Australian Government

Department of Health

# Application 1542:

## Endovascular insertion of flow diversion device for the treatment of unruptured intracranial aneurysms

# Ratified PICO Confirmation

**(To guide a new application to MSAC)**

**(Version 2.0)**

*Summary of PICO/PPICO criteria to define the question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)*

<table>
<tr><th>Component</th><th>Description</th></tr>
<tr><td>Patients</td><td>Four population groups:<br>1) Patients with complex aneurysms (<10 mm), suitable for endovascular or surgical therapy, with wide neck (>4 mm) fusiform or dysplastic morphology.<br>2) Patients with aneurysms ≥10 mm, suitable for endovascular or surgical therapy.<br>3) Patients with aneurysms ≥10 mm, unsuitable for coiling, clipping or parent vessel occlusion (typically giant fusiform aneurysms arising at the skull base).<br>4) Patients with previously treated intracranial aneurysms of any size that have recanalised and require retreatment.</td></tr>
<tr><td>Prior tests</td><td>Although this is a therapeutic procedure prior to surgery patients would require a digital subtraction angiography (or other form of imaging for patients unable to tolerate DSA) to confirm the diagnosis</td></tr>
<tr><td>Intervention</td><td>The endovascular insertion of a wire mesh flow diversion device within the parent vessel spanning across the neck of an unruptured intracranial aneurysm/s reducing blood flow from the parent artery into the aneurysm; blood in the aneurysm stagnates and embolises: resolving the aneurysm.</td></tr>
<tr><td>Comparator</td><td>
<table>
<tr><th colspan="2">Population</th><th>Comparator</th></tr>
<tr><td>1<br>2<br>4</td><td>Patients with aneurysms (<10 mm) suitable for endovascular or surgical therapy, with wide neck (>4 mm), fusiform or dysplastic morphology<br>Patients with aneurysms ≥10 mm, suitable for endovascular or surgical therapy<br>Patients with previously treated intracranial aneurysms of any size that have recanalised and require treatment</td><td>• Coiling alone<br>• Coiling + stenting</td></tr>
<tr><td>3</td><td>Patients with aneurysms ≥10mm, unsuitable for coiling, clipping or parent vessel occlusion typically giant fusiform aneurysms arising at the skull base</td><td>Conservative management</td></tr>
</table>
</td></tr>
<tr><td>Outcomes</td><td>Safety<br>• Device effectiveness (mechanical function, validation, migration, failure)<br>• Clinical (aneurysm rupture, contrast extravasation, access site, thromboembolic event, stroke, anti-platelet therapy etc)<br><br>Clinical<br>• Aneurysm occlusion<br>• Recurrence of aneurysm<br>• Parent artery stenosis<br><br>Patient relevant<br>• Change in functional neurological change<br>• Survival free of disability<br>• Survival<br>• Hospitalisation<br>• Stroke<br>• Post discharge location<br>• Time to return to daily activities</td></tr>
</table>

| Component | Description |
|---|---|
| | Health care resources<br>• Theatre costs<br>• Procedure costs<br>• Hospitalisation<br>• Imaging costs<br>• Long-term care costs<br>• Rehabilitation costs<br><br>On the basis of the clinical claims a cost effectiveness, preferably cost-utility, economic evaluation is appropriate.<br><br>There may be impacts on Total Australian Government healthcare costs. |

### *PICO or PPICO rationale for therapeutic and investigative medical services only*

The purpose of the application is to seek an MBS listing for endovascular insertion of flow diversion device (FDD) for the treatment of unruptured intracranial aneurysms.

## Population

The target population requested in the application is for people with unruptured intracranial aneurysms (UIAs). An intracranial aneurysm (also known as cerebral or intracerebral aneurysm) is a weak or thin spot on a blood vessel in the brain that balloons out and fills with blood. The application noted that UIAs are often asymptomatic and are identified incidentally through imaging for symptoms unrelated to the UIA. However, a bulging aneurysm can put pressure on nerves, meninges, and/or surrounding brain tissue that lead to symptoms of mass effect on the cranial nerves such as headache, nausea/vomiting, visual disturbances or loss of consciousness. Some UIAs are found incidentally due to patients presenting with a ruptured aneurysm.

The application is requesting four main populations as suitable for treatment with the flow diversion device:

1) Patients with complex aneurysm (<10 mm) suitable for endovascular or surgical therapy, with wide neck (>4 mm), fusiform or dysplastic morphology.
2) Patients with aneurysms ≥10 mm, suitable for endovascular or surgical therapy.
3) Patients with aneurysms ≥10 mm, unsuitable for coiling, clipping or parent vessel occlusion (typically giant fusiform aneurysms arising at the skull base).
4) Patients with previously treated intracranial aneurysms of any size that have recanalised and require retreatment.

As noted by the application, UIAs are described by their morphology, size, neck size, neck-to-dome ratio, anatomical locations (and any perforating arteries; relationship to surrounding vessels) to determine treatment options. A fusiform intracranial aneurysms is an elongated, spindle shaped aneurysm involving the entire vessel wall. Certain connective tissue disorders, such as Ehlers-Danlos syndrome and fibromuscular dysplasia, genetically predispose patients to cerebral aneurysms (Caranci et al. 2014).

The purpose of the preventative repair of an unruptured aneurysm is to prevent the risk of aneurysm rupture, which results in aneurysmal subarachnoid haemorrhage (SAH), a subset of stroke that has high case fatality and morbidity, and occurs at a relatively young age compared to other types of stroke (peak age is between 50 and 60 years).

## Risk Factors for Aneurysm Rupture

For patients with an UIA risk of rupture needs to be balanced against risks from the intervention.

Identifying risk factors for rupture is important to identify individual aneurysms at high risk of rupturing. Unruptured aneurysms are usually classified as asymptomatic incidental aneurysms, symptomatic aneurysms, and unruptured (additional) aneurysm in SAH patients (multiple aneurysm cases). By occlusion of an unruptured aneurysm, the high case fatality and morbidity associated with a possible severe SAH can be mitigated by preventive surgical or endovascular intervention. However, the natural history, risk of endovascular treatment, risk factors for rupture and benefits of surgery of UIAs, remain unclear as studies with sufficient patient numbers and length of follow-up are lacking (Steiner et al. 2013). Some of the literature on risk of rupture is summarised below.

A comprehensive analysis of the risk of rupture of UIAs was reported in a pooled analysis in the PHASES study (Greving et al. 2014). Greving et al. (2014) included six prospective cohort studies with 8,382 patients and 10,272 UIAs from Europe (including Finland), North America and Japan. The PHASES study reported a mean observed one-year risk of rupture of 1.4% (95% CI: 1.1, 1.6) and five-year risk of 3.4% (2.9, 4.0). The five-year absolute risk of aneurysm rupture ranged from 0.25% in individuals younger than 70 years without vascular risk factors with a small-sized (<7 mm) internal carotid artery aneurysm, to more than 15% in patients aged 70 years or older with hypertension, a history of SAH, and a giant-sized (>20 mm) posterior circulation aneurysm. Compared to North American and other European countries, Finland and Japan had a 3.6-fold and 2.8-fold increased risk of UIA rupture, respectively. It is noted that although the PHASES study is the largest and most comprehensive pooled data set on UIA rupture to date, important factors for aneurysm rupture could not be included owing to a lack of data or heterogeneous definitions of those data in the underlying study. For example, different imaging modalities and different methods of measuring aneurysm size were used across the included studies. Selecting patients on the basis of age, preventive UIA repair, or geographic location in cohort studies challenges the concept of the natural history of UIAs and underlines that this remains incompletely understood (Hackenberg et al. 2018; Juvela et al. 2017). Six independent predictors for rupture were established by the PHASES study:

1. Geographical region;
2. Arterial hypertension;
3. Patient age
4. Aneurysm size;
5. Earlier SAH from another aneurysm; and
6. Aneurysm site.

Female sex (as well as multiplicity of aneurysms) are assumed risk factors for rupture, but it is argued that more data from non-Japanese populations (data included in the pooled analysis to determine risk factors was derived from a limited number of populations) is needed to further estimate their effect (Hackenberg et al. 2018). Irregular shape of the aneurysm was reported to be associated with the risk of rupture (4.8% [95% CI: 2.7, 8.7]) in a recent systematic review (Kleinloog

et al. 2018) and thus, could also be considered as a predictor. This study also reported evidence for the role of aspect ratio, size ratio, bottleneck factor, height-to-width ratio, contact with the perianeurysmal environment, volume-to-ostium ratio, and dome-direction but the authors cautioned that they should first be confirmed (Kleinloog et al. 2018).

Figure 1 presents a visual presentation of the aneurysm-related risk factors (green represents lowest and red represents highest risk; mainly from the PHASES study, augmented with population-based or case-control studies). This data is derived from selected populations (e.g. Finnish or Japanese) so may not be generalisable to the general population of patients with UIAs, particularly in Australia (it appears some of the higher rates of risk of rupture for the Japanese and Finnish populations may be due to the underlying smoking rate, with a dramatic decline in SAH incidence (as an indirect measure for risk of rupture), alongside a decline of smoking prevalence in Finland (Korja et al. 2013; Hackenberg et al. 2018).

