



Australian Government

Medical Services Advisory Committee

## Public Summary Document

### ***Application No. 1542 – Endovascular insertion of flow diversion device (FDD) for the treatment of unruptured intracranial aneurysms (UIAs)***

**Applicant:** Medtronic Australasia Pty Ltd

**Date of MSAC consideration:** MSAC 77<sup>th</sup> Meeting, 28-29 November 2019

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 of endovascular insertion of flow diversion device (FDD) for the treatment of unruptured intracranial aneurysms (UIAs) was received from Medtronic 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 did not support public funding of endovascular insertion of flow diversion devices (FDD) for unruptured intracranial aneurysms at the cost (procedure plus device) proposed by the applicant. This was due to insufficient evidence to support superiority of FDD over coils for Populations 1 and 2, and an absence of evidence of effectiveness and cost-effectiveness for Populations 3 and 4. MSAC considered that additional data on utilisation from hospitals and private health insurers would be required before the application could be considered again, and that any resubmission would be required to be assessed by the Evaluation Sub-Committee (ESC).

#### **Consumer summary**

Medtronic Australasia Pty Ltd applied for public funding through the Medicare Benefits Schedule (MBS) for the procedure to insert a flow diversion device (FDD) to treat brain aneurysms. An aneurysm occurs when the wall of a blood vessel in the brain weakens and swells out like a balloon. This balloon can burst (rupture) and cause death, stroke or other serious illness. The application was for use of the device for three types of brain aneurysm:

- small, complicated aneurysms
- large aneurysms, including those that cannot currently be treated
- aneurysms that have been treated before and need to be treated again.

A flow diversion device is a small piece of mesh that is placed inside the blood vessel at the base of the aneurysm. This cuts off the blood supply to the aneurysm, which reduces the risk that it will burst.

The Minister would need to approve listing the flow diversion device on the Prostheses List (<https://www1.health.gov.au/internet/main/publishing.nsf/Content/health-privatehealth-prostheseslist.htm>) for this item to be listed on the MBS.

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

MSAC did not support public funding for insertion of a flow diversion device to treat brain aneurysms.

MSAC agreed that there is some evidence that flow diversion devices can be safe and effective. MSAC also agreed that the higher price sought by the applicant for the combination of the procedure and device is not justified by the evidence, which is too weak to show that using this device gives better outcomes for patients than when the procedure is done with other devices already on the Prostheses List.

MSAC agreed the flow diversion device might provide an effective treatment for a small group of people with unruptured brain aneurysms that can't be treated with the devices that are already on the Prostheses List. MSAC encouraged the applicant to make a new application with better evidence and a new price proposal.

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

MSAC did not support the public funding of FDD insertion procedures at the present time primarily because the evidence of improved effectiveness and equivalent safety is too uncertain to support the higher Prostheses List price requested by the applicant for flow diversion devices (FDD) in comparison to currently listed coils and stents.

MSAC accepted there is a small group of patients with aneurysms  $\geq 10$  mm, unsuitable for coiling, clipping or parent vessel occlusion, for whom FDD may provide a viable treatment option (Population 3 in the application).

MSAC indicated it would welcome a new application for FDD and suggested that, in the absence of additional evidence of superior effectiveness compared to current standard of care, an appropriate basis for a new application would be a cost-minimisation analysis for Populations 1 and 2, and a cost effectiveness analysis for Populations 3 and 4, with the final price of FDD weighted across expected use in all populations.

MSAC agreed it would be appropriate to include a multidisciplinary team case conference as a separate MBS item, and noted this should be included in any future economic analyses and associated estimation of financial impact on the MBS and the Prostheses List. MSAC accepted the applicant's assertion that the multidisciplinary team conference is relevant for planning treatment of all unruptured intracranial aneurysms.

MSAC noted the applicant's agreement to mitigate the risk of leakage to smaller, non-complex aneurysms by specifying in the descriptor that FDD is for use in large or complex aneurysms. MSAC agreed the descriptor should also specify that more than one device may be used per procedure, but that FDD and coils with/without stents should not be used in the

same procedure. MSAC noted the 85% rebate was redundant as the procedure is always done in hospital.

MSAC confirmed the four populations and comparators proposed for the application:

- Population 1 – patients with aneurysms (<10 mm) suitable for endovascular or surgical therapy, with wide neck (>4 mm), fusiform or dysplastic morphology. Comparator – coiling alone, or coiling plus stenting.
- Population 2 – patients with aneurysms  $\geq 10$  mm, suitable for endovascular or surgical therapy. Comparator – coiling alone, or coiling plus stenting.
- Population 3 – patients with aneurysms  $\geq 10$  mm, unsuitable for coiling, clipping or parent vessel occlusion, typically giant fusiform aneurysms arising at the skull base. Comparator – conservative management
- Population 4 – patients with previously treated intracranial aneurysms of any size that have recanalised and require treatment. Comparator – coiling alone, or coiling plus stenting.

MSAC noted the evidence presented in the application was derived from ten (10) comparative studies, of which nine (9) were retrospective, and ten (10) non-comparative studies. MSAC noted the application also provided a meta-analysis of the studies representing Populations 1 and 2. However, the comparative data was heterogeneous, of low-overall quality and subject to serious risk of bias, confounding and poor exchangeability between trials, resulting in high uncertainty. In addition, only non-comparative data is available for Populations 3 and 4.

MSAC accepted that for Populations 1 and 2, there were no statistically significant differences in safety outcomes between FDD and coils with or without stents (see Figure 2 and Table 6).

MSAC agreed it is reasonable to conclude the safety of FDD in Populations 3 and 4 is comparable to Populations 1 and 2, with the observed increased procedural complication rate in difficult to treat aneurysms (Population 3) consistent with the complexity of these aneurysms. Regarding effectiveness, MSAC noted that FDD showed statistically significant increases in rates of complete occlusion only compared with coils or coils plus stents in some of the individual trials in Populations 1 and 2. In the meta-analysis, no significant differences were seen between the treatment modalities in retreatment rates or in procedural complications in Population 1 or in procedural complications in Population 2. A statistically significant difference was seen in re-treatment rates in the pooled analysis of two studies for Population 2.

The applicant's pre-MSAC response maintained the claim of superiority for Populations 1 and 2, and claimed similarity of effect for Populations 3 and 4.

However, MSAC did not consider that overall a claim that FDD is clinically superior to coils or coils plus stents to be reasonable for Populations 1 and 2, as it is primarily based on a meta-analysis of poorly-exchangeable trials, and relies on acceptance that a statistically significant difference in occlusion rates translates to a meaningful difference in patient outcomes (in an analysis where no minimum clinically important difference was defined). Overall, MSAC considered the evidence base presented for FDD, although weak, sufficiently supported a claim of non-inferior effectiveness for FDD compared with coils or coils plus stents.

MSAC considered that, although the application presents some data to support the effectiveness of FDD in Populations 3 and 4, the applicant's claim that these are sufficient to establish the comparative effectiveness of FDD in these populations is the same as for Populations 1 and 2 cannot be supported, as the effectiveness of the appropriate comparative treatments in Populations 3 and 4 is unknown.

MSAC noted, the applicant presented a cost utility analysis (CUA) for a co-dependent technology i.e. for the proposed MBS item relating to insertion of the device together with the FDD, which is to be considered by the Prostheses List Advisory Committee (PLAC). Given the proposed fee for the insertion of FDD is consistent with that of insertion of coils, the CUA is presented to justify an increased price for the FD device compared with coils or coils with stents (see Table 12 and Table 13).

However, MSAC considered the economic modelling presented was uninformative, as it relied upon the claim that FDD had non-inferior safety and superior effectiveness over the nominated comparators for Populations 1 and 2, and that the same claims could be extrapolated to Populations 3 and 4. As detailed above, MSAC did not accept these claims.

