NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Medical technology guidance

Assessment report overview

Pipeline embolisation device for the treatment of complex intracranial aneurysms

This assessment report overview has been prepared by the Medical Technologies Evaluation Programme team to highlight the significant findings of the assessment report. It includes key features of the evidence base and the cost analysis, any additional analysis carried out, and additional information, uncertainties and key issues the Committee may wish to discuss. It should be read along with the sponsor's submission of evidence and with the assessment report. The overview forms part of the information received by the Medical Technologies Advisory Committee when it develops its recommendations on the technology.

This overview also contains:

- Appendix A: Sources of evidence
- Appendix B: Comments from professional bodies
- Appendix C: Comments from patient organisations
- Appendix D: Additional analyses
- Appendix E: Additional submission information
- Appendix F: Sponsor's factual check of the assessment report and the External Assessment Centre's responses.

1 The technology

The Pipeline embolisation device (Covidien) is a self-expanding blood flow diverter that is placed across the neck of an intracranial aneurysm. Once in place, the device provides a scaffold for endothelial growth leading to the formation of a biological seal. While blood flow through the parent vessel is maintained, flow within the aneurysm sac is disrupted, leading to stagnation and eventual thrombosis.

The Pipeline embolisation device is a braided, cobalt chromium and platinum stent-like device which is loaded into and delivered via a microcatheter. It is manufactured in lengths of 10–35 mm and is available in different diameters from 2.5 to 5 mm (in 0.25 mm increments). Multiple devices can be used within each other and/or in sequence to increase the overall length of the construct or to increase the metal surface coverage over a particular segment.

The Pipeline embolisation device is indicated for use in patients with unruptured, complex intracranial aneurysms, specifically large and giant, wide-necked and fusiform aneurysms. It may be used in patients whose aneurysms are unsuitable for standard coiling and/or stenting and unsuitable for neurosurgical treatment: also in patients for whom previous coiling/clipping procedures have failed.

2 Proposed use of the technology

2.1 Disease or condition

It is estimated that between 1 and 6% of the population in England has an intracranial aneurysm. Intracranial aneurysms, especially those that are large or giant, may present with mass effect leading to local compressive symptoms or rupture leading to subarachnoid haemorrhage. The estimated risk of rupture of all intracranial aneurysms is 0.05–0.5% per year. Subarachnoid haemorrhage has a poor prognosis with approximately 10% of patients dying before reaching hospital and a further 50% dying within 4 weeks. Overall, an

estimated 1400 people die each year in the UK as a result of a rupture of an intracranial aneurysm leading to subarachnoid haemorrhage. Approximately 50% of those who survive a subarachnoid haemorrhage have a persistent neurological deficit. Data are from NHS Choices (2011).

2.2 Patient group

The Pipeline embolisation device is intended for use in patients with complex intracranial aneurysms, specifically aneurysms that are large or giant, wide necked and/or fusiform.

Risk factors for intracranial aneurysm include atherosclerosis, hypertension, smoking, severe head injury, cocaine misuse and family history. There is a higher reported prevalence of unruptured intracranial aneurysms in women than in men (Vlak et al. 2011). People with polycystic kidney disease and Marfan syndrome are at increased risk of developing an intracranial aneurysm.

2.3 Current management

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.

2.4 Proposed management with new technology

The Pipeline embolisation device provides a further option for managing complex intracranial aneurysms in patients for whom standard coiling and stenting is either unsuitable or has previously failed.

As for neurovascular stents, the patient takes oral dual antiplatelet therapy (typically aspirin and clopidogrel) for 2–7 days before placement of the Pipeline embolisation device and for 3–6 months after.

2.5 Equality issues

No equality issues were identified.

3 Issues for consideration by the Committee

3.1 Claimed benefits

The benefits to patients claimed by the sponsor are:

- A higher rate of complete, permanent occlusion of the large/giant intracranial aneurysm compared with coiling and stent-assisted coiling, leading to reduced rates of retreatment and a decreased risk of haemorrhage.
- Increased accessibility to treatment for patients with complex intracranial aneurysms. The Pipeline embolisation device offers a new option for treating patients with complex intracranial aneurysms which are not suitable for stent-assisted coiling or surgery, or patients for whom previous interventions have failed.
- Patients may experience a resolution of symptoms caused by the mass effect of aneurysms, which causes neurological symptoms as a result of pressure on surrounding areas of the brain.
- Increased long-term vessel patency, preserving blood flow to distal tissues supplied by the aneurysmal artery.

The benefits to the health system claimed by the sponsor are:

- The high rate of complete, permanent occlusion of the target aneurysm with the Pipeline embolisation device may lead to a reduced need for retreatment and an overall decrease in use of NHS resources.

3.2 Main issues

Clinical evidence

Of the 13 studies relevant to the scope and included in the submission, the sponsor relied principally on evidence from two studies. In general, the External Assessment Centre identified the lack of comparative effectiveness studies as a concern. However, comparative data are considered to be difficult to collect because of the nature of the disease and lack of clinical equipoise.

The External Assessment Centre identified additional clinical evidence which was not included in the sponsor's submission. Reasons for this included concerns about duplicate reporting of patients across published studies, the quality of research studies, and the publication of some of this additional clinical evidence after the sponsor's literature search. For completeness, the External Assessment Centre included all studies in its assessment report. Therefore there may be some duplicate reporting of patients, although this is not considered to be a significant issue.

The Committee may wish to define intracranial aneurysm type and size in its main recommendation. The sponsors submission states that ' the Pipeine embolisation device is not recommended as a sole therapy for patients with acutely ruptured aneurysms as it requires pre treatment with dual-antiplatelet therapy and may not, by itself, lead to rapid aneurysm occlusion'. Therefore the Pipeline embolisation device should only be considered for use in unruptured intracranial aneurysms. The sponsor provided definitions of intracranial aneurysm as specified in the clinical studies: large (10–25 mm diameter), giant (≥ 25 mm), wide-necked (≥ 4 mm), fusiform (no discernable necks).

Economic evidence

The sponsor's submission compared the cost consequences of use of the Pipeline embolisation device with five comparators; the device was associated

with a cost saving (of £13,110 per patient in the base-case analysis) in only one scenario, the comparison with stent-assisted coiling.

In addition to the cost consequence analysis, the sponsor submitted data on quality-adjusted life years, life years, ruptures (per 1000 patients) and years free from rupture or retreatment.

The External Assessment Centre concluded that overall the sponsor had clearly identified all data sources and submitted a well-executed model with extensive sensitivity analysis. However, it expressed particular concerns about a key area of uncertainty in the cost analysis.

The key area of uncertainty in the cost analysis is the number of Pipeline embolisation devices and coils needed to treat large and giant aneurysms. In the base case, the number was drawn from the sponsor's 'data on file' which showed that the mean number of Pipeline embolisation devices used in the UK, as of August 2011, was 1.46 per patient. On receipt of further UK hospital data, the sponsor submitted a revised number of 1.658 in October 2011. The External Assessment Centre reviewed the published literature and calculated a mean usage of 2.41 Pipeline embolisation devices per patient which it considered a more appropriate value for the model (appendix 8, External Assessment Centre report).