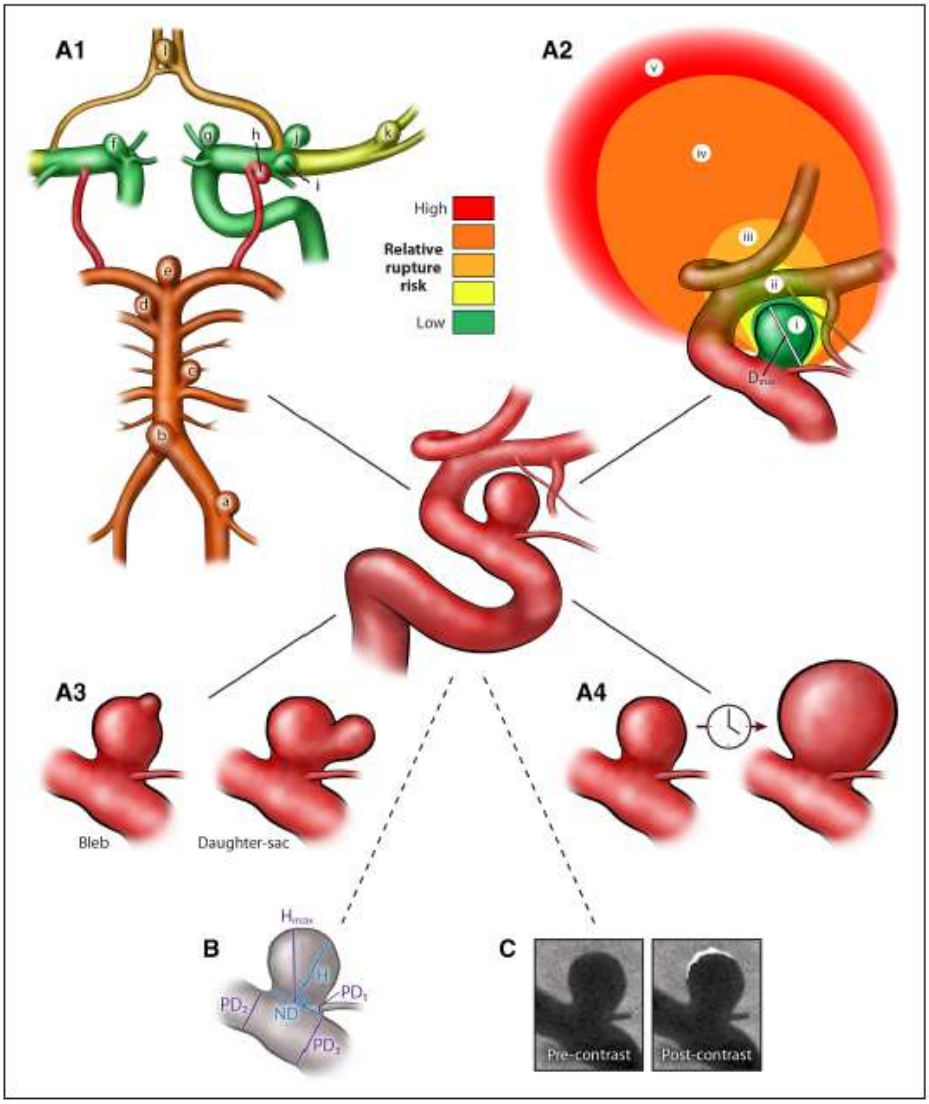


**Figure 1: Risk of Aneurysm rupture**

Established (**A1-A4**) and assumed aneurysm-related (**B** and **C**) risk factors. A paraophthalmic aneurysm of the internal carotid artery (ICA; centre) with a maximum size of 4 mm is illustrated. **A1**, Unruptured intracranial aneurysm (UIA) location (according to PHASES [population, arterial hypertension, patient age, aneurysm size, earlier SAH from another aneurysm, and aneurysm site]). The risk of aneurysm rupture varies with the individual aneurysm location, ranging from the lowest risk (green) at the ICA and the highest risk (red) at the posterior communicating artery (PCOM) [Greving et al. 2014]. Aneurysm locations are (a) posterior inferior cerebellar artery, (b)

junction of vertebral arteries, (c) anterior inferior cerebellar artery, (d) superior cerebellar artery, (e) basilar artery, (f) superior hypophyseal artery (g) ophthalmic artery, (h) PCOM, (i) anterior choroidal artery, (j) ICA terminus, (k) medial cerebral artery, and (l) anterior communicating artery. **A2**, UIA diameter (according to PHASES), the maximum diameter ($D_{max}$) is a significant predictor for rupture. Size categories are (i) <5 mm (ii) 5.0 to 6.9 mm, (iii) 7.0 to 9.9 mm, (iv) 10.0 to 19.9 mm, and (v) ≥20 mm [Greving et al. 2014]. **A3** UIA irregularity, that is, the presence of blebs or daughter sacs increases the risk of rupture by 1.5 fold [Tominari et al. 2015]. **A4**, UIA growth, defined as growth by >1 mm in any diameter, increases the risk of rupture [Villablanca et al. 2013]. **B** UIA morphology. A size ratio (SR) >3 or an aspect ratio (AR) >1.06 seems to be at a higher risk for rupture [Kashiwazaki et al. 2013; Jing et al. 2015] $SR=H_{max}/([PD_1+PD_2+PD_3 1/3)$, AR=H/ND. Where H indicates height perpendicular to neck diameter, $H_{max}$, height maximal, ND, neck diameter and PD, parent vessel diameter. **C,** Aneurysm wall enhancement, as depicted on pre-contrast and post contrast magnetic resonance imaging. Aneurysm wall enhancement seems to reflect aneurysm wall inflammation and thus subsequent aneurysm instability (growth or rupture) [Edjlali et al. 2014].
Source: Hackenberg, et al. 2018

The most important aneurysm-related risk factors for rupture are UIA size, location, UIA irregularity/morphology, UIA growth, and inflammation of the aneurysm wall, Figure 1. Aneurysm morphology measured using size ratio (the largest aneurysm diameter divided by parent artery diameter) or aspect ratio (aneurysm height divided by neck width perpendicular to height), although identified as risk factors in case control studies, remain to be validated.

Table 1 combines the patient-related and aneurysm-related risk factors for rupture of intracranial aneurysm, the populations used in the studies and an evaluation of the level of evidence collated by Hackenberg et al. 2018.

**Table 1: Risk Factors for Rupture**

| Risk Factors | Change in Rupture Risk (95% CI) | Level of Evidence | Geographical Region |
|---|---|---|---|
| **Patient-Related** | | | |
| ***Modifiable*** | | | |
| Arterial hypertension | HR, 1.4 (1.1, 1.8) | IIa | Europe (including Finland), Japan, North America |
| | HR, 1.3 (0.9, 1.9) | IIa | Japan |
| | HR, 7.9 (1.3, 47.4) | IIb | Japan (UIA size, <5 mm) |
| Smoking (current) | RR, 2.2 (1.3, 3.6) | IIa | Europe (including Finland), Asia (including Japan), North America |
| | HR, 3.2 (1.3, 7.6) | IIb | Finland |
| Alcohol (>150 g/wk) | RR, 2.2 (1.5, 2.8) | IIa | Europe (including Finland), Asia (including Japan), North America |
| ***Non Modifiable*** | | | |
| *Age, years* | | | |
| ≥70 | HR, 1.44 (1.05, 1.97) | IIa | Europe (including Finland), Japan, North America |
| <50 | HR, 5.23 (1.03, 26.52) | IIb | Japan (UIA size, <5 mm) |
| Age (per 10yr) | HR, 0.62 (0.39, 0.99) | IIb | Finland |
| *Geographical location* | | | |
| Japan | HR, 2.8 (1.8, 4.2) | IIa | Europe (including Finland), Japan, North America |
| Finland | HR, 3.6 (2.0, 6.3) | IIa | Europe (including Finland), Japan, North America |
| History of SAH | HR, 1.4 (0.9, 2.2) | IIa | Europe (including Finland), Japan, North America |
| Women | RR, 1.6 (1.1, 2.4) | IIa | Europe (including Finland), Japan, North America |
| Multiplicity | HR, 4.9 (1.6, 14.7) | IIb | Japan (UIA size, <5 mm) |
| Family history (≥2 relatives with UIA or SAH) | 17-fold | IIb | North America |
| **Aneurysm-Related** | | | |
| *Size, mm* | | | |
| <5.0 | Reference | IIa | Europe (including Finland), Japan, North America |
| 5.0–6.9 | HR, 1.1 (0.7, 1.7) | | |
| 7.0–9.9 | HR, 2.4 (1.6, 3.6) | | |
| 10.0–19.9 | HR, 5.7 (3.9, 8.3) | | |
| ≥20.0 | HR, 21.3 (13.5, 33.8) | | |
| *Location* | | | |
| ICA | HR, 0.5 (0.3, 0.9) | | |
| MICA | Reference | | |

| Risk Factors | Change in Rupture Risk (95% CI) | Level of Evidence | Geographical Region |
|---|---|---|---|
| Anterior | HR, 1.7 (0.7, 2.6) | IIa | Europe (including Finland), Japan, North America |
| Posterior | HR, 1.9 (1.2, 2.9) | | |
| PCOM | HR, 2.1 (1.4, 3.0) | | |
| *Irregularity* | HR, 1.5 (1.0, 2.2) | IIa | Japan |
| | OR, 4.8 (2.7, 8.7) | IIa | Kleinloog et al. 2018 |
| *Growth* | 12-fold | IIIb | The United States |
| *Aneurysm wall enhancement* | HR, 9.2 (2.9, 29.0)* | IIIb | France |
| *Size ratio* | OR, 5.1 (2.1, 19.1) | IIb | Japan |
| | OR, 9.1 (3.1, 15.0) | IIb | Japan (aneurysm size, <5 mm) |
| *Aspect ratio* | OR, 162.3 (24.8, 1060.8) | IIIb | China |

Source: Hackenberg, et al. 2018 (Table)

HR=hazard ratio; ICA=internal carotid artery; MICA=middle cerebral artery, OR=odds ratio, PCOM=posterior communicating artery; RR=relative risk; SAH=subarachnoid haemorrhage; and UIA=unruptured intracranial aneurysm

*HR of stable vs unstable (ruptured, symptomatic, growth)

## Summary of population

The information above regarding the risk of aneurysm rupture, both aneurysm-related and patient-related, indicates that the populations for whom MBS-listing of FDD is sought are heterogeneous for risk of aneurysm rupture. The following outlines issues relating to each population:

1) Population 1, fusiform or dysplastic UIAs <10 mm. This population does not include location information. Location of the aneurysm is an independent predictor of risk of rupture. Evidence of the effectiveness of FDD may not be generalisable across this population (for example, evidence for UIAs located in the internal carotid artery (ICA) cannot be generalised to an aneurysm located in another cerebral artery). As noted by PASC, most UIAs <5mm are not treated, as the risk of preventative repair generally does not outweigh the low risk of rupture, except where a small risk of rupture remains, such as aneurysm growth.
2) Population 2, aneurysms >10 mm. This population does not include information regarding three independent predictors of rupture: the shape of the UIA, the location of the aneurysm, or the actual size of the UIA. Evidence of the effectiveness of FDD may not be generalisable across this population (for example, an aneurysm located in the ICA, 15 mm in size, with a saccular shape would not support use of the procedure for a wide neck aneurysm, 20 mm in size, located in another cerebral artery).
3) Population 3, patients with aneurysms >10 mm unsuitable for coiling, clipping or parent vessel occlusion. As noted by PASC, this is a population that have no treatment options.
4) Population 4, patients with previously treated intracranial aneurysms of any size that have recanalised. For this population, the previous type of procedure is not specified (if the previous procedure is FDD then this is not a separate population but re-treatment). Whether a patient should be re-treated is a difficult decision (as it is usually based only on angiographic evidence), that requires factors such as the size of the recurrence; the status of the initial lesion (ruptured versus unruptured); time since initial treatment; the purported risk of subarachnoid haemorrhage according to shape (saccular, multilobulated) or location; the likelihood of successful, durable obliteration with re-treatment; estimated procedural risks and a host of other factors specific to the case (e.g. age, history, concomitant diseases). The decision to re-treat is reported to suffer from wide interpersonal variability by clinicians. Similar to the concerns outlined for Populations 1 and 2, the lack of much of this information means that the evidence of effect is unlikely to be

generalisable across this population. It is noted that endovascular trials of devices typically exclude patients with recurrences (Raymond et al. 2011).