MSAC considered it was appropriate for the economic analysis to include use of more than one FDD, coil, or stent per procedure; however, the precise number of devices used in each of the sub-populations is uncertain due to lack of data.

MSAC noted that FDD is currently being used in public hospitals for around 400 patients per year. It was noted that data from records in individual hospitals could be used to reduce uncertainty in various issues, including the size of Populations 3 and 4, and the number of FDD per procedure. In addition, data may be obtained from private health insurers on the number of coils and stents used per procedure, to inform future economic and utilisation estimates. MSAC considered that these data were essential for a resubmission, and that any resubmission including these data should be assessed by ESC before progressing to MSAC.

MSAC noted the listing of this device on the Prostheses List was estimated to result in a net increase in costs to private health insurers of up to \$2 million per year (Table 17) and that this cost could be up to \$5 million per year if the applicant's assumptions around substitution of FDD for coils and stents are not realised (see Table 17). MSAC noted the listing on the Prostheses List would result in no out-of-pocket costs for consumers for the device, as confirmed by the applicant. However, consumers may incur other out-of-pocket costs. MSAC noted the Department's advice that in 2018/19 the average out-of-pocket cost for in-hospital services associated with MBS item 35412 (endovascular coiling) was \$570.06 (actual out-of-pocket is cost dependent on the individual patient's PHI cover).

Although MSAC agreed the descriptor should specify FDD and coils with/without stents should not be used in the same procedure, MSAC considered there was a risk that both coils and stents and FDD will be used in the same procedure. MSAC noted the effectiveness and cost-effectiveness of combined use has not been demonstrated. Even assuming only one MBS fee is payable, combination use will increase the cost to the Prostheses List.

MSAC considered there was high uncertainty in the applicant's claim that this listing will be associated with no additional cost to the MBS, as it is probable that a proportion of the services currently performed in public hospitals will move to the private setting. MSAC noted the applicant estimates that approximately 400 FDD insertion procedures were conducted in Australia in 2017, with the majority of performed in public hospitals. MSAC noted the applicant had examined a scenario in which 35% of these procedures are conducted in the private setting following an MBS and Prostheses List listing. When added to the projected

uptake of FDD in the current MBS market (see Table 18), the applicant estimates a total of 257 and 411 FDD procedures will be performed under the MBS in Years 1 and 5 respectively. This will increase costs both to the MBS and the Prostheses List.

#### **4. Background**

This is the first submission of endovascular insertion of FDD for the treatment of UIAs. MSAC has not previously considered this application.

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

There are a number of FDDs listed on the Australian Register of Therapeutic Goods (ARTG). These include the FRED system sponsored by Culpan Medical Pty Ltd/MicroVention Europe (ARTG no. 220724), the Surpass streamline flow diverter system sponsored by Stryker Australia/Stryker Neurovascular (ARTG no. 283662) and three flexible mesh systems sponsored by Medtronic/Micro Therapeutics Inc (ARTG no. 186413, 251273 and 230661).

The application (submission-based assessment, SBA) stated that each of the entries for FDDs on the ARTG from Medtronic describe improvements to the technology, although the intended purpose remains the same. The TGA listings do not limit the population for use of the FDD to a shape (with the exception of Surpass ARTG 283662) or location of an aneurysm, nor do the registrations require that an aneurysm be unruptured.

The Critique stated that the Surpass streamline flow diverter system is limited to the treatment of the treatment of saccular or fusiform intracranial aneurysms arising from a parent vessel with a diameter of  $\geq 2.5$  mm and  $\leq 5.3$ mm. Apart from this, the TGA has placed no limit on the use of the FDD devices in terms of location of the aneurysm, age of the patient or the size of the aneurysm.

#### **6. Proposal for public funding**

The proposed MBS item descriptor for the insertion of FDD is summarised in Table 1. The application stated the proposed fee for the service is based on that currently provided for endovascular coiling (Item 35412). As stipulated in the ratified PICO, the MBS item descriptor below is modelled on the recent listing of mechanical thrombectomy for stroke, Item 35414.

**Table 1 Proposed MBS item descriptor (as presented in Critique)**

<p><b>Category 3 - THERAPEUTIC PROCEDURES</b></p> <p><b>Group T8 - Surgical Operations</b></p> <p><b>Subgroup 3 - Vascular</b></p> <p><b>Subheading 13 - Interventional Radiology Procedures</b></p>
<p>Endovascular insertion of a flow diversion device, in a patient with a diagnosis of unruptured intracranial aneurysm, including intra-operative imaging and aftercare, if</p> <p>a) The diagnosis is confirmed by an appropriate imaging modality such as angiography, magnetic resonance imaging or computed tomography</p> <p>b) The service is performed by a specialist or consultant physician with appropriate training that is recognised by the Conjoint Committee for Recognition of Training in Interventional Neuroradiology.</p> <p>but in association with the following pre-operative diagnostic imaging items:</p> <ul style="list-style-type: none"> <li>- either 60009 or 60010; and</li> <li>- either 60072, 60073, 60075, 60076, 60078 or 60079</li> </ul>
<p>Fee*: \$2,903.25 Benefit: 75% = \$2,177.45: 85% = \$2,819.85</p>

Source: Table 12, p45 of the SBA; Fees have been updated to reflect MBS fees at 1 July 2019. \* Does not include cost of device(s)

The application also proposed two further MBS item descriptors for (i) coordination of, and (ii) attendance to, multidisciplinary team teleconferences (Table 2). The applicant proposed that the case conference can also be coordinated by a neurosurgery practitioner as indicated by underlined text in the proposed descriptor (Table 2) as it is expected that the utilisation of such case conferences would equally apply to the assessment of patients considered for all treatment modalities relevant to the treatment of UIAs (clipping, coiling, FD).

**Table 1 Proposed MBS item descriptors for multidisciplinary team conferences for UIAs**

<p><b>Category 1 – Professional Attendances</b></p> <p><b>Group A33- Unruptured intracranial aneurysm (UIA) Case Conference</b></p>
<p>MBS item ##1</p> <p>Coordination of an unruptured intracranial aneurysm (UIA) case conference by an endovascular <u>or neurosurgery</u> practitioner, where the UIA case conference is of 10 minutes or more duration (Not payable more than once per patient in a XX year period) Fee: \$50.15 Benefit 75% = \$37.65 85% = \$42.65 See Explanatory Notes</p>
<p>MBS item ##2</p> <p>Attendance at an unruptured intracranial aneurysm (UIA) case conference by a specialist or consultant physician (who does not also perform the coordination service described in item XX1 for that same case conference) where the UIA case conference is of 10 minutes or more duration (Not payable more than twice per patient in a XX year period) Fee: \$37.40 Benefit: 75% = \$28.05 85% = \$31.80 See Explanatory Notes</p>

Source: Table 2, p23 of the submission

The Department noted that the development of the MBS item descriptor may include both FD (flow diversion) and endovascular coiling under the one item for endovascular treatment of UIA, so both techniques reflect the need for appropriate training recognised by the Conjoint Committee for Recognition of Training in Interventional Neuroradiology. Of note, as part of the MBS review, a proposed amendment to item 35412 (coiling) has been made to remove the reference to detachable coils and replace it with “endovascular technique” (not otherwise specified), although amendments have not yet been adopted.

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

Endovascular insertion of a FDD for the treatment of UIAs is supported by the Royal Australian and New Zealand College of Radiologists (RANZCR) and the Australian and New Zealand Association of Neurologists (ANZAN).

