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Healthcare Technology Research Centre

Review report

MTG10 Pipeline embolisation device for the treatment of complex intracranial aneurysms

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This medical technology guidance was published in **May 2012**.

All medical technology guidance is reviewed 3 years after publication.

This review report summarises new evidence and information that has become available since this medical technology guidance was published, and that has been identified as relevant for the purposes of this report. This report will be used to inform NICE's decision on whether this guidance needs to be updated at this time.

Produced by:

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1. Original objective of guidance

To assess the clinical and cost effectiveness of Pipeline embolisation device for the treatment of complex intracranial aneurysm.

2. Current guidance recommendations

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.

3. Methods of review

An updated literature search was performed on the following databases by NICE: MEDLINE (Ovid), MEDLINE In-Process (Ovid), EMBASE (Ovid), CDSR (Ovid, Wiley), Database of Abstracts of Reviews of Effects – DARE (Wiley), Pubmed (follow ICG process), HTA database (Wiley), CENTRAL (Wiley), NHS EED. Please see Appendix C for the full search strategy.

For this review, NICE updated the original literature search to cover from August 2011-December 2017. The EAC re-ran the searches using the same search strategy to cover from December 2017-February 2018 to identify any new evidence that had become available since NICE's updated search. The following criteria were used to identify studies for inclusion in this review:

- Sample size of more than 20 participants with large/giant/complex aneurysms (studies that also included small aneurysms were included provided results were split by aneurysm size)
- Comparative or prospective design
- Unruptured aneurysms only
- Systematic reviews in relation to PED only

A researcher from the EAC reviewed all studies identified by the updated search and shortlisted those thought to be relevant for full text review. This shortlist was quality assured by a second researcher within the EAC.

4. New evidence

4.1. Changes in technology

The Pipeline Embolization Device reviewed in the original 2012 Guidance is now no longer routinely used within the NHS. The device has been superseded by the following CE marked products:

- The Pipeline Flex Embolization Device (received CE Mark in March, 2014)
- The Pipeline Flex Embolization Device with Shield Technology (received CE Mark in March, 2015). This device is now in UK-NHS practice.

For the differences between devices please see Table 1. In summary, the main updates were as follows:

- The capture coil was removed and replaced with polytetrafluoroethylene (PTFE) sleeves (1.5 mm wide x 3 mm long) to eliminate the need to torque the system for detachment. This element also serves to improve both the distal landing zone accuracy and distal end deployment reliability.
- A softer, more atraumatic distal wire tip was created (smaller inner diameter, 55° angle tip).
- A resheathing mechanism was incorporated to allow physicians to reposition and redeploy the Pipeline™ device. The silicone elastomer pad allows for full resheathing (up to 3 deployments and 2 resheathing attempts). The spiral-cut hypotube was added to the proximal end of the proximal bumper for pushability. This element also contains a tapered marker for difficult wire crossing and PTFE jacket for lubricity.

Table 1. 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

4.2. Changes in care pathways

There is currently no NICE pathway relating to intracranial aneurysms. There has been no change to NICE guidance on intracranial aneurysms. 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). However the long-term effects of this and other new approaches remain largely unknown, therefore strict adherence to the US FDAs indications for use is probably indicated until additional trial data demonstrate an incremental improvement in safety and efficacy over existing technologies (Class IIa; Level of Evidence C).

4.3. Results from MTEP MTG review

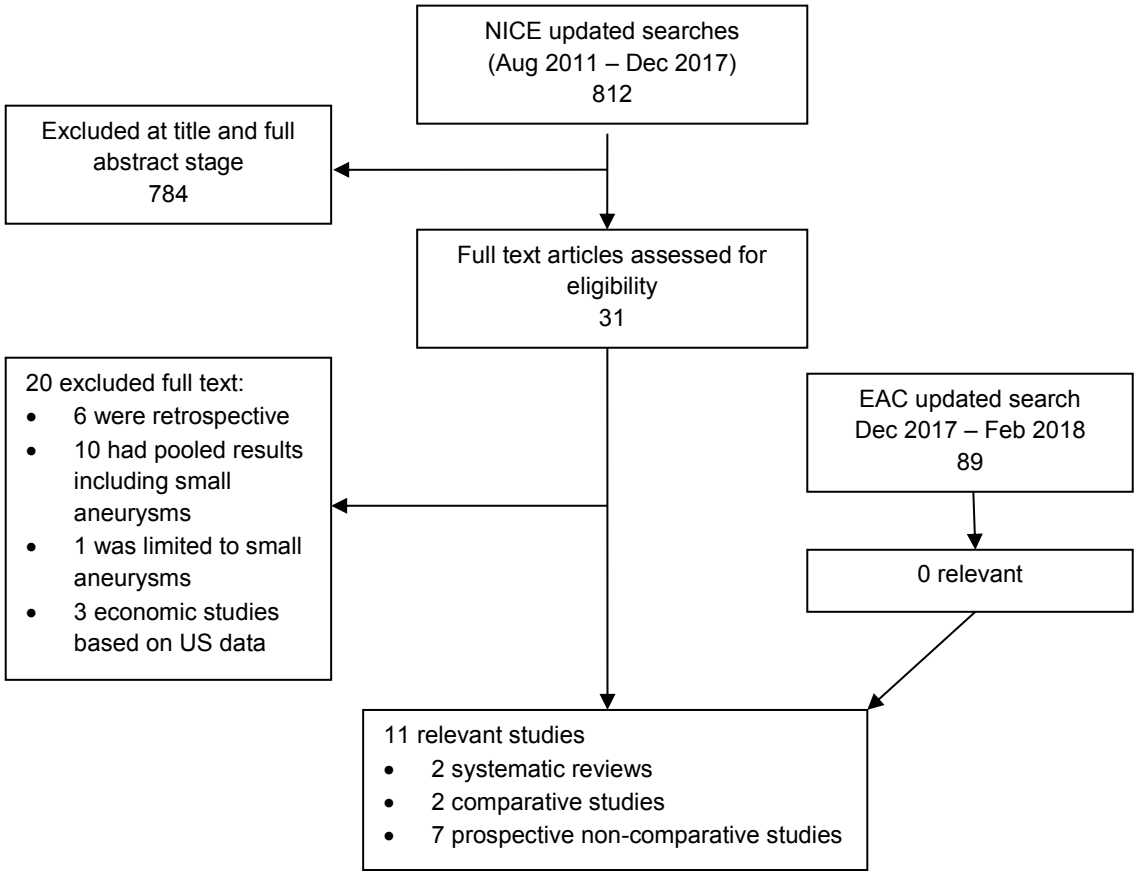
Cedar has identified no other relevant MTGs.

4.4. New studies

The NICE updated searches from August 2011 to December 2017 retrieved 811 papers. Two systematic reviews (Texakalidis et al, 2017; Murthy et al , 2014), 2 prospective comparative studies (Chalouhi et al, 2013; Kim et al, 2014), and 7 single-arm prospective studies (Becske, 2013, 2017 and 2017; Kallmes et al, 2016; Sahlein et al, 2015; Jabbour et al, 2013; Yu et al, 2012) were identified to be relevant. Four of these studies were in relation to the Pipeline for Uncoiled or Failed Aneurysms (PUFS) trial (Becske et al, 2013, 2016, 2017; Sahlein et al, 2015) and one in relation to the Aneurysm Study of Pipeline in an Observational Registry (ASPIRe) trial (Kallmes et al, 2016).

Figure 1 displays a flow diagram showing the study selection process. Studies that were excluded at full text are summarised in brief in Table 3 in Appendix B.

Figure 1. Flow diagram of study inclusion



Systematic reviews

Table 1 in Appendix B summarises the details of each systematic review. Two systematic reviews were included in this evidence review.

The Texakalidis et al (2017) review includes 28 studies (23 retrospective and 5 prospective) in relation to PED and antiplatelet therapy. None of the studies included are reported in this review with only one included in the original MTG10 guidance. All studies used PED with a combined sample of 1556 patients. The treatment strategyin 95% of patients was the administration of preprocedural aspirin combined with 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-PED stenosis (symptomatic 0.3%, asymptomatic 1.1%).

Murthy et al (2014) included 13 prospective studies with 905 patients with unruptured intracranial aneurysms treated with PED. 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%.

Primary studies

Table 2 in Appendix B summarises the details of each primary study.

Becske et al (2017) reported the 5-year follow-up results from the prospective Pipeline for Uncoilable or Failed aneurysms (PUFS) trial. One hundred and eight patients were initially recruited with only large (>10mm) and giant (>25mm) aneurysms (one patient with a small aneurysm was recruited but they were excluded from analysis). The primary outcome measure was complete aneurysm occlusion which had occurred in 60/63 (95.2%) of aneurysms within the safety cohort at 5-year follow-up and 96/106 (90.6%) in the effectiveness cohort. No new serious device related events had occurred between 3 and 5-year follow-up. Seventy-eight out of 81 patients with clinical data at 5 years had good functional outcome with modified Rankin Scale (mRS) scores $\leq$2. No new cases of delayed neurological death or haemorrhagic or ischemic cerebrovascular events were reported.

