NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Health Technology Evaluation

Report for Review Decision

Review of MTG10: Pipeline embolisation device for the treatment of complex intracranial aneurysms

This guidance was issued in May 2012.

NICE proposes an amendment of published guidance if there are no changes to the technology, clinical environment or evidence base which are likely to result in a change to the recommendations. However the recommendations may need revision to correct any inaccuracies, usually in relation to providing a more accurate estimate of the results of the cost modelling. The decision to consult on an amendment of published guidance depends on the impact of the proposed amendments and on NICE's perception of their likely acceptance with stakeholders. NICE proposes an update of published guidance if the evidence base or clinical environment has changed to an extent that is likely to have a material effect on the recommendations in the existing guidance.

1. Recommendation

Amend the guidance and do not consult on the review proposal.

2. Original objective of guidance

To assess the case for adoption of Pipeline embolisation device for the treatment of complex intracranial aneurysms.

3. Current guidance

1.1 The case for adopting the Pipeline embolisation device in the NHS is supported by the current evidence when it is used in patients with complex giant or large intracranial aneurysms which are unsuitable for surgery and being considered for stenting, and where large numbers of coils would be needed during stent-assisted coiling.

1.2 The Pipeline embolisation device is estimated to be cost saving when compared with stent-assisted coiling, in patients with complex giant or large intracranial aneurysms when the number of Pipeline embolisation devices inserted does not exceed two, and when treatment would otherwise require the use of 32 or more coils combined with one stent for stent-assisted coiling. If two Pipeline embolisation devices are used the total procedure cost is estimated as £30,346 compared with

£30,838 for the use of 32 coils for stent-assisted coiling (a saving of £492 using the Pipeline embolisation device).

1.3 Clinicians should submit details of all patients being treated with the Pipeline embolisation device to the UK Neurointerventional Radiology Group audit database, to increase the evidence base and guide future use of this technology.

4. Rationale

No new evidence has been identified which is likely to change the existing recommendations. The proposed amendments to the guidance are factual changes that have no material effect on the recommendations. Since we are proposing not to consult on the amendments the company have provided a factual check of this review proposal.

5. New evidence

The search strategy from the original assessment report was re-run. References from August 2011 onwards were reviewed. Additional searches of clinical trials registries were also carried out and relevant guidance from NICE and other professional bodies was reviewed to determine whether there have been any changes to the care pathways. The company was asked to submit all new literature references relevant to their technology along with updated costs and details of any changes to the technology itself or the CE marked indication for use for their technology. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

5.1 Technology availability and changes

The Pipeline embolisation device evaluated in the 2012 medical technologies guidance is no longer available. The device has been twice superseded and the Pipeline flex embolisation device with shield technology, which was CE marked in 2015, is the current version used in NHS practice. The original manufacturer (Covidien) was acquired by Medtronic which now promotes the product in the UK.

The External Assessment Centre (EAC) analysed the differences and concluded that the strong similarity between the different versions of the device suggests the evidence is generalisable across all Pipeline devices. The detailed technical improvements (described in Table 3) are aimed at improving the ease and accuracy of placement and reducing the thrombogenicity of the implant.

5.2 Clinical practice

There is currently no NICE pathway relating to intracranial aneurysms, and no change to any relevant other guidelines. Current options for managing complex intracranial aneurysms include coiling, often with concomitant use of stent placement, neurosurgical clipping requiring craniotomy (with or without bypass procedures), parent vessel occlusion (by open neurosurgery or be endovascular means) and conservative management. In 2015 the American Heart Association/American Stroke Association published guidance on the management of patients with unruptured intracranial aneurysms recommending that endoluminal flow diversion represents a new treatment strategy that may be considered in carefully selected cases (Class IIb; Level of Evidence B)..

5.3 NICE facilitated research

None for this technology.

5.4 New studies

The EAC re-ran the original literature searches in March 2018 and identified 11 relevant studies which included Pipeline as an intervention (2 systematic reviews, 2 comparative studies and 7 prospective non-comparative studies). The EAC's report will be published alongside the review decision.

Systematic reviews

- Texakalidis et al (2017) is a systematic review with the primary aim of assessing the antiplatelet regime and the platelet function tests used with the Pipeline device and it includes 28 studies (23 retrospective and 5 prospective).. None of the studies included are reported elsewhere in this review with only one included in the original MTG10 guidance. All studies used Pipeline in a combined sample of 1556 patients. The treatment strategy in 95% of patients was the administration of pre-procedural aspirin and clopidrogel. Overall pooled morbidity rate was reported as 2.1% (27/1246) with an overall mortality rate of 2% (31/1556). Adverse events included thrombotic: symptomatic 6.6% (asymptomatic 3.4%, haemorrhagic: symptomatic 3.0%), asymptomatic 0.4% and in-Pipeline stenosis (symptomatic 0.3%, asymptomatic 1.1%).The authors concluded that more prospective studies are needed to compare the efficacy of different antiplatelet agents and reach conclusions regarding use of platelet function test and platelet reaction values in order to decrease haemorrhagic and thromboembolic complications associated with the Pipeline.