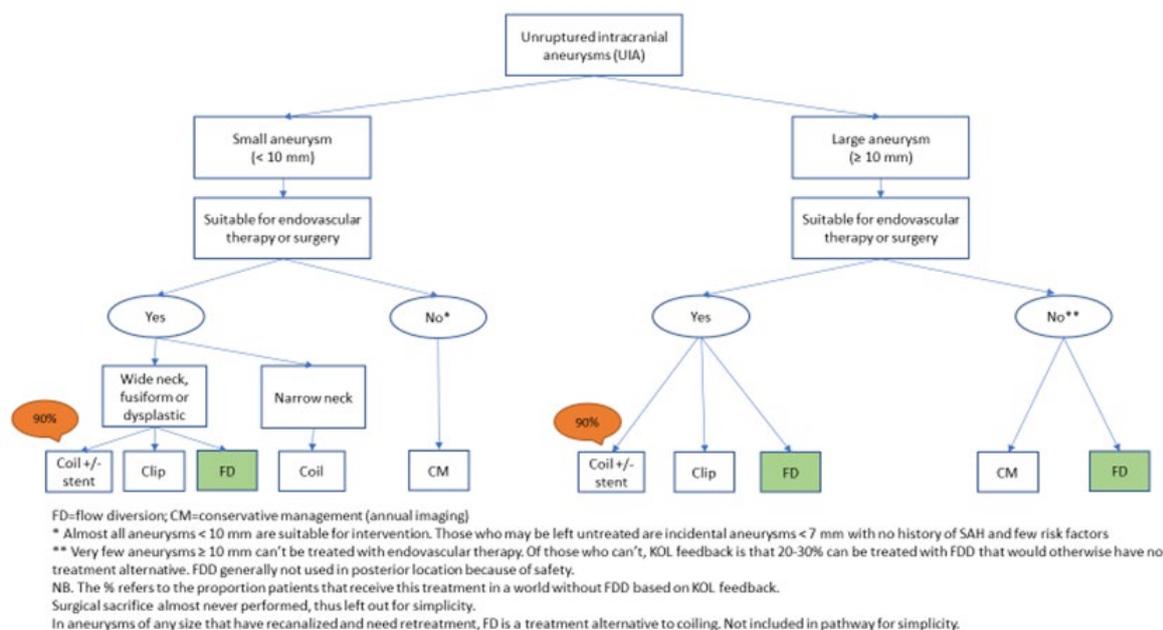
Consultation feedback was received from one specialist on behalf of ANZAN in support of this procedure who opined the FDD has revolutionised treatment of complex aneurysms that are either difficult, dangerous or impossible to treat by endovascular coiling or open surgical clip repair. This specialist also stated that funding through the MBS would help to regulate use of this treatment in correctly selected patients by experienced operators.

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

The application's clinical management algorithm, provided in the ratified PICO, includes the current and proposed clinical management of UIA in the same diagram (Figure 1). Population 4, patients whose aneurysms have recanalised and require re-treatment, is not represented.

The clinical management algorithm assumes that currently, of those patients with a small, complex aneurysm < 10 mm, where the decision to intervene is made, and where the aneurysm is described as a wide neck, fusiform or dysplastic aneurysm, then currently 90% (based on expert advice), will be treated with endovascular coiling. If FD is listed, then a proportion of those currently treated by coiling or clipping will be treated by use of FD. Patients in this population treated with medical management remain conservatively treated.

For Population 2, currently large aneurysm  $\geq 10$  mm, suitable for endovascular therapy or surgery, and where the decision to intervene is made, then currently 90% of patients treated (based on expert advice), will be treated by endovascular coiling. If FD is listed on the MBS, then a proportion of those currently treated by coiling or clipping will be treated by FD.



**Figure 1 Clinical algorithm of treatment of unruptured cerebral aneurysm**

Source: Figure 4 of Ratified PICO 1542.

FD represents a treatment option in a very small proportion of patients with large aneurysms that are not suitable for coiling, clipping or parent vessel occlusion and currently are managed

conservatively. Based on expert advice, very few aneurysm  $\geq 10$  mm are not suitable for coiling, clipping or parent vessel occlusion, and it is estimated that of these, approximately 20-30% currently unsuitable for coiling, clipping or parent vessel occlusion can be managed by FD.

PASC confirmed the proposed clinical algorithm and noted the potential importance of FD for patients who have large aneurysms ( $\geq 10$ mm) but are not suitable for endovascular therapy or surgery (Population 3), as FD provides a treatment option other than conservative management (CM).

## 9. Comparator

The comparators for each of the proposed populations are provided in Table 3.

**Table 3 Comparators to FDD**

Population		Comparator
1	Patients with aneurysms (<10 mm) suitable for endovascular or surgical therapy, with wide neck (>4 mm), fusiform or dysplastic morphology	<u>Coiling ± stent (CS)</u> <ul style="list-style-type: none"> <li>• Coiling alone</li> <li>• Coiling + stenting</li> </ul>
2	Patients with aneurysms $\geq 10$ mm, suitable for endovascular or surgical therapy	
3	Patients with aneurysms $\geq 10$ mm, unsuitable for coiling, clipping or parent vessel occlusion typically giant fusiform aneurysms arising at the skull base	<u>Conservative management (CM)</u> This population is currently not suitable for any intervention. CM consist of 12 monthly MRIs
4	Patients with previously treated intracranial aneurysms of any size that have recanalised and require treatment	<u>Coiling ± stent (CS)</u> <ul style="list-style-type: none"> <li>• Coiling alone</li> <li>• Coiling + stenting</li> </ul>

Abbreviations: MRI=magnetic resonance imaging.

Source: Table 14, p50 of the SBA

## 10. Comparative safety

The submission comprised of ten (10) comparative (one did not satisfy criteria to be categorised as representing a single nominated population) and ten (10) non-comparative studies (two (2) studies provided details relevant to both Populations [3] and [4]).

A list of the included and excluded comparative studies (including reasons for exclusion) is presented in Table 4. Of the 20 potentially relevant studies, a total of ten (10) comparative studies were selected for inclusion.