Beckse et al (2016) reported the 3-year follow-up results of the prospective PUFS trial. Angiographic follow-up data was available on 74 patients with 76 aneurysms in the safety cohort, of these 71 (93.4%) showed complete occlusion. There were 3 (2.6%) delayed device related adverse events, none of which resulted in permanent neurological sequelea. No new major or minor late-onset haemorrhagic or ischemic cerebrovascular events or neurological deaths were observed between previous and 3-year follow-up. Eighty-five out of 103 patients in the effectiveness cohort underwent clinical follow-up with 80 of these achieving favourable outcome with an mRS score of 0-1.

Kallmes et al (2016) reported results from the prospective multi-centre Aneurysm Study of Pipeline in an Observational Registry (ASPIRe) trial. One hundred and ninety one patients were recruited with unruptured intrcranial aneurysms. Median follow-up time was 6.2 months. Neurological morbidity rate was 13/191 (6.8% and the mortality rate was 3/191 (1.6%). The most common adverse events were ischemic stroke (19/191; 4.7%) and spontaneous intracranial haemorrhage (7/191; 3.7%). Those with giant aneurysms had

significantly higher rates of acute ischemic stroke, spontaneous aneurysm rupture and neurological death compared to those with large and small aneurysms.

Sahlein et al (2015) reported neuroophthalmological outcomes from the PUFS trial. Ninety-eight patients had complete neuroophthalmological 6 month follow-up. Thirty-nine (40%) patients presented with a neuroophthalmological (e.g. visual acuity, visual field etc) baseline deficit that was presumed to be attributable to the aneurysm. These patients had significantly larger aneurysms than those with no baseline deficit. In 25 of these patients (64%), the baseline deficit showed some improvement 6 months after PED whereas in one patient the deficits worsened. In 5/98 patients (5%), new deficits developed after treatment and in 6 patients (6%), deficits that were not assumed to be due to the aneurysm improved by 6 months. The size of the aneurysm was significantly larger in those with a new deficit or a worse baseline deficit at 6 months post-procedure. Kim et al (2014) conducted a prospective comparative study between PED and stent-assisted coiling. There were 23 patients in the PED group and 38 patients in the coiling group all with unruptured ICA aneurysms. There were 41 further patients recruited into 2 further groups that were outside the scope of this review and therefore not reported. All aneurysms were complex but sizes and were not reported in full. The mean aneurysm size in the PED group was 10.2mm and 8.4mm in the coiling group. Maximum follow-up was 60 months. Post PED procedure, 2% of the coiling group had significant intraparenchymal haemorrhage and 13% of the PED group had central nerve palsies, 8% had small asymptomatic infarcts and 4% had small asymptomatic remote-site haemorrhages. Ninety-six percent of the coiling group and 100% of the PED group had good functional outcomes with mRS scores of 0-1 after PED treatment.

Becske et al (2013) reported the initial results from the PUFS trial with a 180-day follow-up period. The PUFS trial was a multi-centre, prospective, single arm study of PED for the treatment of unruptured, large or giant, uncoilable or failed aneurysms of the internal carotid artery. A total of 108 patients were enrolled between 2008 and 2009 across 10 centres in the US, Turkey, and Hungary. There were two study arms; safety and effectiveness. Out of 106 aneurysms available for follow-up in the effectiveness arm, 78 demonstrated complete occlusion (73.6%). Six of the 107 patients in the safety cohort experienced a major ipsilateral stroke or neurological death (5.6%). Forty-four patients experienced serious adverse events, of which 21 events were definitely or probably device related. The modified Rankin scores were improved at 180 days in 21/107 patients (19.6%), unchanged in 70 (65.4%), worse in 10 (9.3%).

Chalouhi et al (2013) conducted a retrospective comparison of PED treatment and coiling in 160 patients with large or giant unruptured aneurysms. Median follow-up for clinical outcomes was 8 months. Follow-up for angiographic outcomes were scheduled at intervals up to 5 years. Rates of procedure related complications did not differ between groups (7.5% in both groups). At the latest follow-up, a significantly higher proportion of aneurysms treated with PED achieved complete obliteration compared to those treated with coiling (86% vs. 41% respectively). Multivariate analysis showed coiling to be an independent predictor of nonocclusion. Retreatment was necessary in significantly fewer patients treated with PED than those treated with coiling (2.8% vs. 37% respectively). Ninety-four percent of those in the PED group and 92% of patients in the coiling group achieved a favourable outcome with an mRS score of 0-2.

Jabbour et al (2013) investigated predictors of complications and aneurysm obliteration in a prospective study including 109 patients with unruptured large, giant and/or wide necked intracranial aneurysms. Of the12 patients that suffered procedure related complications, 4 of these were major complications (resulting in death or severe morbidity). In addition, of these 12 patients, 3 (7.1%) had small aneurysms, 3 (10%) medium and 6 (13.3%) had large.

Univariate analysis showed aneurysm size was not predictive of complications and was not a negative predictor of aneurysm obliteration.

Yu et al (2012) conducted a prospective, nonrandomised, multicentre study. This included 143 patients with unruptured saccular or fusiform intracranial aneurysms. Follow-up period was 18 months. Complete occlusion was found in 78/140 aneurysms at 6 months, 61/75 at 12 months and 49/58 at 18 months. Sub group analysis (including aneurysms <10mm vs. aneurysms >10mm) did not identify any factors correlated with early occurrence of complete occlusion of aneurysm within 6 months. No bleeding from an aneurysm occurred in cases of incomplete occlusion, apart from two cases of delayed rupture after PED placement that occurred within 30 days in large aneurysms (>20 mm). There were two cases of haemorrhagic stroke both in large aneurysms (22 mm and 25 mm). Cranial nerve palsy occurred in 14 patients before the PED procedure. One patient died of a Periprocedural complications leaving 13 patients (<10 mm, n=6; 10-25 mm, n=4; >25 mm, n=3). During follow-up 10 of these patients completely recovered.

4.5. Ongoing trials

Nine registered trials were identified; four ongoing and five completed trials. Full details of the trials are in Table 4 in Appendix B.

One trial (NCT00777088) has been completed and results published by Salhein et al (2015) and Becske et al (2016). One trial (NCT02390037) has been completed with results published by Martinez-Galdamez et al (2017). Three trials (NCT01558102, NCT00777907 and NCT02354300) are completed but no results appear to have been published from these studies.

All of the ongoing trials are prospective, observational studies currently registered as still recruiting participants. One study (NCT02719522) uses Pipeline Flex with Shield with an estimated sample size of 200. The primary outcome measure is rate of stroke/neurological death at 1 year. One trial uses Pipeline or Pipeline Flex (NCT02186561 and has an estimated sample size of 141. The primary outcome measure is number of patients with complete aneurysm occlusion at 12 months. One trial (NCT02812108) also uses Pipeline or Pipeline Flex and has an estimated sample size of 200. The primary outcome measure is haemodynamic factors relating to aneurysm recanalisation. The remaining trial (NCT03161769) uses Pipeline Flex only and has an estimated sample size of 30. The primary outcome measure is the occurrence of major stroke or neurological death and complete aneurysm occlusion at 1 year.

4.6. Changes in costs

The Pipeline Embolisation Device has been updated with two new CE marked versions; Pipeline Flex and Pipeline Flex with Shield. The costs of each updated version are the same; however this is more than the original PED (see Table 2).

Table 2 Costs

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

4.7. Other relevant information

None.

5. Conclusion

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.

The two comparative studies suggested PED was beneficial to patients compared to coiling techniques for occlusion rates and need for retreatment. The remaining evidence (7 studies) were single arm studies which did not compare PED to another intervention but did 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 PED compared to standard care.

No randomised controlled trials were identified in relation to PED only during the literature search update. Whilst RCTs tend to provide the most robust evidence on clinical efficacy, practical and ethical considerations may make this study design unfeasible.

The evidence included in this review would suggest that PED is still safe for large and giant complex aneurysms. The comparative evidence also suggests that when compared with coiling techniques, PED 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.

Changes to device

The Pipeline Device has now being superseded within the NHS by the Pipeline Flex and Pipeline FLEX with Shield. The manufacturer has confirmed that Pipeline Flex is identical to Pipeline with respect to design, raw material, and overall manufacturing processes, but Pipeline Flex incorporates a resheathing mechanism as part of a new delivery system to allow physicians the ability to reposition and redeploy the device. Having reviewed the specifications of the different versions and consulted with experts, it would appear the newer versions of the device do not differ significantly from the original and ~~T~~therefore the recommendations from the original MTG10 are still applicable in relation to all versions of the Pipeline device when compared with stent assisted coiling techniques. As experts have stated nothing has significantly changed in the clinical pathway since MTG10 was published, coiling methods would appear to still be the most relevant comparator.

Implications for MTG10

A costing update conducted by Cedar in December 2017 (see Appendix E) concluded the following; *"the use of PED becomes cost saving 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".* This cost update was based on the original PED device with a cost of £10,171. The newer Flex and Flex with Shield versions both cost £10,450 which when accounted for does not change the overall conclusion.

In relation to the final recommendation in MTG10, we suggest no changes should be made and clinicians should still submit all details of patients being treated with any version of the Pipeline device to the UK Neurointerventional Radiology Group audit database.