In addition, all the populations as described do not include patient characteristics identified as predictors of risk of rupture, such as arterial hypertension, patient age, smoking and previous history of subarachnoid haemorrhage. Alongside the aneurysm rupture risk, these patient characteristics can also determine the appropriate surgical approach.

PASC noted that identifying these patient and aneurysm characteristics to enable evaluation of evidence of FDD effectiveness does not align with the clinical realities of treating UIAs, where flexibility is needed regarding treatment decisions.

Preventative aneurysm repair is proposed to eliminate the risk of aneurysm rupture but carries with it its own risk of poor neurological outcomes (approximately 6-10%), which for the majority of UIAs is higher than the risk of rupture (mean 5-year risk, 3.4%, 95% CI: 2.9, 4.0) (Kotowski et al. 2013; Naggara et al. 2010; Greving et al. 2014, Hackenberg et al. 2018). Although, as noted by Thompson et al. (2015), an increasing number of patients are undergoing aneurysm repair, particularly with coiling, a trend replicated in Australia, the benefits of any preventive treatment have never been proven. For example, a study based on hospital data and US Medicare beneficiaries, of increasing procedural rates for UIA repair (mainly driven by increased use of coiling), reported that, although outcomes have tended to improve over time, it has not lead to a population-level decrease in SAH rates (Jalbert et al. 2015).

The risk of rupture for a UIA based on natural history of UIAs, varies. A large prospective study found that patients with no history of SAH, aneurysms <7 mm in diameter and located in the anterior circulation had no ruptures, and the risk was 2.5% per year in those with aneurysm in the posterior circulation or posterior communicating artery. Among those with a history of SAH and an aneurysm <7 mm, the risk of rupture was 1.5% per year in the anterior circulation and 3.4% in the posterior circulation. History of SAH was not a predictor of rupture for aneurysm >7 mm, and rupture risks were higher with larger aneurysms (Wiebers et al. 2003; Thompson et al. 2015).

Further subgrouped into their anatomical locations, in particular, the posterior vasculature has been an indicator of poor clinical outcomes primarily due to the increased risk of rupture (Wiebers et al. 2003). For example, aneurysm in the ICA, anterior communicating artery (AComm), anterior cerebral artery (ACA), or middle cerebral artery (MCA) that were <7 mm, 7-12 mm, 13-24 mm, and ≥25 mm had rupture rates of 0%, 2.6%, 14.5% and 40% respectively, at 5 years (Wiebers et al. 2003). From this same study, rupture rates of 2.5%, 14.5%, 18.4% and 50% were seen, for the same distribution of sizes, for aneurysms located in the posterior circulation and posterior communicating artery. Aneurysms in the posterior circulation have a rupture rate almost three times that of an aneurysm located in the ICA.

Aneurysms can be clinically silent for long periods or prior to rupture, which is often preceded by aneurysm growth. It is reported that UIA growth occurs in approximately 12-18% of patients with UIA during 2.2 to 2.7 year follow-up or approximately 45% of UIAs during 19 years (Villablanca et al. 2013; Backes et al. 2015; Juvela et al. 2001; Hackenberg et al. 2018].

PASC noted that the decision to treat a patient using FDD is made on a case-by-case basis after consideration of a number of factors. Multidisciplinary teams have been suggested as a means of

adequately judging the aneurysm-related risk, patient-related risks, as well as the need for preventative repair.

## Incidence/prevalence

Incidence of UIAs cannot be estimated, only prevalence. Prevalence studies have been a mixture of imaging studies and autopsy studies. The application reported a prevalence of 3.2% based on a 2011 meta-analysis of 83 study populations (68 studies that had 94,912 patients from 21 countries) with 1,450 UIAs (Vlak et al. 2011). The application then applied this prevalence to the estimated Australian population in 2019 (25,862,832) to calculate an estimated patient population of 830,000 with UIAs. This figure is likely to be an overestimate as this prevalence (3.2%, 95% CI: 1.9, 5.2) (Vlak et al. 2011) is an age- and sex- adjusted prevalence for a population without comorbidity and with a mean age of 50 years and consisting of 50% men. The study by Vlak et al. (2011) does not report the age range of included patients but this study is an update of a 1998 systematic review of UIAs (Rinkel et al. 1998) that did report patient ages investigated and no patients aged less than 20 years were included in the data set. Therefore, a more appropriate estimated population should just apply this prevalence figure to a population at least aged over 20 years of age (Table 2). The prevalence varied from 0% to 41.8% between studies included and the mean overall prevalence of UIAs for all included studies, unadjusted for age or sex, was 2.8% (95% CI: 2.0, 3.9). The American Heart Association/American Stroke Association (AHA/ASA) guidelines report an estimated prevalence of 2%-5% (Thompson et al. 2015).

**Table 2: Estimated resident population 2017**

| 2017 | ≥20 Total | ≥20-<50years | ≥50-<100+ years |
|---|---|---|---|
| Females | 9,416,557 | 5,165,557 | 4,251,000 |
| Males | 9,066,234 | 5,143,218 | 3,923,016 |
| Estimated persons | 18,482,791 | 10,308,775 | 8,174,016 |

Source: ABS catalogue 3101059 (estimated resident population 2017)
The median age is 37.4 (but this includes patients <20 years of age)

Based on Table 2 and applying the 3.2% prevalence cited in the application and in the literature, then the potential prevalent population is estimated to be 591,449. This is still likely an overestimate as the 3.2% is a mean prevalence for a middle-aged population.

The natural history of unruptured intracranial aneurysms cannot be extrapolated from evaluation of patients with ruptured aneurysms (Wiebers et al. 2003). The incidence of SAH is estimated at 9.1 [95% CI: 8.8, 9.5] per 100,000 (excluding Finland and Japan) and SAH increases linearly with age, median onset is 50-60 years, is 1.6 times higher in women than men and in general there is a reduction in incidences during later years. Among adults aged >30 years, annual incidence rates of SAH are at least 30-40 per 100,000 (Steiner et al. 2013). The discrepancy between UIA prevalence and SAH annual incidence suggests that only approximately one rupture occurs among 200 to 400 patients per year (Thompson et al. 2015). This indicates that the majority of unruptured aneurysms will never rupture. However, if they rupture it can be devastating with high mortality and morbidity rates.

UIAs are increasingly being diagnosed due to the widespread availability of non-invasive imaging.

Disorders such as polycystic kidney disease, type IV Ehlers-Danlos syndrome, Marfan syndrome, fibromusclar dysplasia, among other clinical conditions, appear to increase the risk of aneurysm formation (Thompson et al. 2015).

## Utilisation

The application estimates utilisation of FDD based on the incidence of diagnosis of and treatment of UIAs and not the underlying prevalence of UIAs. It is proposed that the FDD will be used once per procedure. Although it is possible that more than one will be required if a patient is found to have multiple UIAs which can occur with dysplastic conditions (Scullen et al. 2018).

To estimate likely demand for FDD, the application provided data from the AIHW National hospital morbidity statistics which includes data **from both public and private hospitals** (the data cubes do not differentiate by type of hospital). Specifically, the hospitalisation data includes both unruptured (i.e. UIA; principal diagnosis data) and treatments for ruptured aneurysm (i.e. primarily as result of UIA) (Table 3**)**.

**Table 3: AIHW hospital statistics, 2011-12 to 2015-16**

| | 2011-12 | 2012-13 | 2013-14 | 2014-15 | 2015-16 | *2016-17* |
|---|---|---|---|---|---|---|
| **ACHI 9th ed** | | | | | | |
| Endovascular occlusion of cerebral aneurysm or arteriovenous malformation | 1,150 | 1,122 | 1,280 | 1,416 | 1,518 | *1,628* |
| Clipping of cerebral aneurysm | 874 | 900 | 913 | 838 | 833 | *NR* |
| Total | 2,024 | 2,022 | 2,193 | 2,254 | 2,351 | *NR* |
| **Principal diagnosis ICD-10-AM 9th ed** | | | | | | |
| Cerebral aneurysm, unruptured | 1,983 | 2,080 | 2,249 | 2,318 | 2,674 | *2,959* |

Source: Table 5 of the application; 2016-17 figures not reported in the application

Using the data in Table 3, the application linearly extrapolated the total procedure data out to 2022 assuming once only use and determined the proportion of endovascular and surgical clipping that occurred in a private setting (38.3%) versus a public setting (39%). The application subtracted the number of FDD procedures that occurred in 2017 (400, a number provided by the application) from the total number of endovascular procedures prior to determining these proportions. This is not appropriate, as the purpose was to determine the total number of endovascular procedures to then determine the number likely to be done in a private setting (which has financial implications for the MBS). Using these proportions, and an assumption that FDD will substitute for 25% of the total market (considered to contain clipping and coiling procedures), the application estimated 346 FDD procedures in Year One. This figure appears reasonable given the AIHW data provided. Future year increase in FDD use are assumed to increase by increasing substitution of the open surgery arm for FDD patients and the linear extrapolation based on procedure growth. There are a number of issues with these assumptions:

- The application assumed that the comparator will be endovascular coiling, not surgical clipping, but the utilisation figures assumes surgery will increasingly be substituted.
- The population data includes hospital data to estimate the unruptured UIA population and ruptured aneurysms, which includes a population that is not requested in the listing (i.e. ruptured aneurysms).

It is not clear why the application approached the utilisation estimates using public and private hospital data; MBS data on current services for both aneurysms is available (note the MBS data does not differentiate between unruptured and ruptured aneurysms); see Table 4.

**Table 4: MBS data for endovascular coils and surgical clipping since endovascular coiling listed on MBS**

| | Endovascular coiling 35412 | Surgical clipping 39800 | Surgical clipping 39806 | Total | Overall Change in number of procedures % |
|---|---|---|---|---|---|
| 2006/2007 | 63 | 343 | 3 | 409 | |
| 2007/2008 | 119 | 318 | 4 | 441 | 7.82 |
| 2008/2009 | 125 | 351 | 3 | 479 | 8.62 |
| 2009/2010 | 158 | 363 | 5 | 526 | 9.81 |
| 2010/2011 | 144 | 301 | 3 | 448 | -14.83 |
| 2011/2012 | 211 | 359 | 3 | 573 | 27.90 |
| 2012/2013 | 216 | 361 | 8 | 585 | 2.09 |
| 2013/2014 | 308 | 348 | 5 | 661 | 12.99 |
| 2014/2015 | 362 | 318 | 16 | 696 | 5.30 |
| 2015/2016 | 329 | 340 | 10 | 679 | -2.44 |
| 2016/2017 | 420 | 359 | 16 | 795 | 17.08 |
| 2017/2018 | 500 | 315 | 6 | 821 | 3.27 |
| **Total** | **2,955** | **4076** | **82** | **7,113** | **7.06** |

What is clear from the MBS data is that the listing of endovascular coiling did not substitute for clipping (marginal substitution may have occurred but the numbers for surgical clipping have remained fairly consistent). However, the number of endovascular procedures has grown year on year to outstrip those for surgery, the market for this service (endovascular plus surgical clipping) has increased on average each year by 7%, indicating that patients who were previously not able to be treated are now being treated, most likely patients with unruptured aneurysms as the literature does not record a growth in SAH. The question is whether this growth in the market is likely to continue to increase and what proportion of the endovascular procedures are for ruptured versus unruptured aneurysms?