In addition, the number of coils used in the sponsor's base case (40) was taken from opinion in an editorial review (Wehman 2006). However, the External Assessment Centre sought and received general agreement from three expert advisers that 40 coils may be an overestimate (appendix 9, External Assessment Centre report). Although no expert adviser suggested an alternative value, the External Assessment Centre judged that 25 was more appropriate for use in the model.

The sponsor's base-case analysis did not include costs associated with all adverse events. A separate scenario analysis investigating the impact of

adverse events on total procedure costs was presented alongside the base case. However, not all reported adverse events were included in this analysis and it is not known what effect including costs of all adverse events would have on the total cost of the procedure.

4 The evidence

4.1 Summary of evidence of clinical benefit

The sponsor identified 13 studies relevant to the scope. However, because of a lack of study quality and duplication in patient reporting, the sponsor's submission presented data on a total of 139 patients from only two trials, with a maximum follow-up of 2-years. The trials were Pipeline for Intracranial Treatment of Aneurysms (PITA) and Pipeline for Uncoilable or Failed aneurysms (PUFS).

Nelson et al. (2011) reported outcomes up to 2 years for the PITA study: a prospective, multicentre single-arm feasibility study of 31 patients with 31 intracranial aneurysms that were either wide-necked (neck ≥ 4 mm or dome/neck ratio < 2) or in which previous treatment had failed.

A report to the FDA by the sponsor (FDA 2011) described the clinical evidence at 1 year from the PUFS study: an ongoing prospective, multicentre, single-arm study of 107 patients with 110 intracranial aneurysms that were wide-necked (>4 mm or no discernable neck and a size > 10 mm), large or giant (2.5– 5 mm).

The External Assessment Centre identified a further three case reports and one conference abstract of 96 patients. It discounted one study identified by the sponsor (Matouk et al. 2010) because it was outside the scope. The External Assessment Centre included a total of 16 studies with 379 patients in its report (some duplication may be present).

Success

Across 13 studies with a total of 237 patients (239 complex intracranial aneurysms) successful device placement was reported in 50–100% of patients. Of these 13 studies, eight studies with a total of 25 patients reported successful device placement in all patients (Fiorella et al. 2008, 2009a, 2009b, 2010; Hartmann et al. 2010; Kilsch et al. 2011; Phillips et al. 2010; Sararols et al. 2011).

In the PITA study, Nelson et al. (2011) reported clinical procedure success (defined as successful placement of the device without death or ipsilateral stroke) in 94% (29/31) of patients (2 failures were a result of stroke).

For patients in the PUFS study, the posterior probability that the primary effectiveness endpoint (complete occlusion and absence of stenosis of more than 50% at 180 days) exceeded a pre-determined success threshold of 50% was 0.999999. This probability value exceeds the pre-determined success probability of 0.975 and is therefore statistically significant ($p < 0.0001$) (FDA, 2011).

Retreatment

No secondary treatments were required at 1-year follow up among patients in the FDA report (2011). Need for retreatment was not reported in the other 15 studies included in the External Assessment Centre report.

Death/stroke

Major ipsilateral stroke or neurological death was reported in 6% (6/107) of patients in the FDA report (FDA 2011) at 180 days. Of these, 3 patients died.

Nelson et al. (2011) reported ipsilateral stroke within 30 days in 7% (2/31) of patients.

Five studies including a total of 58 patients (68 complex intracranial aneurysms) reported a stroke rate of 0% at follow-up ranging from 10 weeks to more than 52 weeks (Fiorella et al. 2009a, 2009b; Lylyk et al. 2009a; Klisch et al. 2011; Sararols et al. 2011).

Aneurysm occlusion

Nelson et al. (2011) reported complete occlusion of the target aneurysm in 93% (28/30) of patients at 180 days (95% confidence interval [CI] 77.9–99.2%); it was not possible to assess occlusion in 1 patient who had an arterial ligation. All patients who had complete occlusion at 180 days also had complete occlusion at 2 years as assessed by either catheter angiography or MRI.

Complete occlusion without major stenosis was reported in 74% (78/106) of aneurysms at 180 days and 71% (75/106) of aneurysms at 1-year angiography (FDA 2011).

Eight studies with a total of 131 patients all reported occlusion rates of 100% in patients assessed at follow-up ranging from 3 to 30 months (Fiorella et al. 2008, 2009a, 2009b,. 2010; Klisch et al. 2011; Phillips et al. 2010; Sararols et al. 2011; Szikora et al. 2010b).

Occlusion rates of 93%, 89% and 69% were reported by Lylyk et al. (2009a), Szikora et al. (2010a) and O'Kelly et al. (2011) respectively (absolute figures not reported).

Symptom improvement

In the PITA study 10% (3/31) of patients had an improvement in intracranial aneurysm related symptoms at 30 days (1 of these patients had previously had a stroke). There was no deterioration in neurological status at 30 days in the 28 patients free of stroke (Nelson et al. 2011).

In the PUFS study, Rankin score assessment (a general measure of neurological function) was carried out for 101 patients. The scores improved

from baseline in 20% (21/101) of patients, remained unchanged in 65% (70/101) and deteriorated in 9% (10/101) at 180 days follow-up (FDA 2011).

The FDA report (2011) described an improvement in visual field sensitivity from baseline (not otherwise described) in 19% (19/101) of patients, no change in 65% (65/101) of patients and deterioration in eye function in 5% (5/101) of patients at follow-up of 180 days.

Three case reports described complete resolution of symptoms at a mean follow-up ranging from 10 to 26 weeks (Fiorella et al. 2009a, 2009b; Sararols et al. (2011)).

Szikora et al. (2010b) reported resolution of symptoms in 61% of patients at a mean follow-up of 26 weeks.

Adverse events

A total of 18 adverse events occurred in 9 patients in the PITA study (Nelson et al. 2011). Of these, 2 were considered to be related to the Pipeline embolisation device.

The PUFS study reported 21 adverse events at 1 year that were considered as probably or definitely linked to the Pipeline embolisation device (FDA 2011).

Studies of 96, 18, 8 and 5 patients reported subarachnoid haemorrhage in 1%, 5%, 13% and 20% of patients respectively (follow-up not reported) (Hampton et al. 2011; Hartmann et al. 2010; O'Kelly et al. 2011, Szikora et al. 2010b).

4.2 Summary of economic evidence

No published economic evidence on the Pipeline embolisation device was identified by the sponsor. One unpublished analysis, supplied to NICE by the

device's former sponsor, demonstrated a cost saving of £29,115 per patient for the Pipeline embolisation device compared with stent-assisted coiling. This was considered by the current sponsor to be an overestimate of the cost saving and of insufficient detail to incorporate into the submission. A new cost analysis was therefore carried out by the sponsor.