- Murthy et al (2014) included 13 prospective studies with 905 patients with unruptured intracranial aneurysms treated with Pipeline. Two of these studies are included in this review (Becske et al 2013; Yu et al, 2012) with three included

in the MTG10 guidance (Nelson et al 2011; Szikora et al 2010; Lylyk et al 2009). Overall pooled morbidity was 6.2% (1.9% of patients had a stroke, 2% had a transient ischemic attack and 2.3% had an intracranial haemorrhage) with a cumulative mortality rate of 2.3%.

Comparative studies (n=2)

- Chalouhi et al (2013) conducted a retrospective comparison of Pipeline treatment against coiling in 160 patients with large or giant unruptured aneurysms.

- Kim et al (2014) conducted a prospective comparative study between Pipeline and stent-assisted coiling. There were 23 patients in the Pipeline group and 38 patients in the coiling group all with unruptured ICA aneurysms.

Prospective non-comparative studies (n=7)

- Becske et al. (2017) reported the 5-year follow-up results from the prospective Pipeline for uncoilable or failed aneurysms (PUFS) trial. The study included 109 patients across 10 centres in the US, Turkey, and Hungary.

- Beckse et al (2016) reported the 3-year follow-up results of the prospective PUFS trial. The study included 74 patients across 10 centres in the US, Turkey, and Hungary.

- Kallmes et al (2016) reported results from the prospective multi-centre aneurysm study of Pipeline in an observational registry (ASPIRe) trial. The study included 109 patients in the USA.

- Sahlein et al (2015) reported neuroophthalmological outcomes from the PUFS trial. The study included 98 patients in the across 10 centres in the US, Turkey, and Hungary.

- Becske et al (2013) reported the initial results from the PUFS trial with a 180-day follow-up period. A total of 108 patients were enrolled between 2008 and 2009 across 10 centres in the US, Turkey, and Hungary.

- Jabbour et al (2013) investigated predictors of complications and aneurysm obliteration in a prospective study including 191patients with unruptured large, giant and/or wide necked intracranial aneurysms.

- Yu et al (2012) conducted a prospective, nonrandomised, multicentre study. This included 143 patients with unruptured saccular or fusiform intracranial aneurysms.

The recommendations of MTG10 were based on 16 studies with a total of 380 patients identified within the original assessment report. This review has identified 11 additional studies (two systematic reviews, two comparative studies and 7

prospective non-comparative studies) with 813 participants. It should be noted that 4 of the studies were reporting from the same PUFS trial. Becske et al. (2013, 2016 and 2017) reported results from the PUFS trial at 6 month, 3 year and 5 year follow-up points. The primary outcome for the Becske et al. (2013, 2016 and 2017) studies was complete aneurysm occlusion. Sahlein et al. (2015) reported neuroophthalmological outcomes at 6 months from the PUFS trial.

The EAC concluded that the two comparative studies suggested Pipeline was beneficial to patients compared with coiling techniques for occlusion rates and need for retreatment. The remaining evidence (7 studies) were single-arm studies which suggest PED was safe for large and giant complex aneurysms. These non-comparative studies provide useful information on safety outcomes but do not provide evidence on the clinical-effectiveness of Pipeline devices compared with standard care.

There has been no published report from the UK Neurointerventional Radiology Group regarding the use of this technology. The EAC identified 4 ongoing non-comparative studies which are scheduled to complete between September and December 2019 (further details are in Appendix 2).

5.5 Cost update

The Pipeline Flex with Shield system costs slightly more than the original Pipeline embolisation device (see Table 1).

Table 1 Costs

Item	Original figure for Pipeline embolization device	Updated figure for Pipeline Flex and Pipeline Flex with Shield.
Device price	£10,171	£10,450
Marksman microcatheter[1]	£1030	£995
Coil	£526.01	£609.10

[1]The company informed us the Marksman mircocatheter is superseded by the Phenom the price remains the same.