The last row of Table 3, shows that the number of hospitalisations (public and private) that were primarily a result of UIAs has increased yearly by on average 8.5% (range 4%-15%), approximating the increase in the use of endovascular coiling. This is consistent with the literature, which indicates that the growth in use of non-invasive imaging is increasing the numbers of UIAs being diagnosed and is likely to continue (given the underlying prevalence data).

A proxy for the proportion of UIAs treated medically or surgically, is the study by the Wiebers et al. (2003), that reported 42% of patients are treated medically and the rest surgically (the proportion treated endovascularly compared to open surgery is outdated). With the rise of the popularity of endovascular procedures, the proportion treated medically is likely to have decreased.

Taking this approach results in a potential market of 1,243 people (based on the diagnosis of unruptured aneurysm of 2,595 in Table 3, for 2016-17), who will be treated either by endovascular or surgical clipping. Sixty one percent have an endovascular procedure compared to a surgical procedure based on the 2017/18 MBS data (both ruptured and unruptured aneurysms are included in this proportion), which results in a likely 757 patients who are treated endovascularly (and 485 surgically). Based on the application's assumption the FDD would substitute for 25% of existing endovascular procedures, results in 189 FDD procedures. If 25% of surgical procedures were also substituted for FDD (as assumed in the application), this would result in a further 121 procedures. Using this approach would estimate use of the FDD in private hospitals at approximately 310. The estimates provided in the application do not appear unreasonable. However, future estimates for Year 2-5 would need to both assume an increase in the diagnosis of UIA, reflecting current data.

In summary:

- The estimates of utilisation in Year one do not appear unreasonable.
- The utilisation data will need to include the need for re-treatment by FDD.
- The utilisation data will need to make allowance for patients with multiple aneurysms.
- Demand for this service in future years will need to incorporate the growth in the diagnosis of UIAs of on average 8.5%.
- A more recent estimate of the number of UIAs treated surgically versus medically may need to be sourced.
- The application assumed that FDD would take a proportion of the total market (note the applicant stated that the uncertainty of the substitution rates across the proposed FDD populations will be addressed in assessment phase).
- Underlying worksheets and sources should be provided.

In some cases, FDD is used in conjunction to endovascular coiling in patients with a UIA. PASC were advised that in these circumstances, the specialist would only charge once for the endovascular procedure.

## Current treatments for UIAs

### *Medical management*

In patients with UIAs <5 mm, the option for the majority would be to remain untreated as the risk of preventative repair often does not outweigh the generally low risk of rupture (mean 5-year risk of rupture, <2% (Greving et al. 2014). Nevertheless, a small risk remains, and aneurysm growth may increase the risk of rupture. The AHA/ASA guidelines recommend intermittent imaging studies to follow UIAs managed conservatively as well as addressing modifiable risk factors in these patients, for example, ceasing smoking and/or monitoring and treating hypertension**.**

### *Surgical clipping*

Patients who have an UIA will be scheduled for surgery and will have a number of pre-surgical tests (blood test, chest x-ray, ECG) prior to surgery. Patients receive a general anaesthetic, and their head placed in a three-pin skull fixation device, to hold the head in position during surgery. A lumbar drain may be inserted into the patient's lower back to remove cerebrospinal fluid and allow the brain to relax during surgery, mannitol may also be administered. A bone flap into the skull will usually be made (there are many types of craniotomies) - the surgeon makes a skin incision to expose the skull, the skin and muscles are then lifted off the bone and folded back; next, small burr holes are made in the skull with a drill and the surgeon cuts an outline of the bone window. The cut bone flap is lifted and removed to expose the protective covering of the brain; the dura matter - the bone flap is replaced at the end of the procedure. The dura is opened to expose the brain so the surgeon can locate the artery and follow it to the aneurysm. Before placing the clip, the surgeon controls the blood flow in and out of the aneurysm as handling can cause rupture. If rupture occurs during surgery, a temporary clip can be placed across the parent artery to stop the bleeding. The aneurysm neck is prepared for clipping by freeing the aneurysm from any connective tissue and isolating from other structures (small arteries, perforators, should not be included in the clip). The clip is placed across the aneurysm neck closing off the aneurysm from the parent artery. Multiple clips may be used. The clip is made of titanium and remains on the artery permanently. The surgeon then inspects the clip to ensure it is not narrowing the parent artery or has collected other arteries. The

dome of the aneurysm is punctured with a needle to make sure blood is no longer filling it. Intraoperative angiography may be used to confirm blood flow through the parent artery. The dura is then closed with sutures, the bone flap replaced and is secured to the skull with titanium plates and screws and the muscles and skin sutured back together.

As aneurysms can vary in size and shape and in particular neck configurations, clips are made in a variety of shapes, sizes and lengths. Saccular shaped aneurysms with a neck at their origin on the main artery are the easiest to place a clip across.

### *Neurovascular embolisation coiling*

Endovascular procedures are usually performed in the special procedures room or angiography suite in the radiology department and the procedure can take between 2-4 hours. The type of anaesthesia that is given to patients is dependent on the patient's medical condition, their ability to follow instructions, and the complexity of the case and surgeon preference. Therefore, some patients will have light sedation and others a general anaesthesia. Anti-clotting medication (usually heparin) is injected throughout the procedure to prevent blood clots and the patient's head positioned so that it cannot move during the procedure. A local anaesthetic is inserted into the groin area, next a steerable catheter is inserted into the femoral artery, a contrast agent is injected into the bloodstream through the catheter to make the blood vessels visible on the fluoroscope and the catheter guided to the relevant artery by use of angiography. Once the catheter is placed correctly, additional contrast agent is injected while further x-rays are taken to view all necessary arteries and take measurement of the aneurysm, in particular its neck. A thin microcatheter, usually platinum, is advanced through the catheter and inserted into the aneurysm. Next, small platinum coils (though can be other material) are advanced through the catheter until inside the aneurysm, and contrast agent injected to view the coils on the fluoroscope. If good, the coil is released from the coil guide wire. Coils are inserted until the aneurysm is packed. Sometimes an inflatable balloon is used to guide coils into the aneurysm. Finally further contrast agent is injected, to ensure that blood is no longer flowing into the aneurysm and that the coils are inside and not narrowing the main artery. Then the catheter is removed, the puncture site sealed and the patient observed; nausea and headache are common. Patients are required to lay flat on their backs for the next six hours to keep the leg as straight as possible. Patients are usually discharged the next day unless complications have occurred, such as a ruptured aneurysm. A follow up angiogram usually occurs 3-6 months after the procedure.

If aneurysms have an unusual shape or a wide neck, stents are required to hold the coils in place. The stent (like the coils) remains in the artery permanently holding the coils in place. Coils are made of other materials and variety of shapes, sizes and coatings that promote clotting. Some aneurysms cannot be treated by coiling and must be surgically clipped.

### *Type of evidence in support of current treatments*

The majority of studies examining treatment outcomes related to UIAs have been single-centre retrospective case series (Thompson et al. 2015). The recommendations of the AHA/ASA guidelines for considering surgical clipping as mode of treatment of UIAs are:

- Patient age, aneurysm location and size should be taken into account.
- Imaging after surgical intervention, to document aneurysm obliteration.

- Long-term follow-up imaging may be considered given the combined risk of aneurysm recurrence and *de novo* aneurysm formation.
- Surgical treatment of UIAs is recommended to be performed at higher-volume centres (e.g. performing >20 cases annually).
- The use of specialised intraoperative tools and techniques for avoiding vessel compromise or residual aneurysm may be considered to reduce the adverse outcomes seen with operative management.

The evidence on the endovascular coiling treatment of unruptured aneurysms remain small, single-centre series (Thompson et al. 2015). Publication of the International Subarachnoid Aneurysm Trial (ISAT) report (Molyneux et al. 2002), which showed better outcomes for endovascular coil occlusion of **ruptured aneurysms** compared to surgical clipping in selected cases, has seen a steady increase in the relative proportion of patients with ruptured and unruptured aneurysms undergoing endovascular procedures. From 1998-2003 the proportion of UIAs undergoing endovascular treatment increased from 11% to 43%. Technical failure rates range from 0% to 10% (Thompson et al. 2015).

The AHA/ASA guidelines note that researchers have identified significant potential for bias in the literature on unruptured aneurysm. The absence of large randomised controlled trials and prospective comparative trials means that current recommendations for management of UIAs depend on data from heterogeneous series. Lee et al. (2005) reviewed literature reporting clipping and coiling adverse outcome rates and performed funnel plot analysis to understand how the magnitude of biases affected reported adverse events rates. The results were demonstrated using scattergram technique to demonstrate the magnitude by which literature biases has influenced the outlook on UIAs. They found, in respect to surgical clipping, substantial differences in cumulative adverse events rates between the retrospective series and the prospective, multicentre- and community-based studies. They conclude that major parts of the literature may have underestimated surgical clipping morbidity and mortality, attributed to bias from small retrospective studies more than in coiling studies.

Although an increasing number of patients are undergoing aneurysm repair, particularly with coiling, as noted by Thompson et al. (2015), a trend replicated in Europe and Australia, see Table 4, the benefits of any preventive treatment have never been proven.

With respect to surgery for UIAs, proponents argue that it has superior efficacy and durability compared with coiling. Endovascular repair has the appeal of being a less invasive procedure and perhaps associated with decreased treatment-related morbidity. Neither of these claims have been substantiated in RCTs, however, there is currently an ongoing, investigator-led pragmatic multicentre randomised parallel-group trial being conducted (commenced in 2010), aiming to examine trial feasibility and to compare angiographic and clinical outcomes following clipping and coiling after 1 year. Eligibility criteria for the trial included, aged at least 18 years of age, had at least 10 years of life expectancy, had a modified Rankin Score (mRS) score ≤2, and saccular UIAs 3-25 mm in maximal cross-sectional diameter. An interim analysis, due to slow accrual, reports no differences in morbidity at 1 year between surgical clipping or endovascular coiling of UIAs. The trial is ongoing (Darsaut et al. 2017).