New cost analysis

The cost analysis submitted by the sponsor combined a decision tree with Markov techniques to assess the costs and consequences associated with the Pipeline embolisation device against five comparator interventions. Quality-adjusted life years, life years, ruptures (per 1000 patients) and years free from rupture or retreatment were presented alongside the cost consequence analysis. The patient population for the cost model included those with unruptured large or giant intracranial aneurysms as outlined in the scope, but did not include fusiform or wide-necked aneurysms. The time horizon of the base-case analysis was 10 years and it was assumed by the sponsor that a cycle length of 6 months was appropriate to capture the main consequences of the disease. A discount rate of 3.5% was applied. The sponsor did not consider continuation rules to be appropriate for either the Pipeline embolisation device or the comparators. The costs and consequences associated with adverse events were not included in the base-case analysis because the sponsor considered there to be insufficient reliable and consistent data between treatment groups. However, the sponsor did include in the base case costs associated with mortality at 31 days, rupture and retreatment.

Following the outcome of initial treatment, the five health states used in the base-case analysis were 'no complications', 'new non-fatal rupture', 'post rupture', 'fatal rupture' and 'dead (all cause)'. These are shown in figure 1.

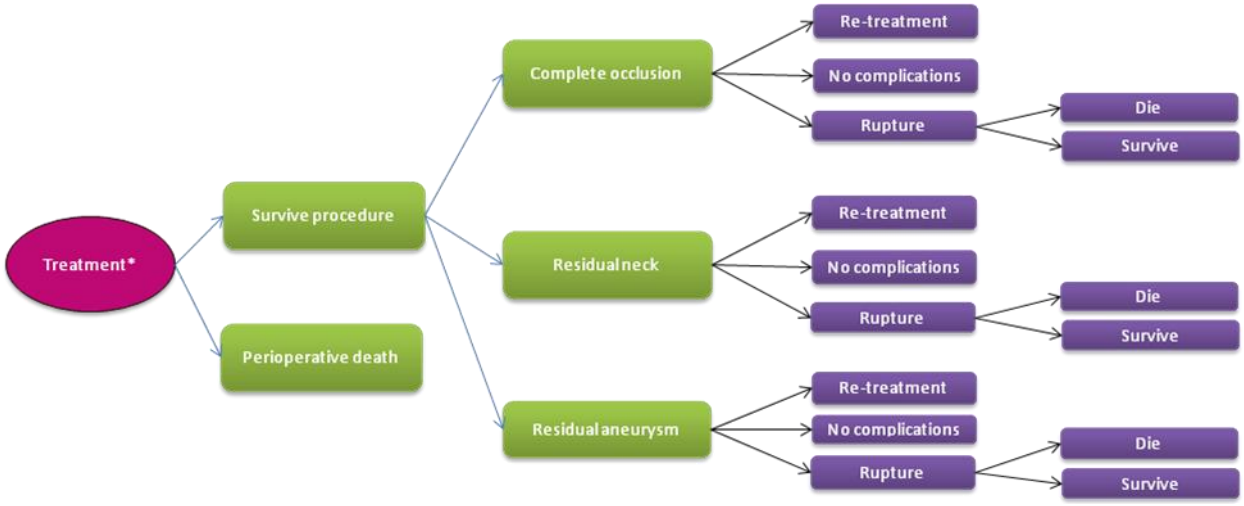

Figure 1 Schematic of the model structure reproduced from the sponsor's submission

The decision tree structure separated patients who had survived the procedure, based on a mortality rate for the procedure, into one of three occlusion categories (complete occlusion, residual neck and residual aneurysm). For each occlusion category, patients were tracked through the health states in 6-month cycles, starting at 6 months after the initial treatment. Probabilities within the base-case Markov model were dependent on the outcome within the short term.

Rupture and retreatment were modelled as the two major possible adverse events and the numbers of patients expecting these outcomes were calculated using the Markov model structure. Rates of rupture and retreatment were extrapolated to the 10-year time horizon assuming the risks for each were constant over the 10-year period.

It was assumed that transition probabilities for the health states would be constant over time and these were based on the rates of rupture and mortality following rupture. Rupture and retreatment rates were based on occlusion category, which was used as a proxy. The purpose of the intervention is to

achieve complete occlusion of the aneurysm. Therefore occlusion rate was used to generate the short-term effectiveness of treatment and the level of occlusion influences the long-term likelihood of rupture. Long-term outcomes differed by treatment based on the proportion of patients in each occlusion category after treatment.

The comparator treatments used in the model were:

- stent-assisted coiling
- neurosurgical clipping
- endovascular parent vessel occlusion
- neurosurgical parent vessel occlusion
- conservative management.

The model was validated by 'stress tests' and no unexpected results were obtained.

The key assumptions in the sponsor's model, as identified by the External Assessment Centre, were as follows:

- Residual neck and residual aneurysm occlusion rates for neurosurgical clipping were based on the ratio of rates from Molyneaux et al. (2005), which was a study not specific to large and giant aneurysms. The sponsor considered this to be a conservative estimate.
- For neurovascular and endovascular parent vessel occlusion, residual neck and residual aneurysm occlusion rates were assumed to be equal.
- Rupture and retreatment rates were drawn from studies that do not specifically refer to large and giant aneurysms. However, it was assumed that the size of the aneurysm affects the occlusion rate and not the rupture and retreatment rate so these sources were considered appropriate.
- Subarachnoid haemorrhage was assumed to occur for all ruptured aneurysms. This allowed the cost of rupture to be measured in the cost

model. The cost of subarachnoid haemorrhage was assumed to be the same as the cost of stroke.

- Anaesthetist time was assumed to be equal to the surgery time plus an additional hour, which is equivalent to 30 minutes before and after the procedure.

The base case did not include costs associated with adverse events because the sponsor considered there to be insufficient reliable, consistent data between treatment groups. The sponsor stated that most healthcare costs are incurred during the peri-procedural period. Two scenario analyses were therefore presented. One included costs associated with the adverse events of subarachnoid haemorrhage, thromboembolic stroke and remote intracranial haemorrhagic stroke using data from the PUFS study and data from Darsault et al. (2001) for comparators. The other scenario analysis restricted the time horizon to 6 months. Conservative management was excluded from the short-term scenario because it does not have a 'peri-procedural' mortality rate.

The sponsor carried out a univariate sensitivity analysis on 34 model parameters to identify the key drivers of the model. The External Assessment Centre carried out additional sensitivity analyses set uniformly at a 20% range.

Costs and benefits

An NHS and Personal Social Services perspective was used. NHS reference costs 2009/2010 were used for the intervention and comparators. The sponsor considered that tariffs were not appropriate because of the substantial differences in actual surgery time and recovery time between treatments.

The main source of clinical evidence for the model was the PUFS study with data for comparators taken from peer-reviewed published studies. Data were extrapolated beyond the study follow-up period in the base case and the adverse event scenario analysis.

The cost analysis included the costs associated with the duration of the procedure, staff time (surgeon, radiologist, nurse, anaesthetist), hospital costs (neurology operating or neurosurgical operating room, and recovery ward), imaging (angiogram, fluoroscopy or MRI), consumables, drugs, and for conservative management only, long-term monitoring with annual MRI. Because there was a lack of evidence for the cost of rupture, the model uses the cost of stroke, which was assumed to be representative of the cost of rupture.