In conclusion, the evidence included in this review would suggest the recommendations made in MTG10 still apply for those patients with complex large or giant intracranial aneurysms. Furthermore, the updated evidence does not highlight any new safety or efficacy concerns. It should be noted that none of the included evidence features the Pipeline Flex or Flex with Shield versions, which are now currently used within the NHS. However, given the strong similarity between versions of the device, the evidence would appear to be generalisable to all Pipeline devices.

Appendix A – Relevant guidance

To be supplied by the NICE gIS team

NICE guidance – published

NICE guidance – in development

Guidance from other professional bodies

Appendix B

Table 1: Systematic reviews

Study ID	Objective	Data source	Selection criteria	Primary studies included	Key findings relevant to this review
Texakalidis et al. 2017	To summarise the antiplatelet regimen and platelet function test used. Also, to summarise aneurysm morphologies and adverse event rates associated with PED use.	PubMed and Cochrane databases were searched up to May 2017.	**Population:** Studies of adults undergoing aneurysm treatment with PED. **Intervention:** PED (studies of other flow diverters excluded) **Comparator:** not specified **Outcomes measure** (relevant to this review): CNS related adverse events, thromboembolism, in-PED stenosis, morbidity (defined as permanent neurologic deficits following an AE), mortality (defined as death occurring during PED placement or as a complication of an AE). **Study design:** no limit reported	28 studies were included (5 prospective, 23 retrospective) including a total of 1556 patients treated with PED. None of these studies are included in this report and one study was included in the original MTG10 assessment report. **Note: 8% of aneurysms were ruptured, and the review included patients with small aneurysms (number not reported).**	Overall morbidity rate: 2.1% (27/1246) Overall mortality rate: 2% (31/1556) Adverse events: • Thrombotic: symptomatic 6.6%, asymptomatic 3.4% • Haemorrhagic: symptomatic 3.0%, asymptomatic 0.4% • In-PED stenosis: symptomatic 0.3%, asymptomatic 1.1%
Murthy et al. 2013	To perform a systematic review of the published literature on PED.	Medline, Embase, and Cochrane library databases were searched for English language studies from 1999 to 2012.	**Population:** Studies of patients undergoing PED treatment for unruptured aneurysms. **Intervention:** PED **Comparator:** not specified **Outcomes measure** (relevant to this review): Peri-procedural (within 30 days of procedure) complications, delayed complications, mortality. Outcomes measures were: i) “event rate” which included peri-procedural complications, delayed complications, and mortality; ii) Aneurysm occlusion rate (AOR) at 6 months after PED placement. **Study design:** prospective studies with >10 patients. Studies with no follow-up were excluded.	13 studies were included with a total of 905 patients treated with PED. Two studies were already included in this report and three studies were included in the original MTG10 assessment report. **Note: 52% of aneurysms were small (<10mm).**	Cumulative mortality rate: 2.3% (95% CI 1.3-3.3%). Peri-procedural complication rate: 5.7% (95% CI 4.2-7.2%). Delayed complication rate: 1.9% (95% CI 1-2.8%). Complications: • Stroke 1.9% • TIA 2.0% • ICH 2.3% • SAH 1.1% • PED migration 0.3% • Haemotoma 1.2% Cumulative event rate: 16.7% (95% CI 10.4-23%). AOR at 6m: 79.7% (95% CI 76.8-82.6%)

AE, adverse event; AOR, aneurysm occlusion rate; CNS, central nervous system; ICH, intracranial haemorrhage; PED, pipeline embolisation device; SAH, subarachnoid haemorrhage; TIA, transient ischemic attack

Table 2: Primary studies

Study ID	Design and Setting	Populations	Intervention	Control	Outcomes	Statistics	Results
Becske et al (2017) Pipeline for uncoilable or failed aneurysms (PUFS) trial.	5 year follow- up results from the PUFS trial (see Becske et al (2013))	See Becske et al (2013)	PED	None	• Complete aneurysm occlusion • Incidence of significant in-stent stenosis (>50%) • Occurrence of delayed device-related adverse events • Functional outcomes based on the modified Rankin Scale (mRS) • Retreatment rates	• Exact binomial confidence intervals for major study endpoints were calculated using R. • A posterior Bayesian distribution of the rate of complete target aneurysm occlusion was calculated by using a non-informative beta prior (1, 1) distribution.	**Angiographic results and retreatment** • Sixty-one patients with 63 aneurysms were included in the safety cohort. Of these the angiographic occlusion rate was 95.2% (60/63). • Between 3 and 5-year follow-up no additional delayed parent vessel occlusions were reported. • In the effectiveness cohort, 104 patients with 106 aneurysms were included. Overall, 90.6% (96/106) aneurysms had 1 cerebral angiogram showing complete occlusion. • Of the fifteen patients with aneurysm or neck remnants at 180 days follow-up, 6 went on to receive further endovascular treatment (5 with PED and 1 with transvenous coils) resulting in 4 complete aneurysm occlusions, 1 persistent neck remnant and 2 aneurysm remnant at 5-year follow-up. **Delayed neurological complications and functional outcomes.** • Between 180 day and 5-year follow-up there were no additional cases of ipsilateral stroke, intracranial haemorrhage or neurological death. • Between 3 and 5-years, there were no additional serious device related adverse events. • There were no additional reported serious device related adverse events. • Seventy-eight out of 81(96.3%) had mRS scores of 0-2.
Study ID	**Design and Setting**	**Populations**	**Intervention**	**Control**	**Outcomes**	**Statistics**	**Results**
Becske et al (2016)	One and 3-year follow-up results from the	See Becske (2013)	PED	None	**Primary endpoints**: • See Becske et al 2013	Summary statistics were tabulated. Exact binomial	• Eighty-five patients with 87 aneurysms had 3-year follow-up. • Overall 71/76 (93.4%) of aneurysms were completely occluded. The lab could not determine complete

	PUFS trial (see Becske et al, 2013)				**Secondary endpoints at 3-year follow-up:** • Complete aneurysm occlusion • Rates of in-stent stenosis • Occurrence of delayed device related adverse events • Functional outcome based on modified Rankin Scale (mRS) score	confidence intervals for major outcomes were calculated.	angiographic occlusion in 1 (1.3%) patient, 2 (2.6%) patients had aneurysm remnants and 2 (2.6%) had neck remnants. • Excluding patients who were retreated prior to 3-year follow-up, complete occlusion was achieved with a single session of PED treatment in 68 patients (89.5%). • Excluding the patient that was retreated with coils, complete occlusion was achieved with one or two sessions of PED alone in 70 patients (92.1%). • Seventy-four of 76 aneurysms were free from significant >50% stenosis 3 years after PED treatment. **Safety Outcomes:** • Between the 180-day and 3-year follow-ups there were no additional occurrences of major ipsilateral stroke or neurological death. • There were 3 serious adverse events deemed 'probably' or 'definitely' related to the PED device; 2 cases of amaurosis fugax and 1 case of a neurologically silent parent vessel occlusion. None of these resulted in permanent neurological sequelae. • Eighty out of 85 (95.2%) had a mRS score of 0 or 1.
Study ID	**Design and Setting**	**Populations**	**Intervention**	**Control**	**Outcomes**	**Statistics**	**Results**
Kallmes et al (2016) Aneurysm Study of Pipeline in an Observational Registry (ASPIRe)	Prospective multicentre study US Europe Canada South-America	191 patients from with 207 unruptured intracranial aneurysm Aneurysm size: • Small n=24	PED	None	**Primary outcomes** • Spontaneous rupture of the Pipeline treated aneurysm • Spontaneous nonaneurysmal intracranial haemorrhage (ICH) ipsilateral or contralateral to	Discrete variables are presented using frequency distributions and cross tabulations. Continuous variables are summarised by presenting the	**Clinical and imaging outcomes** • Major adverse events occurred in 13/191 (6.8%) of patients and minor adverse events occurred in 9/191 (4.7%) of patients. • Of the13 patients with major adverse events 3 suffered an ischemic stroke, 7 an intracranial haemorrhage (ICH) and 3 spontaneous ruptures. Three of these patients suffered neurological mortality. Thus the morbidity rate was 6.8% (13/191)

		• Large n=162 • Giant n=21			the treated aneurysm • Acute ischemic stroke • Symptomatic or asymptomatic parent artery stenosis • Permanent cranial neuropathy. **Secondary outcomes:** • Treatment success defined as complete occlusion of the Pipeline-treated aneurysm at the last follow-up and Morbidity and mortality at the 6-month follow-up. • Adverse events were collected using a standard case report form. An adverse event was defined as any decline of the patient's baseline neurological status.	numbers of observations, mean, standard deviation, median, min and max values	and the mortality rate was 1.6% (3/191) at 6 months follow-up. • Of the 9 patients with minor adverse events, 6 suffered an ischemic stroke and 3 suffered asymptomatic parent artery stenosis. • There were significantly higher rates of ischemic stroke, spontaneous aneurysm rupture and neurological death in patients with giant compared to large or small aneurysms (P=0.03). There was no difference in rates of ICH between those with giant aneurysms and those with small and large aneurysms.
Study ID	**Design and Setting**	**Populations**	**Intervention**	**Control**	**Outcomes**	**Statistics**	**Results**
Sahlein et al (2015)	Analysis of PUFS trial	See Becske et al (2013)	PED	None	• Neuro-ophthalmalogical outcomes – motor, visual	•Categorical variables were analyzed with chi-square or	• Thirty-nine patients had baseline neuroophthalmological deficits at the time of PED treatment. The size of the aneurysm (maximum dimension) was statistically significantly associated