In summary, there is much uncertainty of the risk of aneurysm rupture, the natural history of UIA and the benefit of preventative repair and each aneurysm needs to be analysed **on a per patient basis**. The literature in this area is recommending better approaches to estimating the individual long-term risk of rupture of an individual aneurysm and to balance this against the presumed risk of preventative repair. The use of a multidisciplinary team has been suggested as addressing many of these concerns (Hackenberg et al. 2018; Kleinloog et al. 2018; Darsaut et al. 2017; Juvela et al. 2017). A multidisciplinary team would be expected to consist of, *inter alia*, specialists in interventional neuroradiology, neurosurgery, neurology, anaesthesiology, physician, able to adequately judge, on a case-by-case basis, the aneurysm-related risks but also the patient-related risks and the need for preventative repair.

## Prior test (investigative services only - if prior tests are to be included)

Although this is a therapeutic service, imaging of the aneurysm/s is required prior to endovascular or surgical treatment. The AHA/ASA guidelines recommend digital subtraction angiography (DSA) over computed tomographic angiography (CTA) or magnetic resonance angiography (MRA). DSA is the gold standard for imaging of UIAs but is more invasive than CTA or MRAs (Thompson et al. 2015). Decisions about what is the most appropriate imaging technique for an individual patient would need to include consideration of the age, co-morbidities and frailty of the patient. Imaging of an aneurysm is required irrespective of the modality used to treat the aneurysm, but for this particular service could also determine which technique is most appropriate, surgery or endovascular approach, based on the accurate determination of the UIAs size, neck size, neck-to-dome ratio, relationship to surrounding vessels, and anatomical location as well as the patient's health status.

## Intervention

The application described the medical service as the endovascular insertion of a wire-mesh flow diversion device (FDD) within the parent vessel spanning across the neck of the UIA. The FDD allows for flow through the parent vessel to be preserved whilst reducing blood flow into the aneurysm. The reduction of blood flow from the parent artery into the aneurysm results in the blood within the aneurysm becoming stagnant and consequently undergoing thrombosis. This process promotes the generation of a new endothelium that eventually covers the aneurysm ostium, permanently excluding the aneurysm from the circulation. Excluding the aneurysm from the circulation removes the risk of rupture and thus prevents potentially fatal outcomes. The implanted device is also known as a 'pipeline embolisation device' or 'streamline flow diverter'.

The procedure is generally performed under general anaesthesia but depending on the complexity of the procedure and the medical condition of the patient, may be performed under sedation. The patient is placed on an x-ray table and heparin is injected throughout the procedure to prevent blood clots forming. There are several devices available: *Pipeline Embolization Device* and *Surpass*; a brief description of the procedure for insertion of the *Pipeline Embolization Device* is described below as the applicant informed that this device is used in the majority of the evidence base.

Using standard interventional radiographic technique, the micro catheter tip is placed past the distal edge of the aneurysm. An appropriately sized *Pipeline Embolization Device* is inserted through the micro catheter to correctly position the *Pipeline Embolization Device*. Once in place, the *Pipeline Embolization Device* is delivered by simultaneously unsheathing the device and pushing the delivery wire.

The FDA website contains detailed insertion procedures for both the *Pipeline Embolization Device* (https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100018C.pdf) and *Surpass* (https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170024C.pdf).

## Co-administered therapies

The placement of the FDD in an artery can potentially contribute to vessel-wall injury and alteration in blood flow until embolisation is complete. In the cerebral circulation, in-pipeline thrombosis and distal thromboembolic phenomena can be potentially associated with catastrophic complication and morbidity. To combat this, prophylactic anti-platelet therapy is administered, although silent ischemic events can occur anyway.

The application reported that patients are pre-treated with dual antiplatelet therapy (aspirin and clopidogrel) with treatment continued for at least 6 months post-procedure. The post-procedure antiplatelet protocol in an Australian study stipulated administration for 6 months in the anterior location and 12 months post-procedure in the posterior location (McAuliffe et al. 2012).

A systematic literature review of antiplatelet therapy in patients who were treated by FDD reported differing regimes, depending on whether patients were pre-FDD, during procedure or post-FDD. For the pre-FDD regimen (n=1,300), 61.7% of patients, having elective FDD, received aspirin 300-325 mg (2-14 days) combined with clopidogrel 75 mg (3 to more than 10 days) and aspirin 81 mg with clopridogrel 75mg for 5-10 days in 27% of elective patients. In 6.3 %, a combination of 100-150 mg of aspirin with clopidogrel 75 mg for 5 days (Texakalidis et al. 2017).

During the procedure, intraoperative heparin was prescribed. As this is not described in Texakalidis et al. (2017), a different study (Adeeb et al. 2017), a retrospective comparative analysis of coiling and stent-assisted embolisation and FDD (PED), was used to describe the regimen. Patients (n=91 in the FDD arm) receive general anaesthesia and then anticoagulation with heparin throughout the procedure. Active clotting time was used to guide heparin administration intra-procedurally with a target of 250-300 seconds; typical dosing consisted of a 3000-5000 unit bolus at the start of the procedure, with hourly dosing of 1000 units.

Post-FDD regimen, Texakalidis et al. (2017; n=1,180), reported that 93% of patients received aspirin for more than six months and clopidogrel for 3-12 months and during follow-up clopidogrel was discontinued after six months if the FDD was placed in the anterior circulation and after twelve months if the FDD was placed in the posterior circulation. For the same reasons, aspirin was also discontinued in 4.1% (45/1,098).

As reported by Texakalidis et al. (2017), routine platelet function testing was reported (26/28 studies) but there does not appear to be a consistent anti-platelet therapy regimen. This pertains mainly to the dose and duration (both pre-and post-FDD). Almost 30% of patients are biochemically clopidogrel resistant (Hall et al. 2011). The largest included study in this systematic review (Adeeb et al. 2017a) showed that clopidogrel non-responders that were switched to ticagrelor, were at a statistically significantly lower risk for a thromboembolic event when compared to non-responders (2.7% versus 24.4%, p=0.004). In 93% of studies, at least one platelet function test was performed, however, the optimal strategy for these patients remains debated. The AHA/ASA guidelines do not provide guidelines on the frequency of testing of patients. Expert advice is required from Australian experts to determine optimum anti-platelet therapy and testing and long-term safety.

## Regulatory status

### *Australia*

The application provided a list of currently registered flow diversion products (Table 5), which all fall under the requested MBS listing. Table 5 also includes further descriptive information available on the TGA.

**Table 5:** ***TGA registered intracranial, flow diverter devices***

| ARTG Entry | Class /year listed | Functional description | Variant Information | Sponsor /Manufacturer |
|---|---|---|---|---|
| 186413 | III/2011 | A flexible mesh like device designed for placement in a parent vessel across the neck of an aneurysm. Packaged with an introducer & flexible tapered delivery wire and introduced into a microcatheter. A platinum coil at the distal end provides fluoroscopic visibility. A retaining mechanism at the proximal end allows insertion thru the lumen of a microcatheter. A platinum marker on the delivery wire provides fluoroscopic visibility of the proximal location. | Length (mm) 10-35 Diameter (mm) 2.5-5.0 | Medtronic/ Micro Therapeutics Inc |
| 230661 | III/2014 | The Pipeline Flex device is a braided, multi-alloy, mesh cylinder woven from platinum/tungsten and cobalt-chromium-nickel allow wires. The implant is designed for placement in a parent vessel across the neck of an intracranial aneurysm (IA) and is mounted on a 304 stainless steel micro guide-wire approximately 200 cm long and compressed inside an introducer sheath. | Length (mm) 10-35 Diameter (mm) 2.5-5.0 activated external | Medtronic/ Micro Therapeutics Inc |
| 251273 | III/2015 | The Pipeline Flex with Shield Technology device is a braided, multi-alloy, mesh cylinder woven from platinum/tungsten and cobalt-chromium-nickel alloy wires. The implant is designed for placement in a parent vessel across the neck of an intracranial aneurysm (IA) and is mounted on a 304 stainless steel micro guidewire approximately 200 cm long and compressed inside an introducer sheath. The device has a surface treatment of phosphoryl-choline to reduce the thrombogenicity of the braid. | Length (mm) 10-35 Diameter (mm) 2.5-5.0 activated, external | Medtronic/ Micro Therapeutics Inc |
| 283662* | III/2016 | Surpass Streamline Flow Diverter system is comprised of a self-expandable braided device preloaded in a delivery catheter. Interwoven within the Surpass flow Diverter cobalt chromium braids are platinum-tunsten wires for visualisation under fluoroscopy. It is indicated for use for the treatment of saccular or fusiform intracranial aneurysm arising from a parent vessel with a diameter of 2.5 mm and 5.3 mm | Length (mm) 15-50 Diameter (mm) 3-5 | Stryker Australia/Stryker Neurovascular |
| 220724 | III/2014 | A self-expanding nickel titanium, single wire braid, compliant closed cell paired-stent design than can be simultaneously deployed and retrieved by a single operator. The FRED system features integrated dual layer coverage designed to focus mainly at the neck of an aneurysm. The FRED system has distal and proximal markers on its ends as well as interweaved helical marker strands delineating the inner working length of the stent to provide fluoroscopic visibility. Intended for the endovascular embolization of intracranial neurovascular aneurysms. | Length (mm) Total 13-45 Length (mm) Working 7-39 Diameter (mm) 2.5-5.5 | Culpan Medical Pty Ltd/ MicroVention Europe |

*This is the second FDD stent to gain FDA approval and is indicated for unruptured large and giant posterior communicating artery aneurysm US FDA Pre-market approval press release July16, 2018. For treatment in patients 18 years of age and older. Wide-neck (neck width 4 mm or wider or dome-to-neck ratio less than 2 mm) or fusiform intracranial aneurysms in the internal carotid artery with a diameter between 2.5 mm and 5.3 mm. **It should not be used where the target vessel size falls outside the indicated range.**
Class III refers to high risk.

Each of the entries for FDD on the ARTG from Medtronic describe improvements to the technology, although the intended purpose remains the same. The TGA listing does 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. Additionally, the ARTG listing would allow for the use of the FDD in conjunction with endovascular coiling (ARTG 197947).

The description of this service excludes its use in conjunction with endovascular coils, although expert advice to PASC, acknowledged that FDD is occasionally used in conjunction with coil embolisation. While FDD is intended to be used alone, the study "Pipeline Embolization Device for the Intracranial Treatment of Aneurysm Trial (PITA) (Nelson et al. 2011) reported that 16/31 aneurysms included in this trial used coils in addition to the FDD. Stents used for stent-coiling and the PED differ primarily in the amount of surface coverage (Adeeb et al. 2017).