Retreatment costs are incorporated with the type of retreatment modelled dependent on the initial treatment. Costs applied to each retreatment type are assumed to be the same as the full cost of initial treatment.

The costs and number of consumables used were identified in the sensitivity analysis as one of the key cost drivers, most significantly for the Pipeline embolisation device and endovascular coils (see results section for more information). In the model the cost of the Pipeline embolisation device was £10,171, the cost of one coil was £526.04 and the cost of one stent was £2750.

The number of Pipeline embolisation devices used in the base case was 1.46 based on data submitted to the sponsor from UK hospitals in August 2011. The number of coils used in the base case was 40 and was derived from opinion in an editorial review (Wehman 2006). It was assumed that one stent would be needed for each stent-assisted coiling intervention.

Results

The total procedure costs associated with the Pipeline embolisation device and the comparator interventions in the base case analysis are shown in table 1.

Table 1 Total procedure costs associated with the Pipeline embolisation device and comparator interventions in the base case

Intervention	Total procedure cost
Pipeline embolisation device	£24,341
Stent-assisted coiling	£37,451
Neurosurgical clipping	£11,658
Endovascular parent vessel occlusion	£16,893
Neurosurgical parent vessel occlusion	£11,654
Conservative management	£10,352

In the base case the only intervention against which the Pipeline embolisation device was shown to be cost saving was stent-assisted coiling. This was based on the use of 1.46 Pipeline embolisation devices, 40 coils and 1 stent. The average per-patient cost over the 10-year time horizon was £24,341 for the Pipeline embolisation device and £37,451 for stent-assisted coiling. Therefore the Pipeline embolisation device was associated with a cost saving of £13,110 per patient compared with stent-assisted coiling in the base-case analysis.

In both scenario analyses the Pipeline embolisation device was only cost saving when compared with stent-assisted coiling. The total procedure costs for each scenario analysis are presented in table 2.

Table 2 Total procedure costs associated with the Pipeline embolisation device and comparator interventions in the scenario analyses

	Total procedure cost	
Intervention	**Scenario analysis: including adverse events**	**Scenario analysis: restricted to short-term outcomes[a]**
Pipeline embolisation device	£25,018	£21,924
Stent-assisted coiling	£38,345	£32,240
Neurosurgical clipping	£12,328	£8,608
Endovascular parent vessel occlusion	£18,356	£11,842
Neurosurgical parent vessel occlusion	£12,190	£10,069
Conservative management	£10,352	n/a

[a] Six-month time horizon.

Including adverse events in the scenario analysis showed that conservative management becomes a more cost saving option when compared with the Pipeline embolisation device than in the base-case analysis, and that the surgical treatments become more costly interventions when compared with base-case results. Scenario analysis showed that when costs associated with adverse events are included in the model, the Pipeline embolisation device remained a cost saving intervention compared with stent-assisted coiling. When outcomes were restricted to the short term (6 months) the Pipeline embolisation device remained cost saving compared with stent-assisted coiling. The External Assessment Centre considered that the sponsor had not handled complications and adverse events adequately, although the impact of this on the cost consequence analysis is not known.

Sensitivity analyses carried out by the sponsor showed that the main factors influencing the cost analysis were the number and cost of consumables, in particular the number of Pipeline embolisation devices and endovascular coils. The sponsor carried out sensitivity analysis for the use of 1–3 Pipeline embolisation devices and separately for 5–100 coils. The External Assessment Centre judged that this analysis was extensive and agreed with

all methods and results. However, given that the number of Pipeline embolisation devices is a key driver in the model, it considered the highest number (3) of Pipeline embolisation devices used to be too low.

As shown in table 1, the sponsor presented the costs and cost consequences associated with the use of the Pipeline embolisation device compared to all comparators specified in the scope. Only the comparison with stent assisted coiling was presented by the sponsor as a cost saving scenario. Given that the number of both Pipeline embolisation devices and coils was the key driver in this model, the External Assessment Centre carried out additional analysis around the numbers of Pipeline embolisation devices and coils, above all other comparisions.

The number of Pipeline embolisation devices used in the base case was identified from the sponsor’s 'data on file', which showed that the mean number of used to August 2011 in the UK was 1.46 per patient. A revised number of 1.6 per patient was submitted by the sponsor in September 2011. The External Assessment Centre reviewed the published literature and calculated a mean usage of 2.41 Pipeline embolisation devices per patient, which it considered to be a more appropriate value for the model (appendix 8, External Assessment Centre report). The PUFS study was the main source of clinical evidence for the sponsor's model and this reported an average use of 3.1 Pipeline embolisation devices per patient (FDA 2011).

The number of coils used in the base case was 40 and was taken from opinion in an editorial review (Wehman 2006). The External Assessment Centre received opinion from three expert advisers on this and general agreement was expressed that 40 coils may have been an overestimate (appendix 9, External Assessment Centre report). The External Assessment Centre judged that 25 coils was a more appropriate value to use in the model, although no expert adviser explicitly stated this value.

The number of stents used in the base case for stent-assisted coiling was one. One stent was also used in the sensitivity analysis regardless of the number of coils. The External Assessment Centre considered this estimate to be appropriate.

Additional analyses carried out by the External Assessment Centre to assess the impact of varying the number of Pipeline embolisation devices and the number of coils on the incremental cost is shown in table 3. A graph to illustrate the effect of varying the number of devices and coils on the incremental cost of the Pipeline embolisation device over stent-assisted coiling is included in appendix D of this assessment report overview.

Table 3 reports the base-case analysis submitted by the sponsor and four additional analyses carried out by the External Assessment Centre for the incremental cost of the Pipeline embolisation device compared with stent-assisted coiling. In the additional analyses, for the number of Pipeline embolisation devices presented in the sponsor's base case, the External Assessment Centre investigated how many coils would be needed to make the Pipeline embolisation device cost saving compared with stent-assisted coiling. This was repeated for the External Assessment Centre’s estimate of 2.4 Pipeline embolisation devices per patient, the reported average use of 3.1 Pipeline embolisation devices per patient from the PUFS study and the sponsor's revised estimate of 1.6 Pipeline embolisation devices.

The scenario that the External Assessment Centre judged to be most appropriate for comparing the Pipeline embolisation device with stent-assisted coiling used 2.4 Pipeline embolisation devices per patient compared with 25 coils and one stent per patient. For this scenario the use of the Pipeline embolisation device is associated with an additional cost of £6460 per patient.