	See Becske et al (2013)				acuity, visual field or afferent papillary defects	Fisher's exact tests as appropriate. •Continuous variables were analyzed with Student's t-test or ANOVA	with a baseline deficit (22.0±5.9 mm for patients with a baseline deficit vs. 15.7 ± 5.9 mm for those with no deficits, p<0.001). • The maximum dimension of an aneurysm was significantly larger in patients in whom ophthalmic examinations revealed a new or worse finding at 6 months post-procedure than in those in whom findings were stable or improved after PED treatment; 22.5 ± 4.1 mm for the patients with worse outcomes vs. 17.9 + 6.5 mm in those with stable or improved outcomes (p=0.013). • Four of 5 patients whose examination indicated worsening of their neuroophthalmological findings had large or giant cavernous segment aneurysms.
Study ID	**Design and Setting**	**Populations**	**Intervention**	**Control**	**Outcomes**	**Statistics**	**Results**
Kim et al (2014)	Single-centre comparative study US	102 Patients with complex unruptured internal carotid artery (ICA) aneurysms. Note: Only results from the PED and coiling groups will be reported further. N of aneurysm sizes are not given, Mean size in PED group = 10.2 mm	PED n=23	Stent assisted techniques n=38	• Ischemic stroke • Intraparenchymal haemorrhage • Total stroke (Ischemic + haemorrhagic) • Cranial nerve palsies • Raymond 1 and 2 • Follow up modified Rankin Scale (mRS) score of 0-1 • Recurrence and retreatment	Differences in baseline characteristics were analysed using Mann-Whitney U and Fisher exact tests in SPSS V17.0	**Major neurological/procedure-related complication**: • In the stent assisted coiling group, 1 patient suffered post-treatment intraparenchymal haemorrhage. • In the PED group, three patients had new cranial nerve deficits post-treatment. Two patients had small, asymptomatic, ipsilateral frontal lobe haemorrhage but recovered without deficit. Two patients experienced stent migration that required retreatment. Two cases of intraprocedural incomplete device opening required follow-up balloon angioplasty. **Radiographic outcomes: recurrence and retreatment:** • In the stent assisted coiling group, 90% of patients had a Raymond 1 or 2 score after treatment and 10% were Raymond 3. On follow-up, 3 patients had converted from Raymond 2 to 3. In the 7 total Raymond 3 patients after follow-up, 4 had pre-treatments and 3 were elected for follow-up only. • In the PED group, there were 17 complete obliterations (81%), 3 small residuals (13%) and 3 cases pending follow-up. Raymond 1 or 2 status was confirmed in 20/21 (95%) of aneurysms on follow-up.

		Coiling group = 8.4 mm					**Clinical outcomes:** • In the stent-assisted coiling group, 4 patients presented with cranial nerve damage; 1 fully recovered, 2 had partial functional improvement and 1 did not show any improvement after treatment. At follow-up 92% of patients had mild or no deficit (mRS score 0, 32 patients; mRS score 1, 3 patients), 5.5% returned to baseline function or mRS score of 1 or 2 and 1 patient worsened with a mRS score of 3. • In the PED group, 4 patients (17%) presented with pre-treatment diplopia; 2 patients fully recovered and 2 partially recovered. At follow-up all patients remained or recovered to a mRS score of 0 or 1. • Average hospital stay was 2.6 days in the coiling group and 2.0 days in the PED group.
Study ID	**Design and Setting**	**Populations**	**Intervention**	**Control**	**Outcomes**	**Statistics**	**Results**
Becske et al (2013) *Pipeline for Uncoilable or Failed aneurysms (PUFS) trial*	Prospective, multicentre, interventional, single arm trial. US, Hungary, Turkey, 10 sites in total Patients recruited between 2008 and 2009	108 Patients with unruptured, large and giant (>10 mm) wide necked (>4 mm)aneurysms of the internal carotid artery that were uncoilable or failed aneurysms (n=108) Aneurysm size: Small n=1 (excluded from analysis)	PED	None	**Primary outcomes:** • Primary effectiveness outcome was complete occlusion rates of the target aneurysm without major stenosis of the parent artery or adjunctive use of a complementary embolic agent at 180 days. • Primary safety outcome was incidence of major ipsilateral stroke or neurological death at 180 days	• Complete occlusion rate of the target aneurysm statistically >50%. • Safety analysis statistically <20%. • Analysis was carried out using Bayesian distribution analysis.	**Effectiveness outcomes:** • After patient exclusions there were 106 aneurysms in 104 patients in the effectiveness cohort. • Of the aneurysms 78/106 (73.6%) had complete occlusion at day 180 without major stenosis or use of adjunctive coils (95% posterior probability interval: 64%, 81%, p<0.001 versus fixed rate of 50%). • At 1-year follow-up 89 patients with 91 aneurysms underwent catheter angiography. Complete occlusion was seen in 79/91 (86.8%) **Safety outcomes:** • 107 patients were included in the safety cohort. • Three patients died on postoperative days 4, 11 and 14. • 6/107 (5.6%) were judged to have had a major ipsilateral stroke or neurological death (95% posterior probability interval: 2.6%, 11.7%; p<0.001 versus fixed rate of 20%). • Thirty eight additional adverse events plus 6 qualifying events were recorded up to 180 days post-procedure (number of patients): • Amaurosis fugax 5 (4.7%)

		Large n=85 Giant n=22			**Secondary outcomes:** • Complete occlusion of the target aneurysm at 1, 3, and 5 years • Change in modified Rankin Scale (mRS) score of more than 2 points at 180 days		• Headache 5 (4.7%) • Intracranial hemorrhage 5 (4.7%) • Nonneurologic bleeding 5 (4.7%) • Ischemic stroke 4 (3.7%) • Cardiac arrhythmia 3 (2.8%) • Dizziness or tinnitus 2 (1.9%) • Carotid cavernous fistula 2 (1. 9%) • Carotid occlusion; patient also • counted as ischemic stroke • 1 (0.9%) • Cilioretinal artery embolism 1 (0.9%) • Diplopia 1 (0.9%) • Possible intracranial haemorrhage 1 (0.9%)Colitis 1 (0.9%) • Deep venous thrombosis 1 (0.9%) • Lightheadedness or palpitations 1 (0.9%) • Lung cancer 1 (0.9%) • Pulmonary embolism 1 (0.9%) • Rectovaginal fistula 1 (0.9%) • Recurrent breast cancer 1 (0. 9%) • Pneumonia or urinary tract infection 1 (0.9%) • Visual field worsened 1 (0.9%) At 180 days, mRS scores were available in 101 patients. The mRS scores were improved at 180 days in 21/107 patients (19.6%), unchanged in 70 (65.4%), worse in 10 (9.3%), and not available (due to incomplete study participation) in 6 (5.6%). Ninety-four of 107 patients (87.9%) had a mRS score of 1 or less at 180 days. Causes for worsened mRS scores were death (3), chronic headache (2), residual symptoms from stroke (2), diplopia (1), ptosis (1) and tinnitus (1). Six events were judged as definitely device related, 15 events were judged as probably device related.
Study ID	**Design and Setting**	**Populations**	**Intervention**	**Control**	**Outcomes**	**Statistics**	**Results**

Chalouhi et al (2013)	Single-centre comparative study. Patients identified from retrospective database US Patients enrolled between 2011-2012 (PED and 2004-2011 (coiling).	160 patients with large/giant unruptured aneurysms	PED (n=40)	Coiling (n=120)	• Clinically relevant procedural complications • Clinical outcome classified retrospectively using the modified Rankin Scale (mRS). • Angiographic outcome (aneurysm obliteration).	• Matched pairs analysis was performed as appropriate. • Univariate matched analysis was used to test covariates predictive of the following dependent variables: treatment complication, follow-up obliteration and clinical outcome. Factors were considered predictive with P<0.20. • Predictive factors were entered into a multivariate conditional logistic regression analysis	**Procedural complications:** • Three (7.5.5) occurred in the PED group (1 ischemic event, 1 contralateral and 1 ipsilateral distal haemorrhage). This resulted in 1 death. • In the coil group there were 9 (7.5%) procedure related events (8 thromboembolic or ischemic events and 1 cranial nerve palsy). **Clinical outcome:** • Clinical follow-up data was available for 38 (95%) of PED patients and 103 (86%) of coiling patients. • Favourable outcomes (mRS score 0-2) were achieved in 35/38 (92%) of the PED group and in 97/103 (97%) of the coil group (p=0.8) • Of the 3 patients with poor outcome in the PED group, 1 died from distal parenchymal haemorrhage; the 2 remaining had not experienced any procedural complications. • In univariate analysis, increasing aneurysm size (p=0.1) predicted poor clinical outcome. • In multivariate analysis no factor was significantly predictive of poor clinical outcome. **Angiographic outcome:** • Angiographic follow-up data was available for 35(87.5%) of PED patients and 90 (75%) of coiling patients. • A significantly higher level of aneurysms treated with PED (30/35; 86%) achieved complete obliteration of their aneurysm compared with coiled aneurysms (37/90; 41%; p<0.001). • Retreatment was necessary in 1 PED patients and 33/90 (37%) of coiling patients (p<0.001). • In univariate analysis, factors predicting nonocclusion were coiling (p<0.001) and older patients (p=0.2). • In multivariate analysis, coiling (OR 10.2; 95% CI, 3-35; 0<0.001) was the only significant predictor of nonocclusion. There was a trend for older patients (OR 1.4; 95% CI, 1-2, p=0.09).