**Table 4: List of comparative studies included or excluded by submission**

Author (year)	Citation	Included/excluded, reason
<b>Included</b>		
Chalouhi 2013b	Chalouhi N, Tjoumakaris S, Starke RM, Gonzalez LF, Randazzo C, Hasan D, et al. Comparison of flow diversion and coiling in large unruptured intracranial saccular aneurysms. <i>Stroke</i> . 2013B;44(8):2150-4	Included
Chalouhi 2014	Chalouhi N, Starke RM, Yang S, Bovenzi CD, Tjoumakaris S, Hasan D, et al. Extending the indications of flow diversion to small, unruptured, saccular aneurysms of the anterior circulation. <i>Stroke</i> . 2014;45(1):54-8.	Included
Di Maria 2015	Di Maria et al. 2015. Flow Diversion versus Standard Endovascular Techniques for the Treatment of Unruptured Carotid-Ophthalmic Aneurysms. <i>AJNR Am J Neuroradiol</i> 36:2325–30	Included
Durst 2016	Durst C, Starke R, Gingras J, Hixson H, Liu K, Crowley R, et al. Single center comparison of ophthalmic aneurysm treatment using pipeline embolization device versus coil embolization. <i>Journal of NeuroInterventional Surgery</i> . 2014;6: A54-A5.	Included
Kim 2014	Kim et al 2014. Multimodality Treatment of Complex Unruptured Cavernous and Paraclinoid Aneurysms. <i>Neurosurgery</i> 74:51–61.	Included
Lin 2015	Lin et al 2015. Endovascular management of adjacent tandem intracranial aneurysms: Utilization of stent assisted coiling and flow diversion. <i>Acta Neurochir (2015)</i> 157:379–387	Included
Miller 2014	Miller et al 2014. Impact of Endovascular Technique on Fluoroscopy Usage: Stent Assisted Coiling versus Flow Diversion for Paraclinoid Internal Carotid Artery Aneurysms. <i>The Neuroradiology Journal</i> 27: 725-731.	Included
Petr 2016	Petr O, Brinjikji W, Cloft H, Kallmes DF, Lanzino G. Current trends and results of endovascular treatment of unruptured intracranial aneurysms at a single institution in the flow-diverter era. <i>American Journal of Neuroradiology</i> . 2016;37(6):1106-13.	Included
Zanaty 2014	Zanaty et al 2014. Flow Diversion Versus Conventional Treatment for Carotid Cavernous Aneurysms. <i>Stroke</i> . 2014; 45:2656-2661.	Included
Zhang 2016	Zhang Y, Zhou Y, Yang P, Liu J, Xu Y, Hong B, et al. Comparison of the flow diverter and stent assisted coiling in large and giant aneurysms: safety and efficacy based on a propensity score-matched analysis. <i>European Radiology</i> . 2016;26(7):2369-77.	Included
<b>Wrong/no outcomes</b>		
Chalouhi 2013a	Chalouhi N, McMahon J, Moukarzel L, Starke R, Jabbour P, Dumont A, et al. Flow diversion versus traditional aneurysm embolisation strategies: Analysis of fluoroscopy and procedure times. <i>Journal of NeuroInterventional Surgery</i> . 2013A;5: A22-A3	Excluded, wrong outcomes (only procedure time and fluoroscopy outcomes)
<b>Insufficient detail</b>		
Biondi 2010	Biondi A, Drier A, Sourour N, Di Maria F, Jean B, Dormont D. Endovascular procedure evaluation using 3 Tesla diffusion-weighted MR imaging in patients with intracranial aneurysms treated by Flow Diverter Stents. <i>Neuroradiology Journal</i> . 2010;23:325-6.	Abstract only
Ollenschleger 2014	Ollenschleger M, Mancini M, Ohki S, Spiegel G. Headaches following endovascular treatment of cerebral aneurysms: Coil embolization vs. flow diversion. <i>Neurology</i> . 2014;82(10).	Abstract only
Piotin 2014	Piotin M, Bartolini B, Pistocchi S, Redjem H, Blanc R. Endovascular treatment of small unruptured cerebral aneurysms with flow diverters. <i>Stroke</i> . 2014;45	Abstract only
Iosif 2018	Iosif C, Lecomte JC, Pedrolo-Silveira E, Mendes G, Martel MPB, Saleme S, et al. Evaluation of ischaemic lesion prevalence after endovascular treatment of intracranial aneurysms, as documented by 3-T diffusion-weighted imaging: A 2-year, single-center cohort study. <i>Journal of Neurosurgery</i> . 2018;128(4):982-91.	Excluded, does not provide baseline characteristics; only reports procedural complications by treatment modality
<b>Wrong population</b>		
Chalouhi 2017	Chalouhi et al 2017. Matched Comparison of Flow Diversion and Coiling in Small, Noncomplex Intracranial Aneurysms. <i>Neurosurgery</i> 00:1–6, 2017	Excluded, as includes patients

Author (year)	Citation	Included/excluded, reason
		with small saccular, narrow neck aneurysms (not complex, wide neck)
Zhang 2018	Zhang Y, Zhang Y, Guo F, Liang F, Yan P, Liang S, Jiang C, Treatment of small and tiny aneurysms before and after flow diversion era: a single center experience of 409 aneurysms, <i>World Neurosurgery</i> (2018), doi: 10.1016/j.wneu.2018.04.213.	Excluded, as includes aneurysm size 4-4.3 mm on average that were not complex
<b>Wrong comparator</b>		
Lanzino 2012	Lanzino et al 2012. Efficacy and Safety of Flow Diversion for Paraclinoid Aneurysms: A Matched-Pair Analysis Compared with Standard Endovascular. <i>AJNR</i> 33 Dec 2012 (www.ajnr.org)	Excluded, comparator arm includes parent vessel sacrifice (8/22, 36%) data not stratified by modality
Peschillo 2017	Peschillo S, Caporlingua A, Resta MC, Paul Peluso JP, Burdi N, Sourour N, et al. Endovascular treatment of large and giant carotid aneurysms with flow-diverter stents alone or in combination with coils: A multicenter experience and long-term follow-up. <i>Operative Neurosurgery</i> . 2017;13(4):492-502.	Excluded, wrong comparator (comparator includes FD)

Source: Table 17, p61-63 of the SBA

Additional publications of non-comparative studies were included in the SBA to provide supplementary data for the population treated with FD in a recurrent or recanalised aneurysm (Population 4) or for difficult to treat aneurysms that could not be treated using conventional endovascular methods (Population 3) (Table 5).

**Table 5: Supplementary non-comparative studies included in the SBA**

Study ID	Citation	Comment
<b>Difficult to treat</b>		
Becske 2013 (PUFS)	Becske T et al (2013). Pipeline for uncoilable or failed aneurysms: results from a multicenter clinical trial. <i>Radiology</i> . Jun;267(3):858-68.	Uncoilable or Failed Aneurysms <sup>9</sup>
	Becske T et al. 2016. Pipeline for uncoilable or failed aneurysms: 3-year follow-up results. <i>J Neurosurg</i> October 14, p 1–8.	
	Becske T et al. 2017. Long-Term Clinical and Angiographic Outcomes Following Pipeline Embolization Device Treatment of Complex Internal Carotid Artery Aneurysms: Five-Year Results of the Pipeline for Uncoilable or Failed Aneurysms Trial. <i>Neurosurgery</i> 80:40–48.	
Briganti 2016	Briganti, F., et al. (2016). Mid-term and long-term follow-up of intracranial aneurysms treated by the p64 Flow Modulation Device: A multicenter experience. <i>Journal of NeuroInterventional Surgery</i> 9(1): 70-76.	Aneurysms difficult to treat with other standard endovascular techniques
Cirillo 2012 <sup>a</sup>	Cirillo, L., et al. (2012). Complications in the treatment of intracranial aneurysms with silk stents: An analysis of 30 consecutive patients. <i>Interventional Neuroradiology</i> 18(4): 413-425.	Included large aneurysms and lesions deemed unsuitable for traditional endovascular treatment with coils alone.
Phillips 2012	Phillips T.J. et al. (2012) Safety of the Pipeline Embolization Device in Treatment of Posterior Circulation Aneurysms	Posterior circulation aneurysms deemed not satisfactorily treatable by standard endovascular or surgical techniques

Study ID	Citation	Comment
<b>Retreatment</b>		
Benaissa 2015	Benaissa A, Januel AC, Herbreteau D, et al. Endovascular treatment with flow diverters of recanalised and multitreated aneurysms initially treated by endovascular approach. <i>J Neurointerv Surg</i> 2015; 7:44–9.	Recanalised and multitreated aneurysms
Kühn 2017	Kühn, A. L., et al. (2017). "Use of the Pipeline embolization device for recurrent and residual cerebral aneurysms: A safety and efficacy analysis with short-term follow-up." <i>Journal of NeuroInterventional Surgery</i> 9(12): 1208-1213.	Recurrent and residual cerebral aneurysms
McAuliffe 2012 <sup>a</sup>	McAuliffe, W., et al. (2012). Immediate and midterm results following treatment of unruptured intracranial aneurysms with the pipeline embolization device. <i>American Journal of Neuroradiology</i> 33(1): 164-170.	Failed previous therapy
Yu 2012 <sup>a</sup>	Yu, S. C. H., et al. (2012). Intracranial aneurysms: Midterm outcome of pipeline embolization device - A prospective study in 143 patients with 178 aneurysms. <i>Radiology</i> 265(3): 893-901.	Recurrent aneurysms after previous treatment
<b>Mixed<sup>c</sup></b>		
De Vries 2013	De Vries, J., et al. (2013). New generation of flow diverter (surpass) for unruptured intracranial aneurysms: A prospective single-center study in 37 patients. <i>Stroke</i> 44(6): 1567-1577.	Difficult to treat with standard therapy. OR Recanalisation after previous coiling or failed surgery
Lubicz 2011	Lubicz, B., et al. (2011). Pipeline flow-diverter stent for endovascular treatment of intracranial aneurysms: Preliminary experience in 20 patients with 27 aneurysms. <i>World Neurosurgery</i> 76(1-2): 114-119.	Aneurysms with a high likelihood of failure and/or recurrence with conventional endovascular techniques.