Table 3 Incremental cost of the Pipeline embolisation device over stent-assisted coiling, varying the number of Pipeline embolisation devices and the number of coils

Number used		Total procedure cost		
Pipeline embolisation device	**Coil[b]**	**Pipeline embolisation device**	**Stent-assisted coiling**	**Incremental cost[a]**
1.46	40	£24, 341	£37,451	–£13,110 (base case)
2.4	25	£34,807	£28,348	£6460 (judged most appropriate estimate)
1.46	19	£24,341	£24,706	–£365
1.6	21	£25,9000	£25,920	–£20
2.4	36	£34,807	£35,024	–£216
3.1	49	£42,601	£42,913	–£312

[a] Negative cost indicates cost saving for Pipeline embolisation device versus stent-assisted coiling.

[b] One stent used for each intervention.

5 Ongoing research

NCT00777088 Pipeline for Uncoilable or Failed Aneurysms (PUFS)

Ongoing, not recruiting.

Two- year follow-up data expected November 2011: results of a phone call to study participants to assess medical status and occurrence of adverse events.

Three-year follow-up data expected November 2012: medical history assessment, neurological examination and modifier Rankin score assessment and occurrence of adverse events.

Estimated study completion date June 2014.

UK Neurointerventional Radiology Group audit

All Pipeline embolisation device (and SILK) UK cases to be registered.

Hong Kong Pipeline embolisation device registry

Ongoing. No further details available.

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NICE Medical Technologies Evaluation Programme

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Appendix A: Sources of evidence considered in the preparation of the overview

A Details of assessment report:

- Withers K, Carolan-Rees D, Dale M, et al. External Assessment Centre report: Pipeline embolisation device for the treatment of complex intracranial aneurysms. September 2011.

B Submissions from the following sponsors:

- Covidien

C Related NICE guidance

- Coil embolisation of ruptured intracranial aneurysms. NICE interventional procedure guidance 106 (2005). Available from www.nice.org.uk/guidance/IPG106
- Coil embolisation of unruptured intracranial aneurysms. NICE interventional procedure guidance 105 (2005). Available from www.nice.org.uk/guidance/IPG105
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Molyneux AJ, Kerr RSC, Yu LM et al. (2003) International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. The Lancet 366: 809–17.

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Wong GKC, Kwan MCL, Ng RYT et al. (2011) Flow diverters for treatment of intracranial aneurysms: current status and ongoing clinical trials. Journal of Clinical Neuroscience.18: 737–40.

Appendix B: Comments from professional bodies

Expert advice was sought from experts who have been nominated or ratified by their Specialist Society, Royal College or Professional Body. The advice received is their individual opinion and does not represent the view of the society.

Dr. Tony Goddard
Consultant Diagnostic and Interventional Radiologist, British Society of Neuroradiologists

Dr. Rob Lenthall
Consultant Neuroradiologist, British Society of Neuroradiologists

Dr. Andy Molyneux
Consultant Neuroradiologist, British Society of Neuroradiologists

Dr. Phil White
Consultant Neuroradiologist, British Society of Neuroradiologists

- Two expert advisers had used the Pipeline embolisation device.
- Four expert advisers considered the Pipeline embolisation device to be a significant modification of an existing technology with real potential for different outcomes and impact.
- One expert adviser considered that this technology may have a major role in very difficult to treat cerebral aneurysms, in patients who cannot be treated by coiling and for whom major surgery carries very substantial risks of death or major disability. A different expert adviser commented that although the theoretical benefits of flow-diverting stents are attractive and early reported experience is impressive, the short- and longer-term risk profiles compared with established techniques are poorly defined and the clinical benefits are not proven robustly.

- One expert adviser considered that the Pipeline embolisation device is likely to be used for large aneurysms that are causing mass effect because using a stent in the parent vessel artery rather than filling the sack with coils (or submitting the patient to potentially dangerous surgery) is empirically more attractive and offers advantages in being a shorter procedure, potentially cheaper than coils and involving less cranial irradiation. The same expert adviser considered the Pipeline embolisation device suitable for dysplastic/dissecting aneurysms where parent artery occlusion is not possible and for aggressively recurring aneurysms after previous embolisation. A different expert considered that the technology should be used when the estimated risks associated with use of the Pipeline embolisation device are less than the estimated risk associated with the natural history of the disease. Other expert advisers considered wide-necked or fusiform complex aneurysms to be most appropriate for treatment with the Pipeline embolisation device.
- One expert adviser considered this technology to be a promising development for a minority of patients with complex aneurysms (approximately <2% of patients with aneurysms) because it may offer a real treatment for essentially 'untreatable' lesions.
- The expert advisers considered likely additional benefits for patients to include better outcomes for dysplastic lesions causing compression of the brain, reduced operative time and risk, reduced need for long-term imaging and a reduced number of aneurysm retreatments, hope for patients who are inevitably going to die of their disease and presenting an enhanced prospect for the cure of challenging aneurysms.
- The expert advisers considered likely additional benefits for the healthcare system to include a reduction in need for repeat procedures and some advisers expressed the opinion that this technology could be cost effective for large lesions.
- One expert adviser who had used the Pipeline embolisation device commented that the devices can be difficult and unpredictable to use; they

are easy to ‘lose’ in the microcatheters, need careful handling and can be readily damaged.

- The expert advisers raised the following safety concerns: unexplained deaths (uncommon), delayed aneurysm rupture (more than 30 have been reported worldwide), variable reliability, real issue about developing expertise, uncertainty over risk of delayed/late haemorrhage and bleeds, lack of quality clinical data and expensive devices.
- The expert advisers suggested that the following would be useful to assess patient benefit: a comparison between patients treated with stents and the expected natural history of the disease, a comparison between these devices and standard therapy (if standard therapy is appropriate); for example, a comparison between parent artery occlusion and VRD for symptomatic cavernous aneurysms where both treatments are possible and there is clinical equipoise. They also suggested that rates of technical complications, adverse events, aneurysm neck occlusion, and retreatment, and long-term parent vessel patency should be measured, and that outcomes are needed up to 5 years.

Appendix C: Comments from patient organisations

The following patient organisations were contacted and no response was received.

- Brain and Spinal Injury Charity (BASIC)
- Brain and Spine Foundation
- CORDA – The Coronary Artery Disease Research Association
- Different Strokes
- Headway – the Brain Injury Association
- National Heart Forum (UK)
- Neurological Alliance
- Neurosupport

- Polycystic Kidney Disease Charity
- Stroke Association
- UK Acquired Brain Injury Forum
- Vascular Society

Appendix D: Additional analyses

Additional analysis of the submitted evidence considered relevant to fully address the issues in the scope.

Appendix D was written by the External Assessment Centre who carried out the additional analysis.

Variations in PED and coil use

The most influential uncertainties in the model are the average number of PED and coil devices used per treatment. In this section the different estimates for PED numbers available have been modelled to show at what point they become cost saving for the scenario of PED vs Stent-assisted coiling (Tables 1-4). Figure 1 shows how the number of coils and PED devices used affects the incremental cost over a wide variation of coil numbers. It also illustrates how the cost saving point varies with different inputs.