Flow diverters/embolization devices are sometimes referred to as flow-diverting stents. This is somewhat inaccurate – although both devices are mesh-like metal tubes, the design and intended use is very different. Flow-diverters are less porous than stents, designed to redirect blood flow from intracranial aneurysms and to enable parent artery reconstruction. Intracranial stents are designed to support endovascular embolization of intracranial aneurysms. This is achieved by bridging the aneurysm neck to keep coils deposited inside the aneurysm in place. Medtronic Pipeline embolization devices (PEDs) are a braided, multi-alloy, mesh cylinder woven from platinum/tungsten and cobalt-chromium-nickel alloy wires, with 65-70% porosity. The Medtronic intracranial Solitaire AB stent is laser cut from Nitinol alloy. In addition, the metal surface area of PEDs is 30-35%, far exceeding the 6.5 to 9.5% coverage for regular intracranial stents.

### *USA*

The current FDA indication is *"The Pipeline™ Flex embolization device is indicated for the endovascular treatment of adults (22 years of age or older) with large or giant wide-necked intracranial aneurysms (IAs) in the internal carotid artery from the petrous to the superior hypophyseal segments. The Pipeline™ Flex embolization device is also indicated for use in the internal carotid artery up to the terminus for the endovascular treatment of adults (22 years of age or older) with small and medium wide- necked (neck width ≥ 4 mm or dome-to-neck ratio < 2) saccular or fusiform intracranial aneurysm (IAs) arising from a parent vessel with a diameter ≥ 2 .0 mm and ≤ 5 .0 mm*

Before this, the first flow diverter to receive FDA approval was the Micro Therapeutics DBA EV3 Neurovascular Pipeline Embolization device, which was approved for the endovascular treatment of adults (22 years of age or older) with large or giant wide-necked intracranial aneurysms in the internal carotid artery (ICA) from the petrous to the superior hypophyseal segment. This was an expedited approval, the reasons for which were reported to be (i) because the device would be used to treat a life threatening condition, and (ii) its technology and treatment approach are significantly different from the available options for the condition and it appeared to provide a clinically significant advantage compared to current treatment options. This approval was supported by a single arm, prospective, multicentre clinical trial "Pipeline for Uncoilable or Failed Aneurysms (PUFS)" conducted in the US (8 sites) and outside the US (8 sites; Hungary and Turkey) with 111 enrolled subjects (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=P100018; Becske et al.

2013]. Five year follow up of the cohort to provide additional long-term safety and effectiveness data was one of the conditions of approval (Pipeline post approval study; Becske et al. 2017). Additional studies published in the literature on the FDD include many that involve treatment of aneurysms considered off-label from the FDA approved indications.

Contradictions to the use of the Pipeline™ Embolization Device are in:

- Patients with active bacterial infection.
- Patients in whom antiplatelet therapy is contraindicated.
- Patients who have not received dual antiplatelet agents prior to the procedure.
- Patients in whom a pre-existing stent is in place in the parent artery at the target aneurysm locations.

The Surpass Streamline Flow Diverter is the second FDD stent to gain FDA approval (July 13, 2018) and is indicated for use in the endovascular treatment of patients (18 years of age and older) with unruptured large or giant saccular wide-neck (neck width ≥4 mm or dome-to-neck ratio <2 mm) or fusiform intracranial aneurysms in the internal carotid artery from the petrous segment to the terminus arising from a parent vessel with a diameter ≥2.5 mm and ≤5.3 mm.

The Surplass Streamline Flow Diverter is contraindicated in the following patient types:

- Patients in whom the parent vessel does not fall within the indicated range.
- Patients in whom antiplatelet and/or anticoagulation therapy (e.g. aspirin and clopidogrel) is contraindicated.
- Patients who have not received dual anti-platelet agents prior to the procedure.
- Patients with an active bacterial infection.
- Patients in whom the angiography demonstrates the anatomy is not appropriate for endovascular treatment due to conditions such as:
  - Severe intracranial vessel tortuosity or stenosis; and/or
  - Intracranial vasospasm not responsive to medical therapy.

In summary, the FDA approval of FDD limits their use to the following populations:

- adults with large or giant wide-necked intracranial aneurysms in the internal carotid artery (ICA) from the petrous to the superior hypophyseal segment (Medtronic Pipeline Embolization Device, Table 5); and
- patients 18 years or older with unruptured large or giant saccular wide-neck (neck width ≥4 mm or dome-to-neck ratio <2 mm) or fusiform intracranial aneurysms in the internal carotid artery from the petrous segment to the terminus arising from a parent vessel with a diameter ≥2.5 mm and ≤5 .3 mm (Stryker Surpass Device, Table 5).

The factors consistent in these approvals, which reflect the studies presented to the FDA, are:

- Patients are adults;
- The aneurysms in the studies were located in the internal carotid artery; and
- The aneurysms have wide necks.

What is notable, with the exception of the recent listing for Surpass (with some limiting criteria), is that unlike the FDA, the TGA places no limits on the use of the FDD devices in terms of location of the aneurysm, age of the patient and the size of the aneurysm. It was noted by the applicant's

clinical expert that the FDD is generally not used in the posterior location because of safety concerns.

## Comparator

The comparators nominated in the application for the four nominated populations are provided in Table 6.

**Table 6: Comparators nominated in the application**

| Population | | Comparator |
|---|---|---|
| 1 | Patients with aneurysms (<10 mm) suitable for endovascular or surgical therapy, with wide neck (>4 mm), fusiform or dysplastic morphology | Coiling ± stent<br>• Coiling alone<br>• Coiling + stenting<br>It is important to separate out coiling with stenting from coiling alone as a meta-analysis showed a significantly higher risk of mortality and thrombosis because of stent-assisted coiling compared with simple coiling (Phan et al. 2016) |
| 2 | Patients with aneurysms ≥10 mm, suitable for endovascular or surgical therapy | |
| 4 | Patients with previously treated intracranial aneurysms of any size that have recanalised and require treatment | |
| 3 | Patients with aneurysms ≥10 mm, unsuitable for coiling, clipping or parent vessel occlusion typically giant fusiform aneurysms arising at the skull base | Conservative management<br>The applicant noted that although this population is currently not suitable for any intervention, medical management would consist of 12 monthly MRIs |

In respect of Population 4, the application is not specific about the previous procedure that patients have received, endovascular coiling or clipping, that may determine the likely requirement for a follow-up procedure or whether the initial lesion was a ruptured or unruptured aneurysm and time since the initial treatment. The literature reports that no reliable evidence exists to choose between microsurgical or endovascular treatments and the decision will often be based on clinical judgement (Raymond et al. 2011). Evidence for this population may be scant, as endovascular clinical trials of devices typically exclude patients with recurrences. Most patients in this population will be post-coiling as recurrence post-coiling is a noted problem. It is reported that re-treating a recurrent aneurysm with additional coils fails in approximately 50% of cases (Raymond et al. 2003).

If a decision is made to re-treat, the following require consideration:

- When is it best to proceed?
- How long to wait is a difficult question, since the risks involved in observing a recurrent aneurysm are unknown.
- Delaying retreatment favours both surgical and endovascular treatment, allowing development of more tissue at the neck to accommodate clip blades or conversely, a better neck-to-sac ratio to help coiling without jeopardizing the parent vessel.
- When the recurrence is too small, one immediate option is surgical extraction of the coils from the aneurysm sac, which may increase the risk of re-treatment.

Although it is noted in the application that FDD may at times substitute for surgical clipping, PASC noted surgical clipping was not a suitable comparator, in this instance, because:

1) Both FDD and coiling are endovascular interventions via the femoral artery so have a similar level of invasiveness.

2) Surgical clipping is a more invasive procedure that requires a craniotomy.
3) MBS data, although not differentiating between ruptured or unruptured aneurysms, has recorded increasing utilisation of coiling since its listing, while surgical clipping has remained fairly stable.
4) For these reasons, coiling is the treatment most likely to be replaced.

The following techniques have been developed to assist coiling overcome its limitations, but come with increased risk.

### *Stent Assisted Coiling (SAC) and Balloon Assisted Coiling*

In conjunction with detachable neurovascular embolisation coil technology, stent-assisted coiling (SAC) is another endovascular surgical technique developed mainly to treat wide-neck cerebral aneurysms by placing a neurovascular self-expanding nitinol stent across the neck of the aneurysm and implanted in the parent artery to support neurovascular embolisation coils from herniating out of the aneurysm sac. As concluded by the FDA, from a regulatory perspective, one of the limitations of SAC is that the effectiveness of the technique has not been established in well-controlled clinical studies and it remains unclear which patient population may be best indicated for treatment with SAC in comparison to alternative treatment modalities (FDA 2018).

Another surgical technique to help mitigate the risk of coils protruding into the arterial lumen and occluding flow in the parent artery or causing increased risk of thromboembolic events due to the presence of a coil mass within the parent artery is balloon assisted coiling (BAC). BAC is a technique where a balloon catheter is inflated inside the parent artery after a micro-catheter that will be used to deliver the coils, is placed inside the neck and sac of the aneurysms. The coils are then individually detached while the balloon remains inflated to allow the clinician to more tightly pack the aneurysm without the risk of coils protruding into the parent artery lumen. The applicant's clinical expert noted that a balloon-assisted device may or may not be used, and this is decided by the operator at any time before or during the procedure, as such it is not relevant to be included as a comparator.

## Outcomes

The studies used to determine the risks and benefits for the FDD for approval on the FDA (TGA assessment data is not available) relied on two single arm studies; the PUFS study (Pipeline Embolization Device) and the SCENT study (Surpass Streamline).

Although comparative safety against the comparator is preferred, these single arm studies may be the only information available in support of the safety of FDD devices.

### *Clinical safety*

Comparative () is preferred

- mechanical device failures;
- device migration (acute and delayed); and
- access site issues;
- aneurysm leak, rupture or contrast extravasation;

- distal embolic phenomenon;
- major ipsilateral stroke;
- minor ipsilateral stroke (NIHSS change <4);
- transient ischaemic attacks (TIAs);
- cerebral vasospasm;
- parent artery stenosis;
- neurological death;
- neurological location specific adverse events;
- antiplatelet therapy (adverse events); and
- other adverse events (e.g. headache, vertigo).

### *Clinical Effectiveness*

Comparative is preferred

- percentage assessment of aneurysm occlusion (Raymond classification scale, Attachment A)-this is an angiographic assessment usually an outcome of endovascular procedures (e.g. complete 100% occlusion, near complete 90%, or incomplete <90%);
- aneurysm occlusion by aneurysm morphology;
- recurrence of aneurysm; and
- in cases of incomplete occlusion, rate of rupture post procedure.