Source: Table 19, pp64-65 of SBA

Overall, the risk of bias in all the identified publications was considered high and the evidence base was considered to be of low to very low quality.

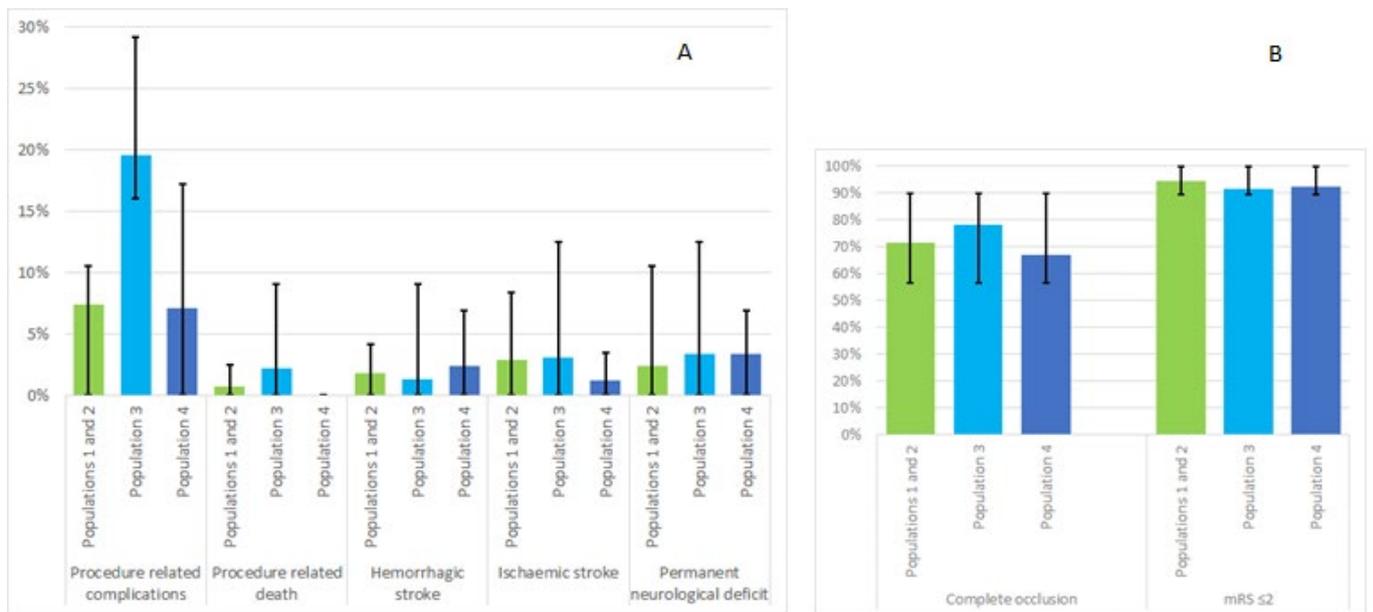
- Population 1 (small, complex UIAs): six comparative studies of FDD versus coiling (two versus coiling ± stent and four versus stent-assisted coiling [SAC]). All but one were retrospective and all but two were considered to be at serious risk of bias for confounding (given differences in baseline characteristics of patients treated with the different modalities). All but one also had differences in mean or median follow-up for the arms in the studies (with generally longer follow-up available for those treated with coils).
- Population 2 (large UIAs): three comparative studies of FDD versus coiling, one versus coiling ± stent, one versus SAC or coiling alone and one versus SAC. All were retrospective and one was considered to be at serious risk of bias for confounding (given differences in baseline characteristics of patients treated with the different modalities). All but one also had differences in mean or median follow-up for the arms in the studies (with generally longer follow-up available for those treated with coils).
- Population 3 (UIAs ≥10 mm, unsuitable for coiling, clipping or parent vessel occlusion): six non-comparative studies.
- Population 4 (previously treated, recanalised UIAs): six non-comparative studies.

For the comparative evidence, the submission also conducted meta-analyses of the studies representing Population 1 and Population 2.

The submission's pooled results for safety outcomes are presented for Populations 1 and 2 (see Table 6) and Populations 3 and 4 (see Table 7).

The Critique stated that no statistically significant differences were observed between FDD and coils ± stent in Populations 1 and 2 for the following safety outcomes: procedural

complications (see Table 6, Table 7, and Figure 2 below); procedure-related death; haemorrhagic or ischaemic stroke; and intraoperative rupture, post-treatment rupture, permanent morbidity/neurological deficit and procedure success/device migration.



**Figure 2 Naïve comparison of safety (A) and effectiveness (B) endpoints across populations**

Error bars represent the range of proportions observed across the individual studies included for each population.

The Critique stated it may also be reasonable to conclude the safety of FDD in Populations 3 and 4 is comparable to Populations 1 and 2, with the observed increased procedural complication rate in difficult to treat aneurysms (Population 3) consistent with the complexity of these aneurysms.

## 11. Comparative effectiveness

The application's results for comparative effectiveness for Populations 1 and 2 and Populations 3 and 4 are presented in Table 6 and Table 7, respectively.

**Table 6 Balance of clinical benefits and harms of FD, relative to coil/SAC, and as measured by the critical patient-relevant outcomes in the key studies: Population 1 and 2**

Outcomes (units) Follow-up	Participants FD/coiling (studies)	Quality of evidence (GRADE)	Relative effect OR (95%CI)	Risk with coil/SAC % (range)	Risk with FD	Comments
<b>Pop 1: small, complex (&lt;10 mm)</b>						
Complete occlusion, at follow-up	N=426 (155/271); k=5	⊕⊕⊕⊕	2.50 [1.56, 4.03]; p=0.0001	Pooled: 62.0% (47.4–70.1%)	Pooled: 77.4% (73.7–80%)	Statistically significantly in favour of FD
Retreatment, at follow-up	N= 484 (183/301); k=5	⊕⊕⊕⊕	0.58 [0.28, 1.20]; p=0.14	Pooled: 11.3% (8.8–28.6%)	Pooled 5.5% (0–10.5%)	Numerically in favour of FD
mRS, at follow-up	N=452 (162/290); k=5	⊕⊕⊕⊕	1.09 [0.35, 3.39]; p=0.22	Pooled: 97.2% (85.6–98.6)	Pooled: 97.5% (89.5–100%)	Majority of patients had mRS 0–2 at follow-up
Procedural complications	N=435 (156/279); k=4	⊕⊕⊕⊕	1.42 [0.57, 3.54]; p=0.46	Pooled: 3.9% (3.1–6.6%)	Pooled 6.4% (0–10.5%)	Numerically in favour of coil/SAC
<b>Pop 2: large (≥ 10 mm)</b>						
Complete occlusion, at follow-up	N=349 (129/220); k=3	⊕⊕⊕⊕	6.04 [3.55, 10.27]; p<0.00001	Pooled: 41.4% (24.3–48.4%)	Pooled 79.1% (68.6–85.7%)	Statistically significantly in favour of FD
Retreatment, at follow-up	N=277 (94/183); k=2	⊕⊕⊕⊕	0.12 [0.04, 0.37]; p=0.0002	Pooled: 30.1% (23.7–36.7%)	Pooled: 4.3% (2.9–5.1%)	Statistically significantly in favour of FD
mRS, at follow-up	N=219 (77/142); k=2	⊕⊕⊕⊕	0.72 [0.17, 3.04]; p=0.66	Pooled: 95.8% (94.2–100%)	Pooled: 96.1% (92.1–100%)	No statistically significant difference
Procedural complications	N=402 (144/258); k=3	⊕⊕⊕⊕	0.73 [0.32, 1.68]; p=0.46	Pooled: 8.1% (7.5–11.1%)	Pooled: 6.3% (3.4–8.9%)	No statistically significant difference

<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.