							• Four patients sustained a haemorrhage after aneurysm treatment at a mean of 25 months. All 4 were in the coil group (3.3%).
Study ID	**Design and Setting**	**Populations**	**Intervention**	**Control**	**Outcomes**	**Statistics**	**Results**
Jabbour et al (2013)	Prospective single-centre study US Patients treated between 2008 and 2011	109 patients with 120 large, giant, and/or wide necked intracranial aneurysms and those that had failed previous treatment, were recurrent or fusiform Aneurysm size: Small n=42 Medium n=30 Large n=45 Giant n=3	PED	None	• Symptomatic procedural complications • Delayed complications • Clinical outcomes at 1, 3 and 6 months follow-up • Angiographic outcomes at 3 to 6 months, 1 year, 2 years and 5 years follow-up • Aneurysm occlusion • In-stent stenosis • Device migration	• Continuous variables and categorical variables were analysed using unpaired t test, chi-square test, Fisher exact and ANOVA as appropriate. • Univariate analysis was used to test covariates predictive of dependent variables. • Factors found to be predictive ($p<0.15$) were entered into a multivariate logistic regression analysis. $P<0.05$ were considered	**Procedure-related complications:** • Symptomatic procedure –related complications occurred in 12 patients. Of these, 4 were major complications (resulting in death or severe morbidity). Of these 12 patients, 3 (7.1%) had small aneurysms, 3 (10%) medium and 6 (13.3%) had large. • Univariate analysis showed aneurysm size was not predictive of complications. **Angiographic outcomes:** • Univariate analysis showed aneurysm size was not a negative predictor of of aneurysm obliteration. Data on obliteration rates was not stratified by aneurysm size.

						statistically significant.	
Study ID	**Design and Setting**	**Populations**	**Intervention**	**Control**	**Outcomes**	**Statistics**	**Results**
Yu et al (2012)	Prospective nonrandomised multi-centre study Hong Kong	143 patients with 178 unruptured saccular or fusiform intracranial aneurysms Aneurysm size: Small n=145 Large n=29 Giant n=4	PED	None	**Primary endpoints** • Aneurysm occlusion at 6, 12 and 18 months • Periprocedural death or major stroke within 30 days **Secondary endpoints:** • Other complications within 30 days • Neurological complications (mRS score) up to 3 years • Clinical outcome of cranial nerve palsy after PED placement up to 3 years • Imaging evidence of occlusion of parent artery and covered arterial branches and infarction due to occlusion of perforating arteries covered by the PED.	•Subgroup analysis of correlation between complete occlusion of aneurysm within 6 months and six potential predictors was performed by using the Pearson x_2 test and the Fisher exact •Subgroup univariate and multivariate analysis of the six potential predictors for occurrence of complete occlusion of aneurysm within 6 months were performed with a binary logistic regression model.	**Aneurysm occlusion:** • Complete occlusion was found in 78/140 aneurysms at 6 months, 61/75 at 12 months and 49/58 at 18 months. Sub group analysis (including aneurysms <10mm vs. aneurysms >10mm) did not identify any factors correlated with early occurrence of complete occlusion of aneurysm within 6 months. • No bleeding from an aneurysm occurred in cases of incomplete occlusion, apart from two cases of delayed rupture after PED placement that occurred within 30 days in large aneurysms (>20 mm). **Complications**: • There were two cases of haemorrhagic stroke (mRS = 5, 6), both in large aneurysms (22 mm and 25 mm). • Cranial nerve palsy involving the third, fourth or sixth nerve occurred in 14 patients before the PED procedure. One patient died of a Periprocedural complications leaving 13 patients (<10 mm, n=6; 10-25 mm, n=4; >25 mm, n=3). During follow-up 10 of these patients completely recovered. However, these 10 are not stratified by aneurysm size.

CI, Confidence Interval; ICA, internal carotid artery; ICH, intracranial haemorrhage; mRS, modified Rankin Scale; OR, Odds Ratio; PED, pipeline embolisation device;

Table 3: Excluded full text studies and summaries

Study ID	Summary of results	Reason for exclusion
Adeeb et al (2017)	Prospective comparative study using PED (n=91) and coiling techniques (n=57). Included small, large and giant aneurysms. • Complete occlusion rates were higher in the PED group compared to the stent group (81.1% vs. 75.9%). • Retreatment was necessary more in the coiling group compared to the PED group. • Good functional outcome was comparable between the two groups (PED = 94.7%; coiling = 96.6%). • The rate of neurological complications was higher in the PED group (9.4%) compared to the coiling group (4.8%)	Result were not split by aneurysm size
Shapiro et al (2017)	A detailed analysis of anterior circulation aneurysms treated with a Pipeline Embolization Device (PED) with nonocclusion at 1 year. • Nineteen aneurysms (21%) remained unoccluded at 12 months. • Further examination of individual cases identified several common mechanisms—device malapposition, inadequate coverage of the aneurysm neck with persistent exchange across the device, and the incorporation of a branch vessel into the aneurysm fundus—potentially contributing to failed treatment in these settings.	Retrospective design
Wali et al (2017) **Economic study**	PEDs vs. coiling for the treatment of large and giant unruptured aneurysms. • The base-case model demonstrated lifetime QALYs of 12.72 for patients in the PED cohort, 12.89 for the endovascular coiling cohort and 9.7 for patients in the no-treatment cohort. • Lifetime rehabilitation and treatment costs were $59,837.52 for PED; $79,025.42 for endovascular coiling; and $193,531.29 in the no-treatment cohort. • Patients who did not undergo elective treatment were subject to increased rates of aneurysm rupture and high treatment and rehabilitation costs. • One-way sensitivity analysis demonstrated that the model was most sensitive to assumptions about the costs and mortality risks for PED and coiling. • Probabilistic sampling demonstrated that PED was the cost-effective strategy in 58.4% of iterations, coiling was the cost-effective strategy in 41.4% of iterations, and the no-treatment option was the cost-effective strategy in only 0.2% of iterations	Economics based on US data
Le et al (2016)	Comparison of outcomes when using the original Pipeline device and the Pipeline Flex device. • Use of Pipeline Flex reduced procedure and fluoroscopy time • Rate of device deployment failure was lower in the Flex group than in the original Pipeline group (7.1% vs. 23.9%)	Only included small aneurysms

Chiu et al (2015)	Follow-up results from McAuliffe et al (2012; see below). • Complete follow-up was available for 103/166 aneurysms, with an occlusion rate of 93.2%. • From 0-6 months TIA, minor stroke and major stroke rates were 4.2%, 3.4% and 0.8% respectively. • After 6 months, 1 patient had a TIA of uncertain cause, with a PED-related mortality rate of 0.8%	Results were not split by aneurysm size
Daou et al (2015)	Assessed the safety and efficacy of PED in the treatment of recurrent previously coiled aneurysms • Complete occlusion occurred in 76.7% of patients • Near complete occlusion occurred in a further 10% of patients • Ninety-seven percent of patients had good clinical outcome (mRS score 0-1). One patient had an unfavourable outcome with a score of 4. • Complications were observed in1 patient who suffered an intracerebral haemorrhage	Results were not split by aneurysm size
Lin et al (2015)	Comparison of results between patients with PED plus coils and patients treated with PED alone. • PED deployment was successful in all 104 patients. At the latest follow-up complete aneurysm occlusion was achieved in a higher proportion of the PED1coils group (93.1% vs 74.7%, • Device foreshortening/migration occurred in 4 patients in the PED-only groupand none in the PED+coils group. • Fewer patients required retreatment in the PED+coils group (3.4% vs 16.0%) • Rates of neurological complications (10.3% PED1coils vs 8.0% PED-only, • Favorable outcome (mRS 0-2) was 93.1% in the PED+coils group vs. 94.7% in the PED only group	Results were not split by aneurysm size
Vendantam et al (2015)	Incidence and Clinical Implications of Carotid Branch Occlusion Following Treatment of Internal Carotid Artery Aneurysms treated with PED. • PEDs were placed across 74 aneurysms. Multiple PEDs were deployed in 16 patients. • ICA branch occlusion was not associated with the number of PEDs covering the ostia or the origin of ICA branches from the aneurysm	Retrospective design
Chalouhi et al (2014)	Comparison of rates of complications and outcomes in patients with a single vs. multiple PEDs. • Complications occurred more frequently with multiple PEDs (15% vs. 5%) • Multivariate analysis showed multiple PEDs was an independent predictor of complications, whereas there was as strong trend towards the use of a single PED predicting favourable outcome. • A similar number of patients in each group achieved adequate aneurysm obliteration (single = 84% and multiple = 87%)	Results were not split by aneurysm size