### *Patient-relevant outcomes*

- functional outcomes as assessed using the modified Rankin scale (Attachment A)—baseline mRS is important to determine as many patients will be asymptomatic i.e. the UIA will be detected incidentally. Change in mRS, before and after the procedure;
- survival free of disability;
- disabling stroke;
- neurological death;
- hospitalisation;
- post-discharge location (home or nursing home); and
- time to return to daily activities.

## Changes in Health care resources

The following are likely changes to health care resources (depending on the comparator/s):

- time in theatre;
- time in ICU;
- time in procedure room;

- staff resources ();
- anaesthetic;
- use of assistance techniques such as stents or balloons;
- re-hospitalisation;
- medical costs (days on ward or in ICU);
- imaging costs;
- intervention costs;
- costs of retreatment;
- cost of follow-up angiograms;
- anti-platelet therapy;
- rehabilitation costs; and
- long-term care costs.

### *Current and proposed clinical management algorithm for identified population*

The clinical management algorithm presented in the application (Figure 2), includes the current and proposed clinical management of UIA in the same diagram. Two of the nominated populations are included. All populations included in the clinical management algorithm are those suitable for endovascular therapy or surgery, but Population 3 includes patients unable to have coiling, clipping or parent vessel occlusion but are suitable for FDD, therefore this population is not represented in the algorithm. Population 4, patients whose aneurysms have recanalised, is also not included as this is a pathway that is difficult to include.

The clinical management algorithm assumes that currently, of those patients with a small 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 FDD is listed, then a proportion of those currently treated by coiling or clipping will be treated by use of a FDD. Patients in this population treated with medical management remain conservatively treated.

For Population 2, currently large aneurysm ≥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 FDD is listed on the MBS, then a proportion of those currently treated by coiling or clipping will be treated by the by FDD as well as a proportion of patients with large aneurysms that are not suitable for coiling, clipping or parent vessel occlusion, approximately 20-30% based on expert advice, that currently are managed conservatively.

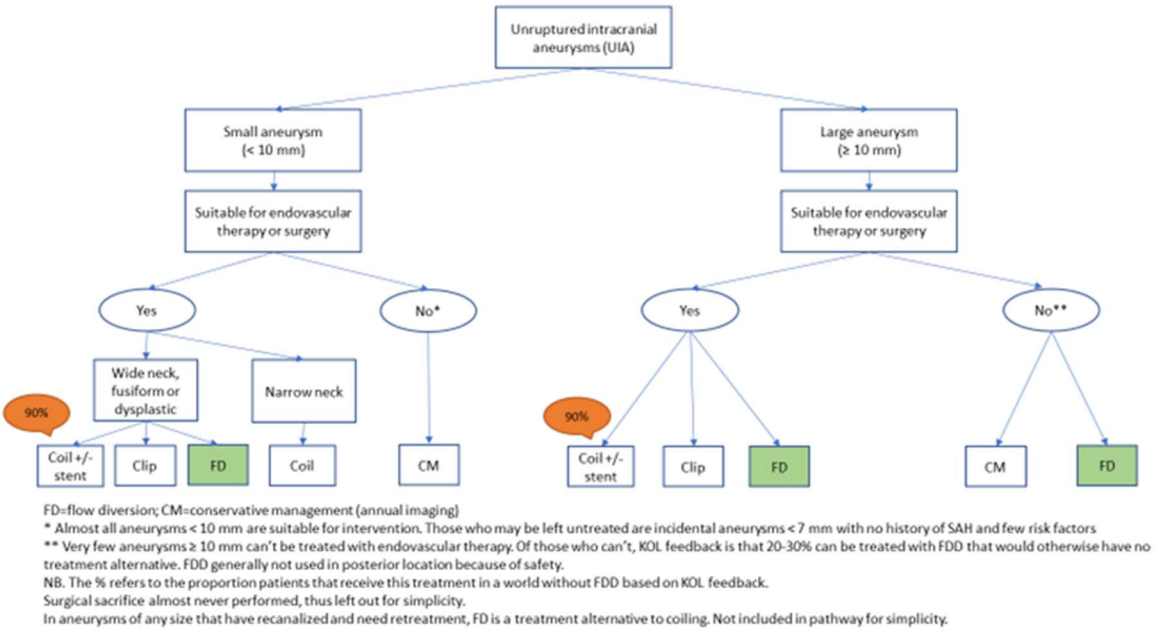


**Figure 2: Clinical algorithm of treatment of unruptured cerebral aneurysm**
Source: Appendix 1 of the application [pg 35]

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

### *Proposed economic evaluation*

The application made the clinical claim of non-inferior safety of FDD compared to endovascular coiling. A separate claim was not made for endovascular coiling plus stents, but the application will need to demonstrate at least non-inferior safety of FDD.

The application made the clinical claim of superior effectiveness of FDD relative to endovascular coiling based on complete occlusion of aneurysm and significantly lower re-treatment rates. A separate claim was not made for endovascular coiling plus stents.

Although not specified in the application, it is assumed that these clinical claims relate to the nominated Populations 1, 2 and 4.

The application made the clinical claim of superior effectiveness of FDD compared to conservative management. Although not specified in the application is assumed that this clinical claim refers to the nominated Population 3. The applicant indicated that conservative management of patients will at least include 12 monthly MRI.

The application did not make a clinical claim of the safety of FDD compared to conservative management but will need to demonstrate this.

On the basis of the clinical claims made by the application, the economic evaluation will require a cost effectiveness, preferably cost utility, analysis to incorporate long-term patient relevant outcomes.

### *Proposed item descriptor*

The application has requested an amendment to MBS item 35412, but this is not considered to be appropriate as this is a separate therapeutic intervention that requires a separate MBS item descriptor. Also, Item 35412, aside from having a broader population than that requested (includes patients with ruptured aneurysms), does not include criteria that align with current requirements of the Conjoint Committee for Recognition of Training in Interventional Neuroradiology (CCINR) for registration of Interventional Radiologists and where these procedures can be undertaken. Therefore a new MBS item descriptor is provided. The MBS item descriptor below is based on the recent listing of mechanical thrombectomy, Item 35414.

**Table 7: MBS Item descriptor**

| Category 3 - THERAPEUTIC PROCEDURES<br><br>Group<br>T8 - Surgical Operations<br>Subgroup<br>3 - Vascular<br>Subheading<br>13 - Interventional Radiology Procedures |
|---|
| *MBS item xxxx*<br><br>*Endovascular insertion of a flow diversion device, in a patient with a diagnosis of unruptured intracranial aneurysm, including intra-operative imaging and aftercare, if*<br>*(a) the diagnosis is confirmed by an appropriate imaging modality such as angiography, magnetic resonance imaging or computed tomography*<br>*(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; and*<br><br>*Fee: $2,857.55 Benefit: 75% = $2,143.20 85% = $2,775.85* |

Consistent with the application, the requested fee is based on that currently provided for endovascular coiling (Item 35412).

The Department noted that development of the MBS item descriptor may include both FDD and endovascular coiling under the one item for endovascular treatment of UIA. This would ensure that both techniques reflect the need for appropriate training recognised by the Conjoint Committee for Recognition of Training in Interventional Neuroradiology.

As per the AHA/ASA guidelines, the recommended investigation prior to neurosurgery or endovascular surgery is digital subtraction angiography (DSA) over CTA and MRA. However, it is likely to be a clinical decision that determines which of these techniques is appropriate.

**Conjoint Committee for Recognition of Training in Interventional Neuroradiology (CCINR)**

CCINR comprises representatives from the Australian and New Zealand Society of Neuroradiology (ANZSNR), the Neurosurgical Society of Australasia (NSA) and the Australian and New Zealand Association of Neurologists (ANZAN). For the purposes of this item, specialists or consultant

physicians performing this procedure must have training recognised by CCINR, and the Department of Human Services notified of that recognition.

As previously stated, PASC noted that the decision to treat a patient with a UIA is made on a case-by-case basis, and multidisciplinary teams may be better able to adequately judge the aneurysm-related risks, as well as the patient-related risks (and need for preventative repair).

The following two proposed additional items are to address the potential need for a multidisciplinary team to identify (on a case-by-case basis) individual aneurysm risk of rupture, patient risk and the need for preventative surgery discussed earlier in the PICO.

These proposed UIA case conference items are based on those for transcatheter aortic valve implantation (TAVI; MBS items 6080 and 6081) that require active participation of a multidisciplinary team to decide the best surgical or medical approach to a patient with severe aortic stenosis. It is proposed that the two UIA items would sit within Group 33, with Group 33 being re-labelled as TAVI and UIA Case Conferences.

**Table 8: Proposed MBS item descriptors for multidisciplinary team conferences for UIAs**

| Category 1 – Professional Attendances<br>Group A33- Unruptured intracranial aneurysm (UIA) Case Conference |
|---|
| MBS item XX1<br><br>Coordination of an unruptured intracranial aneurysm (UIA) case conference by an endovascular practitioner, where the UIA case conference is of 10 minutes or more duration<br>(Not payable more than once per patient in a XX year period)<br><br>Fee: $50.15 Benefit 75% = $37.65 85% = $42.65<br><br>See Explanatory Notes |

| Category 1 – Professional Attendances<br>Group A33- Unruptured intracranial aneurysm (UIA) Case Conference |
|---|
| MBS item XX2<br><br>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<br>(Not payable more than twice per patient in a XX year period)<br><br>Fee: $37.40 Benefit: 75% =$28.05 85% = $31.80<br><br>See Explanatory Notes |

# Attachment A

**Raymond Classification (Raymond-Roy occlusion classification of intracranial aneurysms) (Radiopaedia)**

The Raymond–Roy occlusion classification (RROC) is an angiographic classification scheme for grading the occlusion of endovascularly treated intracranial aneurysms. It is also known as the Raymond class, Montreal scale or the Raymond Montreal scale.

- class I: complete obliteration
- class II: residual neck
- class III: residual aneurysm

The scheme was originally created to evaluate aneurysm occlusion class, and not predict aneurysmal recurrence. Though not truly equivalent these are often equated to aneurysmal obliteration of 100%, >90% and <90% respectively.

Mascitelli et al. (2015) proposed a modified Raymond–Roy classification (mRRC) or modified Montreal scale, where class III is subdivided to reflect progression to occlusion:

- class IIIa: contrast opacification within the coil interstices of a residual aneurysm
- class IIIb: contrast opacification outside the coil interstices, along the residual aneurysm wall

the study by Mascitelli et al. (2015) found that class IIIa aneurysms progress to complete occlusion more than class IIIb aneurysms*.

A validation study by Stapleton et al. (2016) confirmed that the predictive capability of the RROC was improved by the MMRC, showing not only that IIIa occluded more often (53.6% vs 19.2%) but that IIIb lesions would also further recanalise more frequently (65.1% vs 27.4%)**.

*These finding are yet to be validated in a prospective study with independent blinded angiographic grading.