**Table 7 Balance of clinical benefits and harms of FD as measured by the critical patient-relevant outcomes in the key studies: population 3 and 4**

Outcomes (units) Follow-up	Participants (studies)	Level of evidence	Quality of evidence (GRADE)	% (n/N) [Range] with FD
<b>Pop 3: unsuitable for coiling, clipping, PVO</b>				
Complete occlusion, at follow-up	N=235; k=6	Level IV	⊕⊕⊕⊕	78.3% (184/235) [56.3–93.3%]
Complications	N=215; k=6	Level IV	⊕⊕⊕⊕	19.5% (42/215) [16.0–29.2%]
<b>Pop 4: recanalised/retreatment aneurysms</b>				
Complete occlusion, at follow-up	N=106; K=6	Level IV	⊕⊕⊕⊕	67.0% (71/106) [53.8–94.4%]
Procedural complications	N=84; k=6	Level IV)	⊕⊕⊕⊕	7.1% (6/60) [0%–17.2%]

## Clinical claim

On the basis of the benefits and harms reported in the evidence base, the submission proposes that, relative to coiling ± stenting/SAC, FD has:

- In Population 1 (small, complex aneurysm): non-inferior safety and superior effectiveness;
- In Population 2 (large aneurysms): non-inferior safety and superior effectiveness; and
- In Population 4 (recanalised/recurrent aneurysms): non-inferior safety and superior effectiveness.

On the basis of the benefits and harms reported in the evidence base, the submission based assessment proposes that, relative to conservative management, FD has:

- In Population 3 (unsuitable for coiling, clipping or parent vessel occlusion): likely inferior safety and superior effectiveness.

The Critique stated that in Populations 1 and 2 the non-inferior safety claims compared to coiling ± stenting/SAC are likely reasonable, though the level of evidence presented is low with a high risk of bias and poor exchangeability between studies. Claims of superior effectiveness may not be reasonable, as claims were based on meta-analyses of poorly exchangeable studies, with no predefined minimum clinically important difference (MCID) and in patient groups with significant heterogeneity issues.

The Critique stated it was unreasonable to conclude any comparative efficacy or safety in Populations 3 and 4 as no comparative data were provided, and the efficacy and safety in the relevant comparators were unknown.

The Critique stated that the overall quality of evidence is very low, subject to serious risks of bias and likely high uncertainty.

## 12. Economic evaluation

The key features of the modelled economic evaluations presented in the submission for Populations (1) and (2) are summarised in Table 8.

**Table 8 Summary of the economic evaluation**

<b>Perspective</b>	Australian health care system
<b>Comparator</b>	Coiling +/- stent (CS)
<b>Type of economic evaluation</b>	Cost-utility analysis
<b>Sources of evidence</b>	Meta-analysis of FD vs CS comparative studies
<b>Time horizon</b>	Lifetime
<b>Outcomes</b>	QALYs, LYs, retreatments and ruptures,
<b>Methods used to generate results</b>	Markov cohort
<b>Health states</b>	UIA: complete occlusion, UIA: incomplete occlusion, RIA: non-disabling rupture (mRS 0-2), RIA: disabling rupture (mRS 3-5) and Death (underlying and perioperative mortality) <sup>a</sup>
<b>Cycle length</b>	1 year
<b>Discount rate</b>	5%
<b>Software packages used</b>	TreeAge Pro 2019

See Table D.3.1 in the MSAC Therapeutic Guidelines. RIA=ruptured intracranial aneurysms; mRS=modified Rankin Scale.

<sup>a</sup> Death is split into two Markov health states in the economic model; perioperative mortality and underlying mortality. This approach provides transparency with regard to the source of mortality differences between modelled treatment arms.

**Table 9 Model inputs: device utilisation**

Parameter	Small complex: FD	Small complex: CS	Large: FD	Large: CS
<b>Initial UIA treatment</b>				
FDDs	1.125	-	1.46	-
Coils	-	5.3	-	9.65
Stents	-	0.55	-	0.74
<b>Retreatment of UIA</b>				
FDDs	1.04	-	1.175	-
Coils	-	5.3	-	9.65
Stents	-	0.485	-	0.455

Abbreviations: CS, coiling +/- stent; FD, flow diversion; FDD, flow diversion device

### *UIA procedure costs*

The model applies FD and CS procedure costs calculated as a function of device use, medical service use and hospital admission length. The costs applied to these resources in the economic model are discussed below.

### *Device costs*

The price of devices used for CS are derived from the Prostheses List (March 2019), presented in Table 10.

**Table 10 Device cost inputs for flow divertors, coils and stents**

Parameter	Input	Source
Flow divertor device cost	\$redacted	Applicant
Coil device cost	\$1,430	Prostheses List March 2019 <sup>1</sup> (Billing code: JJ960, ARTG codes: 219194, 219195)
Stent device cost	\$7,125	Prostheses List March 2019 (Billing code: ME209, ARTG code: 197947)

The critique calculated the total cost per UIA procedure based on the model inputs (cost of device, number of devices, clinical and hospital costs) as follows:

**Table 11 Cost per UIA procedure, stratified by population**

	FD arm	CS arm
<b>Population 1: small, complex</b>		
Initial treatment of UIA	\$redacted	\$19,053
Retreatment of UIA	\$redacted	\$18,590
<b>Population 2: large</b>		
Initial treatment of UIA	\$redacted	\$26,627
Retreatment of UIA	\$redacted	\$24,596

Abbreviations: CS, coiling +/- stent; FD, flow diversion; RIA, ruptured intracranial aneurysm; UIA, unruptured intracranial aneurysm

### *Population 1 (small, complex aneurysms)*

The Critique's results for Population 1 with the base case assumptions, are summarised in Table 12. The submission stated that the model results for Population 1 are most sensitive to device utilisation per procedure, model duration and rupture rates.

<sup>1</sup> <http://www.health.gov.au/internet/main/publishing.nsf/Content/health-privatehealth-prostheselist.htm>

**Table 12 Disaggregated and aggregated summary of discounted costs and discounted outcomes generated by the model presented in the SBA for Population 1**

	FD arm	CS arm	Increment
<b>Costs</b>			
Costs of initial device (including placement)	\$redacted	\$redacted	\$redacted
Costs of retreatment in patients with UIA	\$redacted	\$redacted	\$redacted
Costs of treating RIA	\$redacted	\$redacted	\$redacted
Costs of retreating RIA	\$redacted	\$redacted	\$redacted
Costs of treating rerupture	\$redacted	\$redacted	\$redacted
Costs associated with management of patients in the UIA: complete occlusion health state	\$redacted	\$redacted	\$redacted
Costs associated with management of patients in the UIA: complete occlusion health state	\$redacted	\$redacted	\$redacted
Costs associated with management of patients in the RIA: non-disabling rupture health state	\$redacted	\$redacted	\$redacted
Costs associated with management of patients in the RIA: disabling rupture health state	\$redacted	\$redacted	\$redacted
<b>Total discounted costs over 43 years</b>	<b>\$redacted</b>	<b>\$redacted</b>	<b>\$redacted</b>
<b>Outcomes</b>			
Total discounted life-years over 43 years	redacted	redacted	redacted
<b>Incremental cost per life-year gained over 43 years</b>			<b>\$redacted</b>
Total discounted QALYs over 43 years	redacted	redacted	redacted
<b>Incremental cost per QALY gained over 43 years</b>			<b>\$redacted</b>

Source: Recalculated during the evaluation incorporating the updated fee for insertion of devices, applying complete occlusion rates and retreatment rates that are not reweighted, and applying the corrected cost of treatment of acute rupture at the chance node where patients in post-RIA health states have been at risk of rerupture, have survived the rupture and "Receive treatment" for the rupture.