	• Those in the single PED group were significantly more likely to achieve favourable outcome compared to those with multiple PEDs (97% vs. 89%)	
el-Chalouhi et al (2014) **Economic study**	Cost comparison of PED and coiling in large and giant intracranial aneurysms. • Overall procedure cost was lower with the PED (mean, $23,911) vs. coiling ($30,522) • Above the median aneurysm volume, PED treatment was significantly less expensive than coiling even if multiple PEDs were used However, below the median aneurysm volume, PED treatment was significantly more expensive than coiling • Treatment with multiple PEDs was not cost-beneficial compared with coiling, even above the median aneurysm volume. • Potential savings associated with the PED were highly dependent on the type of embolic agent used	Economics based on US data
McTaggart et al (2014)	To evaluate the performance of thromboelastography (TEG) as a platelet function test in neurovascular patients treated with the PED • Thirty-four PED procedures were performed on 31 patients. • Technical success with the Pipeline placement was 100% • Two patients had minor strokes and five had TIAs. There were no haemorrhagic complications. No patient had permanent neurologic deficits. Six of eight (75%) of patients with thromboembolic/TIA events were ADP-induced hyporesponders by TEG • The 6- and 12- month angiographic occlusion rates were 78.9% and 89.5%, respectively	Results were not split by aneurysm size
Zanaty et al (2014)	Comparison of PED with conventional coiling techniques in patients with carotid cavernous aneurysms. • The rate of complete occlusion was 81.36% (48 of 59) for PED, 42.25% (39 of 71) for stent-assisted coiling, 27.27% (6 of 22) for coiling, and 73.33% (11 of 15) for carotid vessel destruction. • Retreatment was needed in patients with aneurysm size >15 mm and those who were not treated with PED • The rate of major complications was 6.6% (11 of 167). Patients who were treated with PED or stent-assisted coiling had 3.84 lower odds to develop complications	Results were not split by aneurysm size
Almandoz et al (2013)	Aimed to identify optimal pre-procedure P2T12 reaction units (PRU) value range and determine independent predictors of perioperative complications after PED treatment. • Eight out of 44 patients experienced a thromboembolic or haemorrhagic complication, four (8.3%) of which were major. • Pre-procedure PRU value of<60 or >240 and a technically difficult procedure were independent predictors of all perioperative complications. • Pre-procedure PRU value of >60 or <240 and a history of hypertension were independent predictors of major perioperative complications.	Retrospective design

Cinar et al (2013)	Reported preliminary results of PED use in a single-centre. • Thirty-four patients were available for 6-month angiographic follow-up with a complete occlusion rate of 85.3% • Thirty-seven patients were available for last follow-up with a complete occlusion rate of 91.9%. • There was one case of distal wire fracture of the stent delivery system and two insufficient stent expansions. • There was one fatal nonaneurysmal cerebral haemorrhage leading to an overall mortality rate of 2.2% with no permanent morbidity	Results were not split by aneurysm size
O'Kelly et al (2013)	Assessment of the technical challenges, clinical and radiographic outcomes, and complication rates after the use of flow-diverting stents for unruptured aneurysms • Ninety-seven cases of unruptured aneurysm were treated with the PED, with successful stent deployment in 94 cases. • The overall complete or near-complete occlusion rate was 83% • Complete or near-complete occlusion in 65% of aneurysms followed through 6 months, and 90% of aneurysms followed through 1 year • The overall mortality rate was 6%. Postprocedural aneurysm haemorrhage occurred in 3 patients (3%), while ipsilateral distal territory haemorrhage was observed in 4 patients (3.4%) •	Retrospective design.
Chitale et al (2012)	Single-centre experience with PED • PED placement was successful in all 42 aneurysms • Symptomatic postoperative complications were seen in 5/36 (13.9%) of patients; 4 intracerebral haemorrhages, 1 dissection, 2 strokes and 1 death.	Retrospective design
Colby et al (2012) **Economic study**	Cost comparison of PED and stent-coiling techniques for anterior circulation aneurysms. • The total combined costs of proximal access/guide catheters, microcatheters, and microwires were equivalent between the 2 groups • The cost of implants, however, was significantly lower in the PED group ($13 175 6 726 vs $19 069 6 2015), despite this group having a larger mean aneurysm size • The total procedure cost was significantly lower for the PED group vs. the stent coiling group ($16 445 6 735 vs $22 145 6 2022), a 25.7% cost reduction. This represents a 27.1% reduction in the cost per millimeter of aneurysm treated in the PED group ($2261 6 299) vs the stent-coiling group ($3102 6 193)	Economics based on US data
Kan et al (2012)	Prospective registry of patients treated with PED. • Out of 58 patients, 6 periprocedural thromboembolic events occurred and 4 fatal postprocedural haemorrhages occurred. • The major complication rate was 8.5%. • Of 19 patients who had complete follow-up, 13 (68%) had complete aneurysm occlusion.	Results were not split by aneurysm size

	• Two patients presented with delayed in-stent stenosis that was successfully treated.	
McAuliffe et al (2012)	Immediate and midterm results from a prospective registry of PED patients. • Sixteen out of 54 patients had mass-induced neurological deficits at baseline • Permanent morbidity and mortality was 0% at 6 months. However, 4 TIAs and 1 small retinal branch occlusion occurred • Aneurysm occlusion rate at 1 month was 61.9% and the overall occlusion rate at 6 months was 85.7% • Two patients (3.5%) had asymptomatic in-construct stenosis of >50% • Acute aneurysm-provoked mass effect resolved or improved in all cases	Results were not split by aneurysm size
Saatci et al (2012)	Large single-centre series of patients treated with the PED, including long-term follow-up. • Two hundred fifty-one aneurysms in 191 patients were treated • One aneurysm ruptured post-treatment (0.5%), and symptomatic in-construct stenosis was detected in 1 patient (0.5%) • Permanent morbidity rate was 1% and mortality rate was 0.5% • In 121 aneurysms (48.2%), 1-2 year angiography was available. The overall aneurysm occlusion rate was 91.2% in 6 months increasing to 94.6% • At 6-months, occlusion rates for small aneurysms were 93.6%, large aneurysms were 87.5% and for giant aneurysms were 90%	Retrospective design

ICA, internal carotid artery; ICH, intracranial haemorrhage; mRS, modified Rankin Scale; PED, pipeline embolisation device; PRU, P2T12 reaction units; QALY, quality adjusted life year; TEG, thromboelastography; TIA, transient ischemic attack

Table 4: Ongoing and completed trials

Study ID	Design	Population	Intervention	Comparator	Primary outcomes	Secondary outcomes	Current status	Estimated completion date
Ongoing trials								
NCT02186561	Interventional	Patients with a target intracranial aneurysm (IA) located in the anterior or posterior circulation or a target IA with a wide aneurysm neck.	Pipeline Embolization Device/ Pipeline Flex Embolization Device	N/A	Occurrence of major stroke or neurological death at 1 year Complete aneurysm occlusion at 1 year.	Occurrence of major stroke or neurological death at 1 year. Device-related neurologic adverse event at 1 year. Aneurysm occlusion at 3 years.	Active, not recruiting	November 2019
NCT02719522	Observational	Patients with intracranial aneurysms.	Pipeline Flex Embolization Device with Shield Technology	N/A	Rate of stroke/neurologic death occurred at 1 year.		Recruiting	September 2019
NCT03161769	Observational	Patients with unruptured intracranial aneurysms undergoing elective surgery.	Pipeline Flex	N/A	Number of participants with complete aneurysm occlusion at 12 months based on contrast agent volume measurement in angiography.	Number of participants with complete aneurysm occlusion at 6 months based on contrast agent volume measurement in angiography. High sensitivity and specificity (> 80%) of the MAFA ratio to determine aneurysm occlusion rates based on ROC statistical calculations at 1 year. Number of participants with treatment complications as assessed by an	Recruiting	September 2019

						electronic patient record at 1 year.		
NCT02812108	Observational	Patients with intracranial aneurysms, ruptured or unruptured, treated by endovascular treatment	• Low profile Visualized Intraluminal Device (LVIS) • Pipeline (or Flex) Embolizatio n Device	N/A	Hemodynamic factors related to aneurysm recanalization as assessed by computational blood flow simulation at 6 months.	Clinical factors related to aneurysm recanalization as recorded from medical chart at 6 months.	Recruiting	December 2017
Completed trials								
NCT00777088	Interventional	Patients with large or giant aneurysms of the internal carotid artery.	Pipeline Embolization Device	N/A	Occurrence of ipsilateral stroke or neurovascular death at 5 years.	Rate of complete target aneurysm occlusion at 3 and 5 years. Incidence of device-related adverse events at 3 and 5 years. Stenosis of the parent artery in PED at 3 and 5 years.	Published: Becske (2016) Salhein (2015)	Completed September 2016
NCT01558102	Observational (retrospective)	Patients with brain aneurysms who were treated with Pipeline Embolization Device	Pipeline Embolization Device	N/A	Relative incidence of neurologic clinical events that occurred after treatment with PED up to 5 years post procedure.	Incidence of neurologic events from the time of Approval of the Pipeline Embolization Device in the country of use until IRB approval at facility	Completed	Expected April 2017
NCT00777907	RCT	Patients with coilable wide-necked intracranial aneurysms	Pipeline Embolization Device	Coil Embolization	Effectiveness: Proportion of subjects whose target aneurysm shows complete occlusion on angiogram with <=50% stenosis of	Rate of complete target aneurysm occlusion at 1, 3 and 5 years. Incidence of ipsilateral major stroke at 180 days. Change in modified Rankin scale (MRS)	Completed	Expected April 2015

					the parent artery over 180 days. Safety: Proportion of subjects with ipsilateral major stroke or neurologic death over 180 days.	at 180 days, 1, 3 and 5 years. Incidence of device-related adverse events at 180 days, 1, 3 and 5 years. Change from baseline in neurologic signs or symptoms related to the target aneurysm at 180 days.		
NCT02390037	Observational	Patient has unruptured target intracranial aneurysm (IA) located in the anterior or posterior circulation.	Pipeline Flex Embolization device with SHIELD technology	N/A	Occurrence of major stroke or neurological death at 1 year.	Device related neurologic adverse event rate at 1 year.	Published: Martinez-Galdamez (2017)	Completed November 2016
NCT02354300		Patients with intracranial aneurysms that will be treated with a flow diverter	Pipeline Embolization Device in Conjunction with Transcranial Dopplers	N/A	The number of subjects who experience microemboli during device placement at 1 day.		Completed	Expected April 2015