The EAC updated the staffing, hospital, imaging, equipment/consumables, drug, rupture repair and adverse events costs. Using updated costs, the EAC re-ran the original model, varying the numbers of Pipeline devices and coils. In the original guidance, using 2 Pipeline devices gave a cost of £30,346 compared to stent assisted coiling using 32 coils and 1 stent at a cost of £30,838, a saving of £492. Using the updated inputs the use of 2 Pipeline devices increased costs to £37,625 while using 32 coils and one stent gave a cost of £36,915 making Pipeline cost incurring by £710. Using 33 coils and one stent gave a cost of £37,617, incurring additional costs compared with 2 Pipeline devices of £8. The use of 34 coils and one stent gave an estimated cost of £38,320 which when compared with the use of 2

Pipeline devices made the Pipeline cost saving at £695 less. This is illustrated in table 2 below.

Table 2. Pipeline vs. Coil costs

No of Pipeline devices	No of Coils*	Cost of Pipeline devices	Cost of coils	Incremental cost **
2	32	£37,625	£36,915	£710
2	33	£37,625	£37,617	£8
2	34	£37,625	£38,320	-£695

* Assuming one stent for each intervention
** A negative cost indicates cost saving for Pipeline device versus stent-assisted coiling

6. Summary of new information and implications for review

The additional clinical evidence identified since the guidance was published in 2012 supports the current recommendations. The EAC concluded that the comparative evidence suggests that compared with coiling techniques, Pipeline provides higher occlusion rates with similar morbidity and mortality rates and a lower need for retreatment. This could potentially lead to cost savings in the future. However, no UK economic studies were identified from the updated search to support this conclusion.

The revisions to the cost model indicate that the use of Pipeline becomes cost saving when the number of Pipeline devices inserted does not exceed two, and when treatment would otherwise require the use of 34 or more coils combined with one stent. The review proposal is to amend the guidance without a consultation to include the new estimates for the cost saving. The company have reviewed this review proposal document for factual accuracy.

7. Implementation

Three experts have stated that Pipeline and other flow diverter technologies are now considered the standard of care for appropriately selected anatomies. One expert considered Pipeline and other flow diverter technologies as a safe and effective treatment option for appropriately selected complex intracranial aneurysm.

8. Equality issues

No new equality issues were identified in the original guidance or the guidance review.

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Appendix 1 – explanation of options

If the published Medical Technologies Guidance needs updating NICE must select one of the options in the table below:

Options	Consequences	Selected – 'Yes/No'
Amend the guidance and consult on the review proposal	The guidance is amended but the factual changes proposed have no material effect on the recommendations.	No
Amend the guidance and do not consult on the review proposal	The guidance is amended but the factual changes proposed have no material effect on the recommendations.	Yes
Standard update of the guidance	A standard update of the Medical Technologies Guidance will be planned into NICE's work programme.	No
Update of the guidance within another piece of NICE guidance	The guidance is updated according to the processes and timetable of that programme.	No

If the published Medical Technologies Guidance does not need updating NICE must select one of the options in the table below:

Options	Consequences	Selected – 'Yes/No'
Transfer the guidance to the 'static guidance list'	The guidance remains valid and is designated as static guidance. Literature searches are carried out every 5 years to check whether any of the Medical Technologies Guidance on the static list should be flagged for review.	No
Defer the decision to review the guidance	NICE will reconsider whether a review is necessary at the specified date.	No
Withdraw the guidance	The Medical Technologies Guidance is no longer valid and is withdrawn.	No

Appendix 2 – supporting information

Table 3. Summary of Pipeline, Pipeline Flex and Pipeline Shield technical characteristics

Feature	Pipeline™	Pipeline™ Flex	Pipeline™ Shield
Device (Braid)	Braided mesh cylinder fabricated from Platinum/8% Tungsten and 35N LT alloy wires	Same as Pipeline™	Braided mesh cylinder fabricated from Platinum/8% Tungsten and 35N LT alloy wires with PC surface treatment
Proximal marker	Platinum-iridium alloy	Same as Pipeline™	Same as Pipeline™
Distal, mid and proximal solder joints	Tin-silver mixture	Same as Pipeline™	Same as Pipeline™
Guidewire	304 stainless steel with PTFE Green coating	304L stainless steel cut hypotube and 304 stainless steel proximal wire with PTFE jacket	Same as Pipeline™ Flex
Deployment control	Protective coil	ePTFE protective sleeves	Same as Pipeline™ Flex
Tip and protective component(s)	Platinum-tungsten alloy coils	Platinum-tungsten alloy coils and ePTFE protective sleeves	Same as Pipeline™ Flex
Fluoroscopy marker	Platinum alloy capture coil	Platinum alloy restraints	Same as Pipeline™ Flex
Resheathing Pad	None	Silicone Elastomer	Same as Pipeline™ Flex
Design construction	The coil holds the braided implant until the coil is released from the device, allowing the braided implant to spontaneously expand into the parent artery	Soft PTFE sleeves hold the braided implant until it is deployed from the catheter. The soft pre-shaped tip has a small diameter and a 55° angle. The resheathing mechanism allows repositioning/redeployment of the implant which expands spontaneously once deployed into the parent artery.	Same as Pipeline™ Flex