Abbreviations: CS = coiling ± stenting; FD = flow diversion; QALY = quality-adjusted life-year; RIA = ruptured intracranial aneurysm; SBA = submission-based assessment; UIA = ruptured intracranial aneurysm

### *Population 2 (large aneurysms)*

The Critique's results for Population 2 with the base case assumptions, are summarised in Table 13. The submission stated that the model results for Population 2 remain dominant or highly cost-effective across most conducted sensitivity analyses.

**Table 13 Disaggregated and aggregated summary of discounted costs and discounted outcomes generated by the model presented in the SBA for Population 2**

	FD arm	CS arm	Increment
<b>Costs</b>			
Costs of initial device (including placement)	\$redacted	\$redacted	\$redacted
Costs of retreatment in patients with UIA	\$redacted	\$redacted	\$redacted
Costs of treating RIA	\$redacted	\$redacted	\$redacted
Costs of retreating RIA	\$redacted	\$redacted	\$redacted
Costs of treating rerupture	\$redacted	\$redacted	\$redacted
Costs associated with management of patients in the UIA: complete occlusion health state	\$redacted	\$redacted	\$redacted
Costs associated with management of patients in the UIA: complete occlusion health state	\$redacted	\$redacted	\$redacted
Costs associated with management of patients in the RIA: non-disabling rupture health state	\$redacted	\$redacted	\$redacted
Costs associated with management of patients in the RIA: disabling rupture health state	\$redacted	\$redacted	\$redacted
<b>Total discounted costs over 43 years</b>	<b>\$redacted</b>	<b>\$redacted</b>	<b>\$redacted</b>
<b>Outcomes</b>			
Total discounted life-years over 43 years	redacted	redacted	redacted
<b>Incremental cost per life-year gained over 43 years</b>			<b>DOMINANT</b>
Total discounted QALYs over 43 years	redacted	redacted	redacted
<b>Incremental cost per QALY gained over 43 years</b>			<b>DOMINANT (Less costly and more effective)</b>

Source: Recalculated during the evaluation incorporating the updated fee for insertion of devices, applying complete occlusion rates and retreatment rates that are not reweighted, and applying the corrected cost of treatment of acute rupture at the chance node where patients in post-RIA health states have been at risk of rerupture, have survived the rupture and "Receive treatment" for the rupture.

Abbreviations: CS = coiling ± stenting; FD = flow diversion; QALY = quality-adjusted life-year; RIA = ruptured intracranial aneurysm; SBA = submission-based assessment; UIA = ruptured intracranial aneurysm

*Populations 3 and 4 (difficult to treat and recanalised/recurrent aneurysms)*

No economic evaluations are provided for Populations 3 or 4.

The application considers that there is insufficient clinical evidence to support modelling of the cost-effectiveness of FD in Populations 3 and 4. The submission noted that the proportion of patients with complete occlusion in Populations 3 and 4 were 73.8% (56.3% - 93.3%) and 67% (range 53.8% - 94.4%) respectively. It claims that these estimates are reasonably comparable to those observed in the FD treated patients in Populations 1 and 2 (77.6% and 78.8%, respectively).

Thus, the application asserts it might be reasonable to assume results for the Populations 1 and 2 are applicable given that the proportion of patients with complete occlusion in Populations 3 and 4 are similar to those observed in the FD treated patients in Populations 1 and 2.

However, the Critique stated this claim is not valid because background risks of rupture vary from population to population and because the comparator will be different or could perform differently in the different populations.

### 13. Financial/budgetary impacts

A market share approach has been used to estimate the financial implications of MBS listing FD for the treatment of UIAs. The expected MBS market is based on current utilisation of coiling (35412) and clipping (39800) services summarised in Table 14. The application stated as all these services have the same MBS fee, FD listing is not expected to result in financial implications to the MBS (Table 14).

**Table 14 Total costs to the MBS associated with insertion of FDD**

	2015-16	2016-17	2017-18	2018-19	2019-20
<b>FDD insertion</b>					
Population 1	38	50	62	75	89
Population 2	78	102	127	153	182
Population 3			Not estimated		
Population 4					
Total number of services	116	151	189	228	270
<b>Total cost (75% rebate)<sup>a</sup></b>	<b>\$253,273</b>	<b>\$329,451</b>	<b>\$410,773</b>	<b>\$497,238</b>	<b>\$588,848</b>
<b>Financial implications</b>					
Net impact to the MBS	\$0	\$0	\$0	\$0	\$0

Source: compiled from Table 10 of the SBA and Table 12 of the Critique

<sup>a</sup> assuming an MBS fee of \$2,903.25

In terms of number of FDD insertions, the submission assumed that FD would be used as a substitute for 20% of the proportion of CS and neurosurgical clipping (NC) procedures eligible for FD in Year 1, increasing to 40% in Year 5. However, the Critique stated that no justification for the uptake rates was provided or for the proposed 80%/20% CS to NC substitution split.

Thus, the Critique considered the estimates highly uncertain. In addition, the Critique said no estimates were provided for Populations 3 and 4 and that neurosurgical clipping procedures are assumed to be substituted (but this procedure has not been nominated as a relevant comparator).

The applicant estimate of the number of FDD that will be used is presented in Table 15.

**Table 15: Estimated number of FDD used**

-	2015-16	2016-17	2017-18	2018-19	2019-20
No of services (From Table 14)	redacted	redacted	redacted	redacted	redacted
No of devices	redacted	redacted	redacted	redacted	redacted

Source: compiled from Table 152 of the SBA

The applicant's estimate of the number of coils and stents that will be substituted is given in Table 16.

**Table 16: Estimated number of substituted coils and stents**

-	2015-16	2016-17	2017-18	2018-19	2019-20
No of FDDs (From Table 15)	redacted	redacted	redacted	redacted	redacted
No of coils substituted	redacted	redacted	redacted	redacted	redacted
No of stents substituted	redacted	redacted	redacted	redacted	redacted

Source: compiled from Table 154 of the SBA

The applicant's estimate of the cost to the prosthesis list of the inclusion of FDD is given in Table 17.

**Table 17: Estimated cost to private health insurers**

-	2015-16	2016-17	2017-18	2018-19	2019-20
FDD costs	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Substituted device costs	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Net cost to private health	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted

Source: Table 155 of SBA

The applicant estimated that around 400 FDD insertion procedures were conducted in Australia in 2017, with the majority of procedures currently performed in a public. The applicant examined a scenario in which 35% of these procedures are conducted in the private setting following an MBS and prosthesis list listing. When added to the projected uptake of FDD in the current MBS market (see Table 15), the applicant estimates a total of 257 and 411 FDD procedures will be performed under the MBS in Years 1 and 5 respectively (see Table 18).