Appendix C – Search strategy

Database: Medline
1 Aneurysm/ or Aneurysm, Ruptured/ (28562) 2 exp brain/ or exp meninges/ or exp cerebral arteries/ (1261727) 3 1 and 2 (1965) 4 Intracranial Aneurysm/ (27743) 5 ((anterior communicating or posterior communicating or basilar or berry or brain or cerebral or cranial or fusiform or intracerebral or intracranial or saccular) adj4 aneur*).tw. (22172) 6 or/3-5 (33210) 7 (pipeline or pflex or PED).tw. (12629) 8 (chestnut or EV3 or covidien or medtronic).tw. (6409) 9 or/7-8 (18993) 10 6 and 9 (419) 11 animals/ not humans/ (4773501) 12 10 not 11 (411) 13 limit 12 to english language (401) 14 limit 13 to (letter or editorial) (6) 15 13 not 14 (395) 16 (201108* or 201109* or 201110* or 201111* or 201112* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017*).ed. (5892667) 17 15 and 16 (364)

Database: Medline in process
1 Aneurysm/ or Aneurysm, Ruptured/ (0) 2 exp brain/ or exp meninges/ or exp cerebral arteries/ (77) 3 1 and 2 (0) 4 Intracranial Aneurysm/ (0) 5 ((anterior communicating or posterior communicating or basilar or berry or brain or cerebral or cranial or fusiform or intracerebral or intracranial or saccular) adj4 aneur*).tw. (2340) 6 or/3-5 (2340) 7 (pipeline or pflex or PED).tw. (2875) 8 (chestnut or EV3 or covidien or medtronic).tw. (700) 9 or/7-8 (3563) 10 6 and 9 (90) 11 animals/ not humans/ (221) 12 10 not 11 (90) 13 limit 12 to english language (89) 14 limit 13 to (letter or editorial) (2) 15 13 not 14 (87) 16 (201108* or 201109* or 201110* or 201111* or 201112* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017*).dc. (1866858) 17 15 and 16 (83)

Database: Embase
1 aneurysm/ or aneurysm rupture/ (44518) 2 exp brain/ or exp meninx/ or exp brain artery/ (1313817) 3 1 and 2 (5301) 4 exp intracranial aneurysm/ (31371) 5 anterior communicating artery aneurysm/ or saccular aneurysm/ (3523) 6 ((anterior communicating or posterior communicating or basilar or berry or brain or cerebral or cranial or fusiform or intracerebral or intracranial or saccular) adj4 aneur*).tw. (28686) 7 or/3-6 (42602) 8 (pipeline or pflex or PED).tw. (20721) 9 (chestnut or EV3 or covidien or medtronic).tw. (13195) 10 or/8-9 (33822) 11 7 and 10 (742)

12 (pipeline or pflex or pipelineflex or ped).dv. (275)
13 11 or 12 (935)
14 nonhuman/ not human/ (4140782)
15 13 not 14 (910)
16 limit 15 to english language (887)
17 (letter or editorial).pt. (1557255)
18 16 not 17 (869)
19 (201108* or 201109* or 201110* or 201111* or 201112* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017*).dc. (10269255)
20 18 and 19 (753)

Database: Wiley

ID Search Hits
#1 MeSH descriptor: [Aneurysm] this term only 51
#2 MeSH descriptor: [Aneurysm, Ruptured] this term only 150
#3 #1 or #2 200
#4 MeSH descriptor: [Brain] explode all trees 10700
#5 MeSH descriptor: [Meninges] explode all trees 296
#6 MeSH descriptor: [Cerebral Arteries] explode all trees 485
#7 #4 or #5 or #6 11381
#8 #3 and #7 17
#9 MeSH descriptor: [Intracranial Aneurysm] this term only 463
#10 ((anterior communicating or posterior communicating or basilar or berry or brain or cerebral or cranial or fusiform or intracerebral or intracranial or saccular) near/4 aneur*):ti,ab,kw (Word variations have been searched) 1034
#11 {or #8-#10} 1036
#12 (pipeline or pflex or PED):ti,ab,kw (Word variations have been searched) 449
#13 (chestnut or EV3 or covidien or medtronic):ti,ab,kw (Word variations have been searched) 947
#14 {or #12-#13} 1393
#15 #11 and #14 30

Database: Pubmed

#6	Search (#4 OR #5)	30
#5	Search (#3 AND “2017/12/05”[Entrez Date]: “3000”[Entrez Date])	2
#4	Search (#3 AND publisher [sb])	28
#3	Search (#1 AND #2)	497
#2	Search ((pipeline[Title/Abstract] OR pflex[Title/Abstract] OR PED[Title/Abstract])) OR (chestnut[Title/Abstract] OR EV3[Title/Abstract] OR covidien[Title/Abstract] OR medtronic[Title/Abstract])	21064
#1	Search ((anterior communicating[Title/Abstract] OR posterior communicating[Title/Abstract] OR basilar[Title/Abstract] OR berry[Title/Abstract] OR brain[Title/Abstract] OR cerebral[Title/Abstract] OR cranial[Title/Abstract] OR fusiform[Title/Abstract] OR intracerebral[Title/Abstract] OR intracranial[Title/Abstract] OR saccular[Title/Abstract])) AND aneur*[Title/Abstract]	31919

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Appendix E

Cedar
Healthcare Technology Research Centre

MTG10 Pipeline embolisation device for the treatment of complex intracranial aneurysms

Cost Update, December 2017

Authors: Kathleen Withers, Cedar Researcher
Grace Carolan-Rees, Cedar Director

Date: 18/12/2017

Version: V1.0

Contents

1. Background

The Pipeline embolisation device (PED) is a self expanding blood flow diverter used to treat intracranial aneurysms. The device is placed across the neck of the aneurysm allowing blood to flow freely through the parent vessel, while disrupting flow into the aneurysm sac. This causes stagnation within the sac followed by the formation of a thrombosis. The device forms a scaffold to support endothelial growth which leads to biological seal across the neck of the aneurysm excluding it from the circulation.

In May 2012 NICE published guidance on the first generation Pipeline embolisation device (NICE 2012). In June 2014, the manufacturer, Covidien, announced the European launch of the Pipeline Flex embolisation device (Medtronic 2014). The Pipeline Flex device incorporates a new delivery system; however it uses the same implant as the original device. In January 2015 Covidien was acquired by Medtronic Inc. with the companies combining under the name Medtronic plc (Medtronic 2015).

The existing NICE Guidance for the PED covers patients with unruptured, complex intracranial aneurysms, particularly those that are large or giant, wide necked or fusiform. It can also be used in patients who have aneurysms unsuitable for treatment with standard stenting or coiling, as well as in patients who have had had previous failed coiling or clipping procedures. When producing the current guidance, the NICE Medical Technologies Advisory Committee acknowledged that in UK clinical practice, those patients who would be considered for treatment with the PED, are those for who surgery is not feasible and who would only be otherwise suitable for treatment with stent assisted coiling. Comparison with this option was therefore particularly relevant.

The sponsor provided a decision tree with Markov model to assess the costs and consequences of using the Pipeline device and five comparators including stent assisted coiling. The time horizon of the base-case analysis was 10 years. An NHS and personal social services perspective was used.

Following the EACs assessment of the model, and comments received from clinical experts during consultation several changes were made to the cost model. This

resulted in the PED being estimated as cost saving when compared to stent assisted coiling when the number of Pipeline devices does not exceed two, and when the treatment would otherwise require the use of 32 or more coils and one stent for stent assisted coiling. In the scenario where 2 PEDs are used the total cost was estimated to be £30,346 compared to £30,838 for the use of stent assisted coiling with 32 coils and 1 stent. This gives a cost saving of £492 when using the Pipeline embolisation device.

NICE are currently reviewing the guidance on PED, and as part of this process have requested an update to the cost analysis of the original assessment.