Registered and unpublished trials

Trial name and registration number	Details
NCT02186561 Prospective Study on Embolization of Intracranial Aneurysms With Pipeline™ Embolization Device (PREMIER).	Non-comparative study assessing occurrence of major stroke or neurological death at 1 year and complete aneurysm occlusion at 1 year. Active, not recruiting. Estimated completion date November 2019.
NCT02719522 Pipeline Flex With SHield Technology Embolization - An International MulticEnter ObservationaL Post Market StuDy (SHIELD)	Non-comparative observational study assessing rate of stroke/neurologic death occurred at 1 year. Recruiting. Estimated completion date September 2019.
NCT03161769 MAXimizing Flow Diversion Effect On the Treatment of Large Intracranial Aneurysms With Embolization Devices (MAX-PIPE)	Non-comparative observational study assessing the number of participants with complete aneurysm occlusion at 12 months based on contrast agent volume measurement in angiography. Recruiting. Estimated completion date September 2019.
NCT02812108 Hemodynamic Analysis for Intracranial Aneurysms Recanalization After Endovascular Treatment (HARET)	Non-comparative observational study assessing hemodynamic factors related to aneurysm recanalization as assessed by computational blood flow simulation at 6 months. Interventions include low profile visualized intraluminal device (LVIS) and Pipeline (or Flex) Embolization Device. Recruiting. Estimated completion date December 2019.

Appendix 3 – changes to guidance

Proposed amendments to original guidance

Section of MTG	Original MTG	Proposed amendment
Title	Pipeline embolisation device for the treatment of complex intracranial aneurysms	Pipeline Flex embolisation device with Shield Technology for the treatment of complex intracranial aneurysms
Section 1 and 2.1	Pipeline embolisation device	Pipeline Flex embolisation device with Shield Technology
Whole document (after section 2.1, see amended 2.1)	Pipeline embolisation device	Pipeline
1.2	The Pipeline embolisation device is estimated to be cost saving when compared with stent-assisted coiling, in patients with complex giant or large intracranial aneurysms when the number of Pipeline embolisation devices inserted does not exceed two, and when treatment would otherwise require the use of 32 or more coils combined with one stent for stent-assisted coiling. If two Pipeline embolisation devices are used the total procedure cost is estimated as £30,346 compared with £30,838 for the use of 32 coils for stent-assisted coiling (a saving of £492 using the Pipeline embolisation device).	The Pipeline Flex embolisation device with Shield Technology is estimated to be cost saving when compared with stent-assisted coiling, in patients with complex giant or large intracranial aneurysms when the number of Pipeline embolisation devices inserted does not exceed two, and when treatment would otherwise require the use of 34 or more coils combined with one stent for stent-assisted coiling. If two Pipeline embolisation devices are used the total procedure cost is estimated as £37,625 compared with £38,320 for the use of 34 coils for stent-assisted coiling (a saving of £695 using the Pipeline embolisation device). [2018]
2.1	The Pipeline embolisation device (Covidien) is a self-expanding blood flow diverter that is placed across the neck of an intracranial aneurysm. While blood flow through the parent vessel is maintained via the device, flow within the aneurysm sac is disrupted, leading to stagnation and eventual thrombosis formation. The Pipeline embolisation device provides a scaffold for endothelial growth leading to the formation of a	The Pipeline Flex embolisation device with Shield Technology (~~Covidien~~Medtronic) is a self-expanding blood flow diverter that is placed across the neck of an intracranial aneurysm. While blood flow through the parent vessel is maintained via the device, flow within the aneurysm sac is disrupted, leading to stagnation and eventual thrombosis formation. The Pipeline Flex embolisation device with Shield Technology provides a scaffold for endothelial growth leading to the

	biological seal and exclusion of the aneurysm from the circulation.	formation of a biological seal and exclusion of the aneurysm from the circulation. Pipeline Flex embolisation device with Shield Technology is referred to as Pipeline in the main body of this guidance. [2018]
2.4	The cost of the Pipeline embolisation device stated in the sponsor's submission is £10,171.	The cost of ~~the~~ Pipeline ~~embolisation device~~ stated in the sponsor's submission is £10,171. These costs have been updated in the 2018 revision of the cost model to £10,450. [2018]
5.29		For the guidance review, the external assessment centre revised the model to reflect 2017 costs. The main parameter changes were costs associated with staff, hospital imaging equipment, drugs, rupture and adverse event costs. Further details of the 2017 revised model are in the revised model summary. [2018]

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