**Table 18: Estimated additional utilisation of FDD procedures in private setting**

-	2015-16	2016-17	2017-18	2018-19	2019-20
MBS FD services from substitution (from table 14)	116	151	189	228	270
MBS New FD services	141	141	141	141	141
Net cost to private health	257	292	329	369	411

Source: Table 157 of SBA

## 14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Poor evidence base	Very low quality evidence for populations 1 and 2, at moderate-to-high risk of bias Predominantly for Medtronic devices; unclear whether generalisable to other devices Even more limited for posterior circulation UIAs – reflects FDA approval Limited follow-up duration relative to comparators No comparative data for populations 3 and 4
Safety	<i>Probably</i> non-inferior to comparators for populations 1 and 2 – short to intermediate term Long-term safety to be established No comparative data for populations 3 and 4
Effectiveness	Claim of superior effectiveness may not be reasonable Marginally superior for population 1 – occlusion rate only <i>Probably</i> superior for population 2 – occlusion and retreatment rate only No comparative data for populations 3 and 4 – no or limited other options
Cost-effectiveness	Cost-utility approach for populations 1 and 2 may not be justified on basis of clinical data. MSAC may wish to consider if a cost-minimisation approach is more reasonable for populations 1 and 2. No cost-effectiveness information provided for populations 3 or 4. MSAC may wish to consider if a cost-effectiveness analysis should be conducted in these populations.
Financial impact	Claim that inclusion on MBS will be cost neutral may not be reasonable because of: <ul style="list-style-type: none"> <li>• Risk of leakage to small, non-complex UIAs</li> <li>• Submission states there will be an increase in the proportion of patients in populations 1 and 2 who will be treated</li> <li>• Submission provides no information on size of population 3 which currently has no available treatment options, or population 4.</li> <li>• Submission does not address potential for patient out-of-pocket expenses if cost of FDD is higher than amount reimbursed by Private Health Insurer.</li> </ul>
Descriptor	Descriptor should be updated to: <ul style="list-style-type: none"> <li>• prevent potential for leakage to small (&lt;10 mm) non-complex UIAs</li> <li>• include insertion of a FD device OR FD devices recognising that &gt;1 is used on average.</li> <li>• include specialist accreditation</li> <li>• include 85% rebate, although this is redundant if it is only an in-hospital procedure.</li> <li>• Separate MBS items for multidisciplinary teams</li> </ul>

### ESC Discussion

ESC noted that the MBS Review recommended amending item number 35412 to replace ‘detachable coils’ with ‘endovascular technique’; however, 35412 applies to ruptured or unruptured aneurysms, whereas the proposed service is restricted to unruptured aneurysms. Therefore, a new descriptor (plus explanatory note) is preferred by PASC and the Department (as detailed in the ESC Report).

ESC considered it was reasonable to specify appropriate accreditation for people inserting flow diversion devices (FDD).

ESC noted that the application indicates that most patients will be admitted overnight (Type A procedure) which means the 85% Medicare benefit is not relevant.

ESC noted that there are several FD devices on the Australian Register of Therapeutic Goods, most of which are from Medtronic. ESC also noted that the only restriction placed on their use by the TGA related to the Surpass device (ARTG no. 283662: “for the treatment of saccular or fusiform intracranial aneurysm arising from a parent vessel with a diameter of  $\geq 2.5\text{mm}$  and  $\leq 5.3\text{mm}$ ”); however, the US Food and Drug Administration (FDA) does have several restrictions in place.

ESC noted that the safety and effectiveness data were of poor quality, with no comparative data available for Population 3 (patients with aneurysms  $\geq 10\text{ mm}$ , unsuitable for current

treatments) or Population 4 (patients with previously treated intracranial aneurysms that require retreatment).

ESC noted that the follow-up period for FDD in the majority of studies was significantly shorter than follow-up for coiling ± stenting (CS)/stenting-assisted coiling (SAC), which biases long-term safety in favour of FDD. However, ESC noted the sponsor contends the shorter follow up biases effectiveness in favour of the comparators since complete occlusion increases over time with FDD.

Overall, the evidence for superior efficacy of FDD relative to coiling with or without stenting was considered by the ESC to be weak for Populations 1 and 2. These claims were based on meta-analyses of poorly exchangeable studies and in patient groups with significant heterogeneity issues.

ESC also noted the lack of clinical evidence to support of the clinical claims for FDD in Populations 3 and 4. Although, ESC noted Population 3 currently has no treatment options and Population 4 only has limited options, the ESC did not accept the sponsor's argument that the safety and effectiveness of FD in these populations could be inferred from the results seen in Populations 1 and 2. The ESC noted this claim is invalid because background risks of rupture vary from population to population and because the comparator is different or could perform differently in the different populations.

ESC also noted the Flow Diversion in Aneurysms Trial study (FIAT; Raymond J *et al*: *J Neurosurg* 2017;127:454-462; doi:10.3171/2016.4.JNS152662) which was designed to examine the safety and efficacy of flow diversion compared with other means of aneurysm treatment, study was halted due to failure to demonstrate superior safety or efficacy targets compared to best standard care on interim analysis.

The ESC noted the cost-utility analysis presented for Populations 1 and 2 is only valid if the MSAC accepts the clinical claim of superior effectiveness in these populations. If the clinical claim is not accepted, then a cost-minimisation analysis would be more appropriate.

The ESC noted that the submission states the model adopts a health care system perspective, however it does not include patient out-of-pocket costs (for example, only the minimum benefit payable by the private health insurer [as per the Prostheses List] is included in the analysis rather than the total price of the device. Similarly, in relation to MBS costs, only the MBS fee is included where the total fee charged to patients can be greater than the MBS fee). In this regard, the economic analysis is incomplete and the costs of treatment from a health care perspective appear to have been underestimated in the economic analysis.

The ESC noted the differences in rates of complete occlusion and retreatment rates are the primary drivers of differences in outcomes across the two arms in the model (i.e., are the sources of treatment effect captured in the model). Although the results of the modelled analysis are not highly sensitive to the re-treatment rate, the application of a difference in retreatment rates in the model which was not statistically significant (see Table 34 of the Critique) is inappropriate. However the results of the modelled analysis are highly sensitive to assumed differences in complete occlusion rates for FDD vs CS, and the evidence for this difference is weak.

ESC noted that the model was most sensitive to device utilisation, rupture rates and time horizon.

In Population 1, the incremental costs over a lifetime as estimated by the model are relatively low (\$redacted). However, the magnitude of life-years and QALYs gained over 43 years is also small (redacted life-years & redacted QALYs).

In Population 2, the results of the modelled analysis are most sensitive to the number of devices used in the procedure. The relative increase in the number of coils assumed to be required to treat large UIAs compared with small UIAs (9.65 vs 5.3 in the base case) is larger than the relative increase in the number of FDDs required for large UIAs compared with small UIAs (1.46 vs 1.125 in the SBA's base case). Thus, lower cost due to lower device use is a key driver of the economic dominance of FD over CS in the submission's analyses.

ESC noted the submission's claim that FD listing is not expected to result in financial implications to the MBS. ESC considered this claim to be implausible as it does not take account of the larger proportions of Populations 1 and 2 the submission claims will be treated with FD compared to CS, it does not include any patients for Populations 3 and 4 and it does not take account of the potential for leakage into less complex aneurysms. Although the submission stated FD will substitute for clipping in these populations, clipping was not considered an appropriate comparator (by PASC or the submission).

The ESC also noted recent MBS data that show an average 20% per year increase in the number of coiling procedures since 2011, even though data from the Australian Institute of Health and Welfare report only a 7.2% per year increase in separations for UIAs over this period. The impact of the inclusion of FD procedures on the MBS on this rate of increase is not known.

ESC noted the inclusion of this procedure on the MBS may result in additional out-of-pocket costs for patients.

#### **15. Other significant factors**

Nil.

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

The Applicant is disappointed with MSAC's decision to not support public funding for insertion of a flow diversion device to treat unruptured brain aneurysms. However, the Applicant is pleased that MSAC acknowledged the clinical need for flow diversion in a small population currently untreated and at risk of aneurysm rupture. The Applicant will continue to work with MSAC and all relevant stakeholders to ensure flow diversion therapy becomes available on the MBS to patients with unruptured intracranial aneurysms.

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

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