Variations on quantities of PED devices that were modelled are:

1.46 PED from the original manufacturer submission

1.6, PED a revised figure submitted by the manufacturer in the factual check

2.4 PED from the EAC analysis of clinical evidence (Appendix 8, EAC assessment report)

3.1 PED from the PUFS study (FDA 2011)

Table 1 - PED vs stent assisted coiling, scenario with PED just cost saving. 3.1 PED, 49 coils

		PED	Stent-assisted coiling	Incremental
(3.1 PEDs, 49 coils)	Equipment costs	£33,510	£31,394	£2,116
	Retreatment costs	£3,656	£5,684	-£2,028
	Total cost	£42,601	£42,913	-£312

Table 2 - PED vs stent assisted coiling, scenario with PED just cost saving. 2.4 PED, 36 coils

		PED	Stent-assisted coiling	Incremental
(2.4 PEDs, 36 coils)	Equipment costs	£26,390	£24,556	£1,834
	Retreatment costs	£2,982	£4,633	-£1651
	Total cost	£34,807	£35,024	-£216

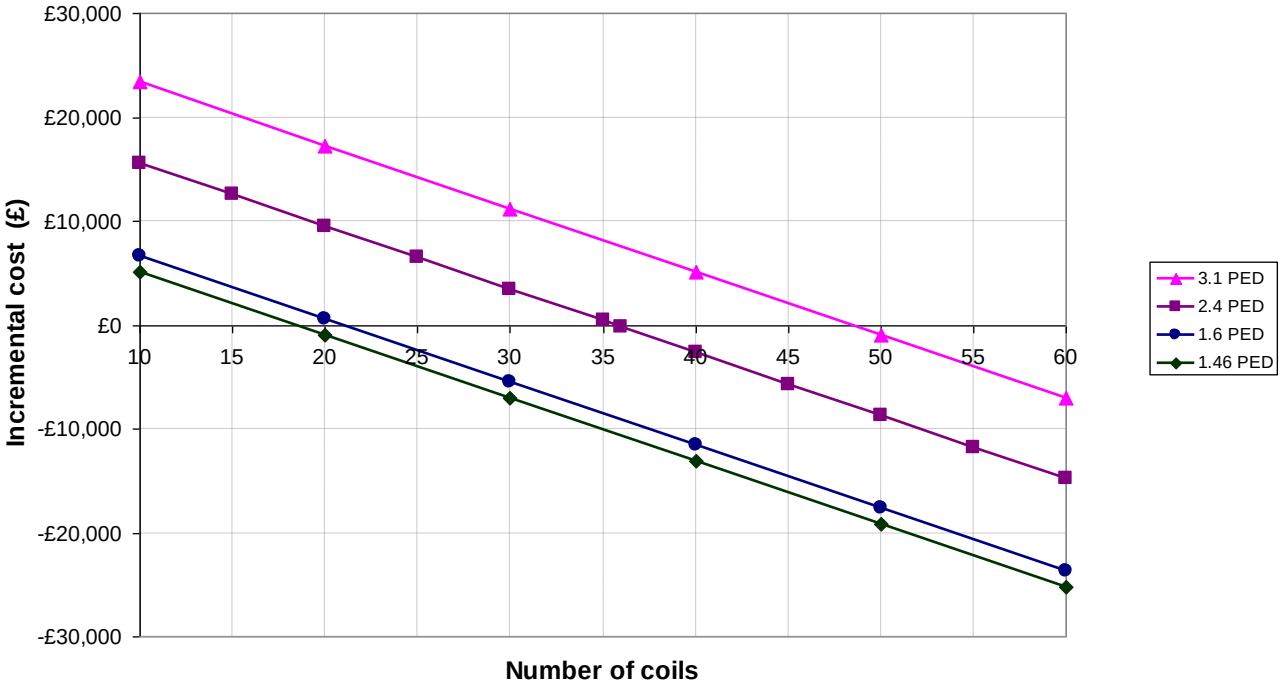
Table 3 - PED vs stent assisted coiling, scenario with PED just cost saving. 1.6 PED, 21 coils

		PED	Stent-assisted coiling	Incremental
(1.6 PEDs, 21 coils)	Equipment costs	£18,254	£16,665	£1,588
	Retreatment costs	£2,211	£3,420	-£1,209
	Total cost	£25,900	£25,920	-£20

Table 4 - PED vs stent assisted coiling, scenario with PED just cost saving. 1.46 PED, 19 coils

		PED	Stent-assisted coiling	Incremental
(1.46 PEDs, 19 coils)	Equipment costs	£16,830	£15,613	£1,216
	Retreatment costs	£2,076	£3,258	-£1,182
	Total cost	£24,341	£24,706	-£365

Figure 1. Incremental cost of PED over Stent-assisted coiling, varying number of PED devices and coils per procedure



Outcomes and adverse events

The outcomes included in the main body of the model, and in all the results presented include:

Procedural mortality

Rupture, post treatment, including fatalities

Retreatment

The acute and long term costs and disutilities for these outcomes are modelled and presented in the results shown. These are considered to be normal outcomes from the treatment, and not adverse events.

In addition to this, the model has an optional additional scenario to show adverse events. These are not included in the results presented except in table B6.31, Manufacturer submission.

The effect of including the adverse events compared with the base case tends to improve the position of conservative management within the list of comparators, and worsens the position of the surgical treatments. This is because there are no procedure related adverse events for conservative management and surgery is relatively risky. Including adverse events does not impact on the position of PED as the most favourable outcome in terms of QALYS.

There are several issues with the adverse events scenario:

Adverse events included are restricted to stroke

Not all of the comparator stroke types are included

Comparator events include fatalities that also contribute to the procedural mortality rate, meaning that these are counted twice.

Long term costs and disutility of stroke are not included in the model

Retreatment costs

The EAC felt that the retreatment method assumed in the model did not always reflect the NICE Scope. For this reason table B6.14 from the manufacturer submission was recalculated as table 5 in the EAC assessment report, which is also reproduced here. The costs in this table are the costs that are incurred for any single patient undergoing retreatment.

Table 5 - adapts Table B6.14 from the manufacturer submission to reflect the model as submitted by the manufacturer, and also updated to reflect the NICE scope.

Initial Treatment	Costs and assumptions in model as submitted		Assumptions in NICE scope, with costs from model (as submitted) to reflect this	
	Cost of retreatment	Assumed retreatment method	Cost of retreatment	Assumed retreatment method
PED	£21,924	PED	£21,924	PED
Stent assisted coiling	£32,240	Stent assisted coiling	£32,240	Stent assisted coiling
Neurosurgical clipping	£32,240	Stent assisted coiling	£8,608	Neurosurgical clipping
Endovascular PVO	£32,240	Stent assisted coiling	£32,240	Stent assisted coiling
Neurosurgical PVO	£8,608	Neurosurgical clipping	£8,608	Neurosurgical clipping
Conservative management	£32,240	Stent assisted coiling	£0	Conservative

The retreatment cost that is presented in the results tables (eg tables 1-4) is this retreatment cost multiplied by the likelihood of requiring retreatment, and then discounted over time and presented as an average cost per patient undergoing the initial treatment.