** stenosis of the parent vessel is not included in this classification

**Modified Rankin Scale for Neurologic Disability (mRS)**

Measures the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. It is the most popular outcome measure in acute stroke trials and is considered a robust measure of functional outcome, with reference to pre-stroke activities rather than an observed performance of a specific task (Modified Rankin Scale).

| **The Modified Rankin Scale**<br>**Description** | **Score** |
|---|---|
| No symptoms | 0 |
| No significant disability. Able to carry out all usual activities despite some symptoms | 1 |
| Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities | 2 |
| Moderate disability. Requires some help, but able to walk unassisted | 3 |
| Moderately severe disability. Unable to attend to own body needs without assistance and unable to walk unassisted | 4 |
| Severe disability. Requires constant nursing care and attention, bedridden, incontinent. | 5 |
| Dead | 6 |

## References


Adeeb N, Griesenauer C, Foreman P, Moore J, Motiei-Langroudi R, Chua M et al. Comparison of Stent-Assisted Coil Embolization and the Pipeline Embolization Device for Endovascular Treatment of Ophathalmic Segment Aneurysms: A Multicenter Cohort Study. *World Neurosurgery.* 2017; 105:206-213.

Adeeb N, Griessenauer C, Foreman P, Moore H et al. Use of Platelet Function testing Before Pipeline Embolization Device Placement A Multicenter Cohort Study. *Stroke*. 2017a; 48(5): 1322-1330.

Backes D, Vergouwen MD, Tiel Groenestege AT, Bor AS, Velthuis BK, Greving JP, Algra A, Wermer MJ, van Walderveen MA, terBrugge KG, Agid R, Rinkel GJ. PHASES Score for Prediction of Intracranial Aneurysm Growth. *Stroke*. 2015; 46(5): 1221-1226.

Becske T, Brinjikji W, Potts MB, Kallmes DF, Shapiro M, Moran CJ, Levy EI, McDougall CG, et al. 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. *Neurosurgery*. 2017; 80(1): 48-48.

Becske T, Kallmes D, Saatchi I, McDougall C, Szikora I et al. Pipeline for Uncoilable or Failed Aneurysms: Results from a Multicenter Clinical Trial. *Radiology.* 2013; 267(3): 858-868.

Caranci F, Briganti F, Cirillo L, Leonardi M, Muto M. Epidemiology and genetics of intracranial aneurysms. *Eur J Radiol.* 2013; 82(10):1598-1605.

Darsaut T, Findlay m, Magro E, Kotowski M, Roy D et al. Surgical clipping or endovascular coiling for unruptured intracranial aneurysms: a pragmatic randomised trial. *J Neurol Neurosrug Psychiatry.* 2017; 88:663-668.

Edjlai M, Gentric JC, Regent-Rodriguez D, Trystram D, Hassem WB, Lion S, et al. Does aneurysmal wall enhancement on vessel wall MRI help to distinguish stable from unstable intracranial aneurysms? *Stroke.* 2014; 45:3704-3706.

FDA. General Issues: Meeting to Discuss the Evaluation of Safety and Effectiveness of Endovascular Medical Devices Intended to Treat Intracranial Aneurysms. 2018. https://www.fda.gov/media/111329/download

Greving JP, Wermer MJ, Brown RD Jr, Morita A, Juvela S, Yonekura M, Ishibashi T, Nakayama T, Rinkel GJ, Algra A. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. *Lancet Neurol.* 2014; 13(1):59-66.

Hackenberg K, Hanggi D, Etminan N. Unrupture Intracranial Aneurysms-Contemporary Data and Management. *Stroke.* 2018; 49:2268-2275.

Hall R, Mazer CD. Antiplatelet drugs: a review of their pharmacology and management in the perioperative period. *Anesth. Analg*. 2011; 112:292-318.

Jalbert JJ, Isaacs AJ, Kamel H, Sedrakyan A. Clipping and Coiling of Unruptured Intracranial Aneurysms among Medicare Beneficiaries, 2000 to 2010. *Stroke.* 2015; 46(9):2452-2457.

Jing L, Fan J, Wang Y, Li H, Wang S, Yang X, et al. Morphologic and hemodynamic analysis in the patients with multiple intracranial aneurysms: ruptured versus unruptured. *PLoS One*. 2015; 10:e0132494. Doi:10.1371/journal.pone.0132494.

Juvela S, Korja M. Intracranial Aneurysm Parameters for Predicting a Future Subarachnoid Hemorrhage: A Long-Term Follow-up Study. *Neurosurgery*. 2017; 81(3):430-440.

Juvela S, Poussa K, Porras M. Factors affecting formation and growth of intracranial aneurysms: a long-term follow-up study. *Stroke.* 2001; 32(2):485-491.

Kashiwazaki D, Kuroda S; Sapporo SAH Study Group. Size ratio can highly predict rupture risk in intracranial small (<5mm) aneurysms. *Stroke.* 2013; 44:2169-2173

Kleinloog R, de Mul N, Verweij BH, Post JA, Rinkel GJE, Ruigrok YM. Risk Factors for Intracranial Aneurysm Rupture: A Systematic Review. *Neurosurgery*. 2018; 82(4): 431-440.

Korja M, Lehto H, Juvela S, Kaprio J. Incidence of subarachnoid haemorrhage is decreasing together with decreasing smoking rates. *Neurology*. 2013; 80:2154-2165.

Kotowski M, Naggara O, Darsaut TE, Nolet S, Gevry G, Kouznetsov E, Raymond J. Safety and occlusion rates of surgical treatment of unruptured intracranial aneurysms: a systematic review and meta-analysis of the literature from 1990 to 2011. *J Neurol Neurosurg Psychiatry.* 2013; 84(1): 42-48.

Lee YJ, Kim DJ, Suh SH, Lee SK, Kim J, Kim DI. Stent-assisted coil embolization of intracranial wide-necked aneurysms. *Neuroradiology.* 2005; 49(9): 680-689.

Mascitelli JR, Moyle H, Oermann EK, Polykarpou MF, Patel AA, Doshi AH, Gologorsky Y, Bederson JB, Patel AB. An update to the Raymond-Roy Occlusion Classification of intracranial aneurysms treated with coil embolization. *J Neurointerv Surg*. 2015; 7(7):496-502.

McAuliffe W, Wycoco V, Rice H, Phatouros C, Singh TJ, Wenderoth J. Immediate and midterm results following treatment of unruptured intracranial aneurysms with the pipeline embolization device. *AJNR Am J Neuroradiol.* 2012; 33(1):164-170.

Molyneux A, Kerr R, Stratton L, et al. International Subarachnoid Aneurysm trial (ISAT) of neurosurgical clipping verus endovascular coiling in 2143 patients with rupture intracranial aneurysm: a randomised trial. *Lancet.* 2002; 360:1267-1274.

Naggara ON, White PM, Guilbert F, Roy D, Weill A, Raymond J. Endovascular treatment of intracranial unruptured aneurysms: systematic review and meta-analysis of the literature on safety and efficacy. *Radiology*. 2010; 256(3): 887-897.

Nelson P, Lylyk P, Szikora S, Wetzel G, Wanke I and Fiorella D. The Pipeline Embolization Device for the Intracranial Treatment of Aneurysms Trial. *American Journal of Neuroradiology*.2011; 32(1): 34-40.

Phan K, Huo YR, Jia F, Phan S, Rao PJ, Mobbs RJ, Mortimer AM. Meta-analysis of stent-assisted coiling versus coiling-only for the treatment of intracranial aneurysms. *J Clin Neurosci.* 2016; 31:15-22.

Raymond J and Darsaut T. An approach to recurrent aneurysms following endovascular coiling. *J NeuroIntervent Surg.* 2011; 3:314-318.

Raymond J, Guilbert F, Weill A, Georganos SA, Juravsky L, Lambert A, Lamoureux J, Chagnon M, Roy D. Long-term angiographic recurrences after selective endovascular treatment of aneurysms with detachable coils. *Stroke.* 2003; 34(6): 1398-1403.

Rinkel GJ, Djibuti M, Algra A, van Gijn J. Prevalence and risk of rupture of intracranial aneurysms: a systematic review. *Stroke.* 1998; 29(1): 251-256.

Scullen T, Mathkour M, Lockwood J, Ott L, Medel R, Dumont A and Amenta P. Endovascular Management of Multiple Dysplastic Aneurysms in a Young Man with an Unknown Underlying Cause: A Case Report and Review of the Literature. *World Neurosurgery.* 2018; 111:349-357

Stapleton CJ, Torok CM, Rabinov JD, Walcott BP, Mascitelli JR, Leslie-Mazwi TM, Hirsch JA, Yoo AJ, Ogilvy CS, Patel AB. Validation of the Modified Raymond-Roy classification for intracranial aneurysms treated with coil embolization. *J Neurointerv Surg*. 2016; 8(9): 927-933.

Steiner T, Juvela S, Unterberg A, Jung C, Forsting M and Rinkel G. European Stroke Organization Guidelines for the Management of Intracranial Aneurysms and Subarachnoid Haemorrhage. *Cerebrovascular Diseases*. 2013; 35:93-112.

Texakalidis P, Bekelis K, Atallah E, Tjoumakaris S, Rosenwasser R, Jabbour P. Flow diversion with the pipeline embolization device for patients with intracranial aneurysms and antiplatelet therapy: A systematic literature review. *Clinical Neurology and Neurosurgery*. 2017; 161:78-87.

Thompson BG, Brown RD Jr, Amin-Hanjani S, Broderick JP, Cockroft KM, et al. Guidelines for the Management of Patients With Unruptured Intracranial Aneurysms: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke.* 2015; 48(8): 2368-2400.

Tominari S, Morita A, Ishibashi T, Yamazaki T, Takao H, Murayama Y, et al. Unruptured Cerebral Aneurysm Study Japan Investigators. Prediction model for 3-year rupture risk of unruptured cerebral aneurysm in Japanese patients. *Ann Neurol*. 2015; 77: 1050-1059.

Villablanca JP, Duckwiler GR, Tateshima S, Martin NA, Frazee J et al. Natural history of asymptomatic unruptured cerebral aneurysms evaluated at CT angiography: growth and rupture incidence and correlation with epidemiologic risk factors. *Radiology*. 2013; 269-258.

Vlak MH, Algra A, Brandenburg R, Rinkel GJ. Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis. *Lancet Neurol.* 2011; 10(7): 626-636.

Wiebers DO, Whisnant JP, Huston J 3rd, Meissner I, Brown RD Jr, Piepgras DG, Forbes GS, Thielen K, Nichols D, O'Fallon WM, Peacock J, Jaeger L, Kassell NF, Kongable-Beckman GL, Torner JC; International Study of Unruptured Intracranial Aneurysms Investigators. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. *Lancet*. 2003; 362(9378):103-110.