

ESC noted that the financial implications are uncertain because of uncertainty around usage. ESC agreed with the pre-ESC response (p2) that it was unlikely that 94.7% of TAVI patients would be suitable for CEP as this figure did not account for a larger number of patients been screened and deemed unsuitable for CEP before randomisation in the SENTINEL RCT. ESC also noted that applications for TAVI in the intermediate and low surgical risk populations may increase the population undergoing TAVI and the eligible population for CEP. ESC noted that recent MBS data have shown that the actual use of TAVI is greater than the predicted usage and that the likely utilisation of TAVI in the intermediate risk population was uncertain (refer to Table 13). ESC also noted that, over time, as the technology improves and the device diameter gets smaller, utilisation rates will increase because more patients will be suitable for the procedure.

ESC noted an ongoing RCT, PROTECTED TAVR, which is comparing TAVI+CEP and TAVI alone in patients with aortic stenosis (n=3,000). The primary endpoint in this study is stroke at 72 hours. ESC considered that this would significantly improve the evidence base (which is currently 300 patients in three small RCTs). ESC noted that the estimated completion is July 2022, but that the results are delayed due to COVID-19.

## **15. Other significant factors**

Nil.

## **16. Applicant comments on MSAC's Public Summary Document**

The Applicant is pleased with the MSAC's decision to recommend the creation of a new MBS item for a dual-filter CEP device, during TAVI in patients with symptomatic severe aortic stenosis who meet MBS eligibility criteria for TAVI (high risk/inoperable and intermediate risk for surgery).

## **17. Further information on MSAC**

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)