Calculation of fatal rupture rate

The EAC have found a typographical error in the calculation of fatal ruptures (Worksheet: Effectiveness, Cell D171-173, submitted model). This means that the number of fatal ruptures in 6 months is calculated using the total rupture

rate, rather than the fatal rupture rate. This overestimates the number of fatal ruptures throughout the model.

The effect for total or incremental cost is very small and the correction favours PED for all scenarios.

The effect for QALY and ICER calculation is also small for most scenarios, but the direction of effect varies.

For PED vs Conservative treatment the error has a significant impact on the incremental QALY and ICER. Correction favours conservative treatment.

The results for the model as submitted are shown with the error corrected in table XXX. The results do not include any of the variations in PED or coil numbers, or in retreatment method that have been discussed in the EAC assessment report.

Table 6 Results corrected to give fatal rupture rates

	variation	Total cost		QALY		Incremental costs	Incremental QALYs	ICER
		PED	Comparator	PED	Comparator			
PED vs Stent-assisted coiling	As submitted	£24,341	£37,451	5.506	4.503	-£13,110	1.003	Dominant
	error corrected	£24,384	£37,570	5.572	4.591	-£13,186	0.981	Dominant
PED vs Endovascular PVO	As submitted	£24,341	£16,893	5.506	4.241	£7,448	1.265	£5,887
	error corrected	£24,384	£17,102	5.572	4.385	£7,282	1.187	£6,136
PED vs Neurosurgical clipping	As submitted	£24,341	£11,658	5.506	4.932	£12,684	0.574	£22,079
	error corrected	£24,384	£11,708	5.572	4.986	£12,676	0.585	£21,650
PED vs Neurosurgical PVO	As submitted	£24,341	£11,654	5.506	4.552	£12,687	0.954	£13,297
	error corrected	£24,384	£11,699	5.572	4.666	£12,684	0.906	£14,002

PED vs Conservative	As submitted	£24,341	£10,352	5.506	4.643	£13,989	0.863	£16,202
	error corrected	£24,384	£11,202	5.572	5.106	£13,182	0.466	£28,301

The increased QALY for conservative treatment means that in an incremental analysis conservative treatment is dominant over neurosurgical clipping.

Summary of evidence of clinical benefit

The evidence for clinical effectiveness was based on two primary studies. Nelson et al. (2011) the PITA study is a four centre (Europe and South America) prospective single arm feasibility study of a 180 day duration. The study included 31 wide neck IAs in 31 patients that were unsuitable for treatment with coils. The PUFS study is a currently unpublished study of wide neck large and giant aneurysms. It is a prospective single arm trial in ten centres with up to five year follow up on-going. 108 patients with 110 IAs are included in the study.

In the PITA study the primary outcome measures were death and ipsilateral stroke at 30 days after implantation. Successful device placement was 96.8% in the PITA study at 30 days. Of the 30 patients successfully treated 93.3% had occluded IAs at 180 days on angiography. Two patients had a stroke within 30 days (6.5%).

In the PUFS study the primary endpoint was complete angiographic occlusion of the IA at 180 days without >50% stenosis in the parent artery. The primary safety endpoint was ipsilateral stroke or neurological death occurring within 180 days of the procedure. Successful device placement was 97.7% and the IA occlusion rate in assessed patients was 73.6% at 180 days. The stroke rate

was 5.6% and the rate of neurological death was 5.6%, both determined at 180 days.

The EAC included additional studies in their clinical appraisal of evidence, which were of a lower level of evidence. In addition to the two trials (PITA and PUFS), there were six case series (where n >5) and eight case reports (where n ≤5). None of the studies included were comparative. In three of the six case series only abstracts are available, leading to a scarcity of details such as inclusion / exclusion criteria and are therefore open to the possibility of selection bias. Furthermore, confusion arises due to the potential duplication of numerous patients between reports.

Outcome measures including successful device placement, target aneurysm occlusion, neurological death and ipsilateral stroke and were therefore highly appropriate.

Twelve of the fifteen papers assessed for study outcomes discussed device placement with a high success rate reported overall. Issues regarding placement included:

Diminished blood flow in the parent internal carotid artery (ICA) following device placement. Angioplasty was performed to correct the attenuated flow and the ICA beyond the implant was ruptured leading to ultimate ligation of the carotid artery (Nelson 2011)

Aneurysm could not be crossed the micro guide wire (FDA 2011)

The proximal aspect of the PED was deployed into the aneurysm and was subsequently retrieved and repositioned (Lylyk 2009a)

Two PEDs could not be deployed due to friction in a highly tortuous ICA (Szikora 2010)

Balloon dilation was needed to open the distal section of one device (Szikora 2010)

One device shortened more than expected requiring an additional PED to be placed telescopically (van Rooij 2010)

Since the PITA trial reported by Nelson a new microcatheter (the Marksman catheter) has been developed and approved. This may facilitate device deployment of PED.

Twelve studies discussed occlusion rates with seven of these studies reporting 100% success. The lowest occlusion rate was 69% reported by O'Kelly in his study of 96 patients. The follow up for these patients ranged from 3 – 30 months.

Altered size of aneurysm mass was poorly reported with only one paper giving specific data. In this case a patient developed worsening short term memory three months after PED placement. MRI showed enlargement of the aneurysm with worsening mass effect and extensive vasogenic oedema throughout the left medial temporal lobe. The lateral margin of the aneurysm had become lobulated and irregular. The patient was told to cease clopidogrel and three months later repeat MRI showed some mass resolution (Hampton 2011). Although there are few data directly related to the altered size of aneurysms, this may be reflected in other outcomes such as resolution of symptoms.

Only five papers discussed symptom resolution/improvement with three of these being individual case studies with a complete resolution of symptoms. The PUFS study (FDA 2011) reported symptom improvement in 34% of patients (n=100) while 24 of these subjects were asymptomatic at baseline and follow up. Szikora (2010) reported improvements in 61% of patients (n=18).

Six studies specified stroke rate, three of these being case reports of one or two patients. Three larger studies with 31, 108 and 53 patients specified stroke rates of 6.5%, 5.6% and 0 respectively.

This gives an overall stroke rate of 4.2% over these three studies combined (8 of 192 patients)

Neurovascular death was reported in four studies. Two of these studies had patient number of <10 (Hampton 2011; Hartmann 2011), with both reporting one incidence of neurovascular death. The two larger studies (FDA 2011; O'Kelly 2011) reported respective rates of 5.6% and 4.2%.

Three reports of delayed parent vessel occlusion were identified in the literature by Fiorella (2010) and Klisch (2011) occurring 12 to 23 months post PED placement. Two of these patients subsequently died, the third patient was maintained on aspirin therapy and remains neurologically intact.

Case 1 - Fiorella (2010) reported a single patient who had received dual antiplatelet therapy for six months followed by 150mg of clopidogrel for the following 12 month. Double dose clopidogrel was required due to a poor response at standard doses. Eighteen months post treatment the patient was transferred to aspirin monotherapy. In the 23rd month post treatment blurred vision and diplopia developed which led to the cessation of aspirin with transferral to normal dose clopidogrel. Three weeks later right sided weakness developed, angiography showed complete occlusion of the left vertebral artery. Five months after this episode the patient developed severe dysarthria and progressive right sided hemiparesis. A fatal brainstem infarction subsequently occurred.