2. Input updates

In their original submission, the sponsor provided a de novo cost analysis for the Pipeline embolisation device. During consultation, questions regarding several parameters in the cost model were raised. The EAC also made corrections to the model. Subsequent changes to the model were related to:

- The type (and related cost) of microcatheters used in stent assisted coiling compared to insertion of PED;
- use of balloons in stent assisted coiling
- difference in drug use between the two groups
- calculation errors in the length of drug therapy within the treatment groups
- unjustified use of additional endovascular equipment in stent assisted coiling

Table 1 below provides the costs that were used in the model following the changes noted above, together with the costs used in the 2017 update.

Table 1. Model inputs

Input	Original source	Original figure	Updated source	Updated figure
Staff costs (per hour)				
Surgeon	Curtis, L. (2010). Unit Costs of Health & Social Care. Personal Social Services Research Unit.	£403.00	As original inflated to 2016 prices using the Hospital & Community Health Services Pay & Prices Index.	£428.53
Radiologist	Curtis, L. (2010). Unit Costs of Health & Social Care. Personal Social Services Research Unit.	£403.00	As original inflated to 2016 prices using the Hospital & Community Health Services Pay & Prices Index.	£428.53
Nurse	Curtis, L. (2010). Unit Costs of Health & Social Care. Personal Social Services Research Unit.	£47.00	As original inflated to 2016 prices using the Hospital & Community Health Services Pay & Prices Index.	£49.98
Anaesthetist	Curtis, L. (2010). Unit Costs of Health & Social Care. Personal Social Services Research Unit.	£403.00	As original inflated to 2016 prices using the Hospital & Community Health Services Pay & Prices Index.	£428.53
Hospital Costs				
Neurology operating room (per hour)	Taken from supplementary material for Riverio-Arias et al. (2009). Inflated to 2010 prices using the Hospital & Community Health Services Pay & Prices Index. Cost per day converted to cost per hour.	£18.59	As original inflated to 2016 prices using the Hospital & Community Health Services Pay & Prices Index.	£19.11
Neurosurgery operating room (per hour)	Taken from supplementary material for Riverio-Arias et al. (2009). Inflated to 2010 prices using the Hospital & Community Health Services Pay & Prices Index. Cost per day converted to cost per hour.	£19.11	As original inflated to 2016 prices using the Hospital & Community Health Services Pay & Prices Index.	£21.53
Recovery ward	NHS Reference Costs 2010. AA23Z: Haemorrhagic Cerebrovascular Disorders. Elective excess bed day.	£327.01	NHS Reference Costs 2016. Average of AA23C to AA23G Haemorrhagic Cerebrovascular Disorders. Elective excess bed day.	£449.69
Imaging				
Angiogram	Wolstenholme et al. (2008). Inflated to 2010 prices using the Hospital & Community Health Services Pay & Prices Index.	£715.57	As original inflated to 2016 prices using the Hospital & Community Health Services Pay & Prices Index.	£828.55
Fluroscopy	NHS Reference Costs 2010. Diagnostic Imaging: Outpatients RA18Z: Contrast fluroscopy procedures more than 40 minutes	£189.91	NHS Reference Costs 2016. Diagnostic Imaging: Outpatients RD32Z: Contrast fluoroscopy procedures more than 40 minutes	£233.00
Magnetic resonance imaging	NHS Reference Costs 2010. Diagnostic Imaging: Outpatients RA02Z: Magnetic Resonance Imaging Scan, one area, post-contrast only	£189.13	NHS Reference Costs 2016. Diagnostic Imaging: Outpatients RA02A: Magnetic Resonance Imaging Scan, one area, post-contrast only 19 years and over	£191.00
Equipment / consumables				
PED	List price from sponsors submission	£10,171.00	NHS Supply Chain Dec 2017	£12,927.84*

Standard microcatheter	Price established during consultation period	£460.50	NHS Supply Chain Dec 2017	£550.52
Marksman microcatheter	List price from sponsors submission	£1,030.00	NHS Supply Chain Dec 2017	£1,230.93
Guidewire	List price from sponsors submission	£160.00	NHS Supply Chain Dec 2017	£185.26
Distal access catheter	List price from sponsors submission	£500.00	As original inflated to 2016 prices using the Hospital & Community Health Services Pay & Prices Index	£578.94
Guide catheter	List price from sponsors submission	£290.00	As original inflated to 2016 prices using the Hospital & Community Health Services Pay & Prices Index	£335.79
Coil	Taken from supplementary material for Riverio-Arias et al. (2009). Inflated to 2010 prices using the Hospital & Community Health Services Pay & Prices Index. Cost per day converted to cost per hour.	£526.04	As original inflated to 2016 prices using the Hospital & Community Health Services Pay & Prices Index	£609.10
Stent	List price for Enterprise stent	£2,750.00	NHS Supply Chain Dec 2017 cost for the average Leo self expanding intracranial nitinol stent (price for the Codman Enterprise stent not on NHS supply chain)	£3,649.48
Clip	Taken from supplementary material for Riverio-Arias et al. (2009). Inflated to 2010 prices using the Hospital & Community Health Services Pay & Prices Index. Cost per day converted to cost per hour.	£210.19	As original inflated to 2016 prices using the Hospital & Community Health Services Pay & Prices Index	£243.38
Endovascular equip (per hour)	Wolstenholme et al. (2008). Inflated to 2010 prices using the Hospital & Community Health Services Pay & Prices Index.	£89.40	As original inflated to 2016 prices using the Hospital & Community Health Services Pay & Prices Index	£103.27
Neurosurgical equip (per hour)	Wolstenholme et al. (2008). Converted to cost per hour Inflated to 2010 prices using the Hospital & Community Health Services Pay & Prices Index.	£10.20	As original inflated to 2016 prices using the Hospital & Community Health Services Pay & Prices Index	£12.01
Drug costs (per mg)				
Aspirin	British National Formulary 61. Price per mg. Based on 32-tab pack of 300mg tablets = £0.31	£0.00003	British National Formulary 69 Price per mg Based on 32-tab pack of 300mg tablets = £0.31	£0.00003
Clopidogrel	British National Formulary 61. Price per mg. Based on 30-tab pack of 75mg tablets.	£0.002	British National Formulary Price per mg. Based on 30-tab pack of 75mg tablets.	£0.060
Cost of rupture				
Initial (not-fatal)	The National Collaborating Centre for Chronic Condition (2006). Hypertension: Management in Adults in Primary Care: Pharmacological Update. Royal College of Physicians, London.	£8,046.00	National Clinical Guidelines Centre (2011). Hypertension: The Clinical Management of Primary Hypertension in Adults: Update of Clinical Guidelines 18 and 34. Update. Royal College of Physicians, London.	£10,190.00

Initial (fatal)	Assumes cost of one emergency ambulance journey (£246) and one non-elective inpatient short stay (£535). Cost of emergency ambulance visit taken from: Curtis, L. (2010). Unit Costs of Health & Social Care. Personal Social Services Research Unit. Cost of non-elective inpatient short stay taken from NHS Reference Costs 2010.	£781.00	Unchanged. No comparable recent source identified	£781.00
Subsequent (six-monthly cost)	The National Collaborating Centre for Chronic Condition (2006). Hypertension: Management in Adults in Primary Care: Pharmacological Update. Royal College of Physicians, London.	£1,080.00	Unchanged. No comparable recent source identified	£1,080.00
Adverse event costs				
SAH	The National Collaborating Centre for Chronic Condition (2006). Hypertension: Management in Adults in Primary Care: Pharmacological Update. Royal College of Physicians	£8,046	National Clinical Guidelines Centre (2011). Hypertension: The Clinical Management of Primary Hypertension in Adults: Update of Clinical Guidelines 18 and 34. Update. Royal College of Physicians	£10,190
Thrombo-embolic stroke	The National Collaborating Centre for Chronic Condition (2006). Hypertension: Management in Adults in Primary Care: Pharmacological Update. Royal College of Physicians	£8,046	National Clinical Guidelines Centre (2011). Hypertension: The Clinical Management of Primary Hypertension in Adults: Update of Clinical Guidelines 18 and 34. Update. Royal College of Physicians	£10,190
Remote ICH stroke	The National Collaborating Centre for Chronic Condition (2006). Hypertension: Management in Adults in Primary Care: Pharmacological Update. Royal College of Physicians	£8,046	National Clinical Guidelines Centre (2011). Hypertension: The Clinical Management of Primary Hypertension in Adults: Update of Clinical Guidelines 18 and 34. Update. Royal College of Physicians	£10,190

*NHS Supply chain has costs available for both the Pipeline embolisation device and the Pipeline Flex embolisation device. As of December 2017 these were the same at £12,927.84

3. Results from updated changes

Using these updated costs, the EAC re-ran the original model using varying 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 with a cost of £30,838 provided a cost saving of £492. Using the updated inputs the use of 2 PEDs increased to £37,625 while using 32 coils and one stent gave a cost of £36,915 making PED cost incurring at £710. Using 33 coils and one stent gave a cost impact of £37,617, incurring additional costs compared to 2 PEDs of £8. The use of 34 coils and one stent gave an estimated cost of £38,320 which when compared to the use of 2 PEDs made the PED cost saving at £695 less. This is illustrated in table 2 below.

Table 2. PED vs. Coil costs

No of PEDs	No of Coils*	Cost of PEDs	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 embolisation device versus stent-assisted coiling

4. Conclusions

Using updated costs in the original model as detailed above, the use of PED becomes cost saving 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.

5. References

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