Case 2 – Following PED placement, this patient reported by Klisch was maintained on dual antiplatelet therapy for 12 months. Following a 12 month angiogram which found the intra-aneurysmal mass had not significantly reduced in volume, the patient was advised to discontinue clopidogrel. Five

days later, flu-like symptoms and headache developed, an angiogram at this stage found complete occlusion of the aneurysm and basilar trunk artery over the entire reconstructed segment. The patient was managed on aspirin and symptoms were treated with analgesia and corticosteroids. She remains neurologically intact.

Case 3 – The second patient reported by Klisch was maintained on dual antiplatelet therapy for 11 months post treatment at which stage clopidogrel was discontinued. Two weeks later the patient presented with basilar occlusion syndrome. Despite revascularisation the patient had a large posterior circulation infarct and ultimately died.

Four authors reported SAH in their studies with prevalence rates of 5.3% (n=18), 12.5% (n=8) 1% (n=96) and 20% (n=5). (Szikora 2010) (n=18) discussed a single patient who suffered a diffuse SAH with five hours of treatment. Hartmann (2011) reported a SAH and subsequent death due to mass effect in a single patient 72 hours after device placement. A fatal SAH was also reported by Hampton (n=5) in a patient who developed initial post procedure features five days post PED placement. O'Kelly (n=96) reported a single case of delayed aneurysm rupture with no further details.

One device failure was reported in the PUFS study whereby part of the delivery wire broke. The wire fragment was pulled into the proximal parent artery and "sealed" in place with two additional PEDs placed in a normal segment of the proximal ICA.

Summary of Economic Evidence

The economic evidence for pipeline comprised a new economic model comprising a cost analysis and a cost-effectiveness analysis for pipeline compared with stent-assisted coiling, endovascular PVO, neurosurgical clipping, neurosurgical PVO and conservative management.

Model structure

The de novo model takes the form of a decision tree with addition of Markov elements for the longer term outcomes, which are extrapolated from secondary outcomes. The model structure is complex with long term outcomes (rupture and retreatment) being predicted from initial outcomes (in terms of degree of occlusion). The economic evidence submission is from the perspective of the NHS and PSS. The excel model is generally well executed and includes clear identification of the sources for model inputs. An additional scenario is introduced to incorporate adverse events and this is selectable at the start of the model. The base case does not include the costs of adverse events. A second scenario analysis considers short-term outcomes only, by restricting the time horizon of the model to six months.

Costs and benefits

The number of PED devices used in the model (1.46) was taken from data on file at Covidien; however several other sources indicate that this is an underestimate. The PUFS study (FDA 2011) was used for most other clinical data for Pipeline and gave a mean of 3.1 PEDs per patient. The EAC found a mean device use per patient of 2.41 from the studies used in the clinical evidence (Appendix 8 EAC report). Since the majority of the cost of treatment with PED is the cost of the device, this has a highly significant effect on the total treatment cost. Any increase in devices used will result in greatly increased cost of treatment with Pipeline. Sensitivity analysis incorporated a range of 1-3 for the number of PED's. The EAC consider the upper end of the range to be too low, particularly for a key driver of the model.

The number of coils used in the model (40) is taken from a statement in an editorial (Wehman 2006). The EAC consulted 4 clinical advisors, 3 replied and it was widely agreed that this value was too high. The full responses are shown in Appendix 9 of the EAC report. The range of values incorporated in the sensitivity analysis is appropriately broad from 5 to 100 coils.

The costs associated with health states used in the model are given in Table B6.13 of the manufacturer submission. The manufacturer acknowledges (section 6.4.6) that there is an assumption that the cost of rupture, (assumed to result in SAH) is the same as the cost of stroke although this was not listed in the assumptions in section 6.3.8. The EAC considers that data specific for subarachnoid haemorrhage should have been used.

The value for cost of fatal rupture taken from Curtis (2010) and NHS reference costs assumed one ambulance visit and one non-elective in-patient short stay to give an overall cost of £781. A cost for fatal stroke of £7041 is available from the same original source as the costs used for non-fatal stroke (Ward 2007; Youman 2003); it is not clear why this was not used and suggests that the value in the model may be an underestimate. This will have an impact in favour of PED when compared with conservative treatment. The impact is likely to be small in other cases

The costs for non-fatal stroke are indirectly derived from a study on 457 acute stroke patients in the UK (Kalra 2000; Youman 2003). They include a range of mild to moderate strokes, with 8% of non-fatal strokes resulting in discharge to a full time care institution, the majority of the remainder being discharged home. If ruptures resulting in SAH have a less favourable outcome, then the cost will increase.

Any of these costs associated with health states are only likely to have appreciable an impact on the PED vs Conservative model, resulting in a reduced incremental cost for the use of PED.

The costs associated with retreatment are given in Table B6.14 of the manufacturer submission; however the figures used are not those from the submitted model. In addition, some of the assumptions listed in Table B6.14 of the manufacturer submission do not match the scope and in some cases do not describe the model implementation.

The impact of these discrepancies is moderate for conservative management, and low for the other comparators.

The effect of including the adverse events compared with the base case tends to improve the position of conservative management within the list of comparators, and worsens the position of the surgical treatments. This is because there are no procedure related adverse events for conservative management and surgery is relatively risky. Including adverse events does not impact on the position of PED as the most favourable outcome in terms of QALYS and PED remains the most cost-effective option at a willingness to pay threshold of £30,000. As used in the model, it would appear that adverse events are over reported for comparators, however the whole structure of the model regarding adverse events and complications is unsatisfactory, therefore it is difficult for the EAC to judge the full impact.

QoL weights were derived from sources in the literature. The selection of the sources and the derivation of QoL weights was not well researched. The QoL after SAH value was explored in sensitivity analysis across an appropriate range of values with a small impact on the results for PED compared with conservative management, but minimal impact against the other comparators.

Results

The results of the model showed that compared with stent assisted coiling, pipeline was dominant. The key drivers of the model are the number of PEDs and coils used and uncertainty remains around these values. The manufacturer's values of 1.46 PEDs and 40 coils were found to be inappropriate by the EAC who suggested 2.4 PEDs based on evidence from the literature and 25 coils based on the opinion of three NICE expert advisers. This changes the outcome of the model such that PED is no longer cost saving compared with stent assisted coiling. The EAC investigated the impact on the outcome of a number of scenarios and demonstrated cases where PED is cost saving.

The cost-effectiveness analysis demonstrated that PED is the most cost effective alternative at a willingness to pay threshold of £30,000. The EAC found that the methods of retreatment incorporated in the model did not always match the scope given by NICE. The EAC undertook additional work to change the retreatment methods to match the scope. This showed that neurosurgical clipping is the most cost-effective alternative at a willingness to pay threshold of £30,000.

Further analysis presented to the Committee:

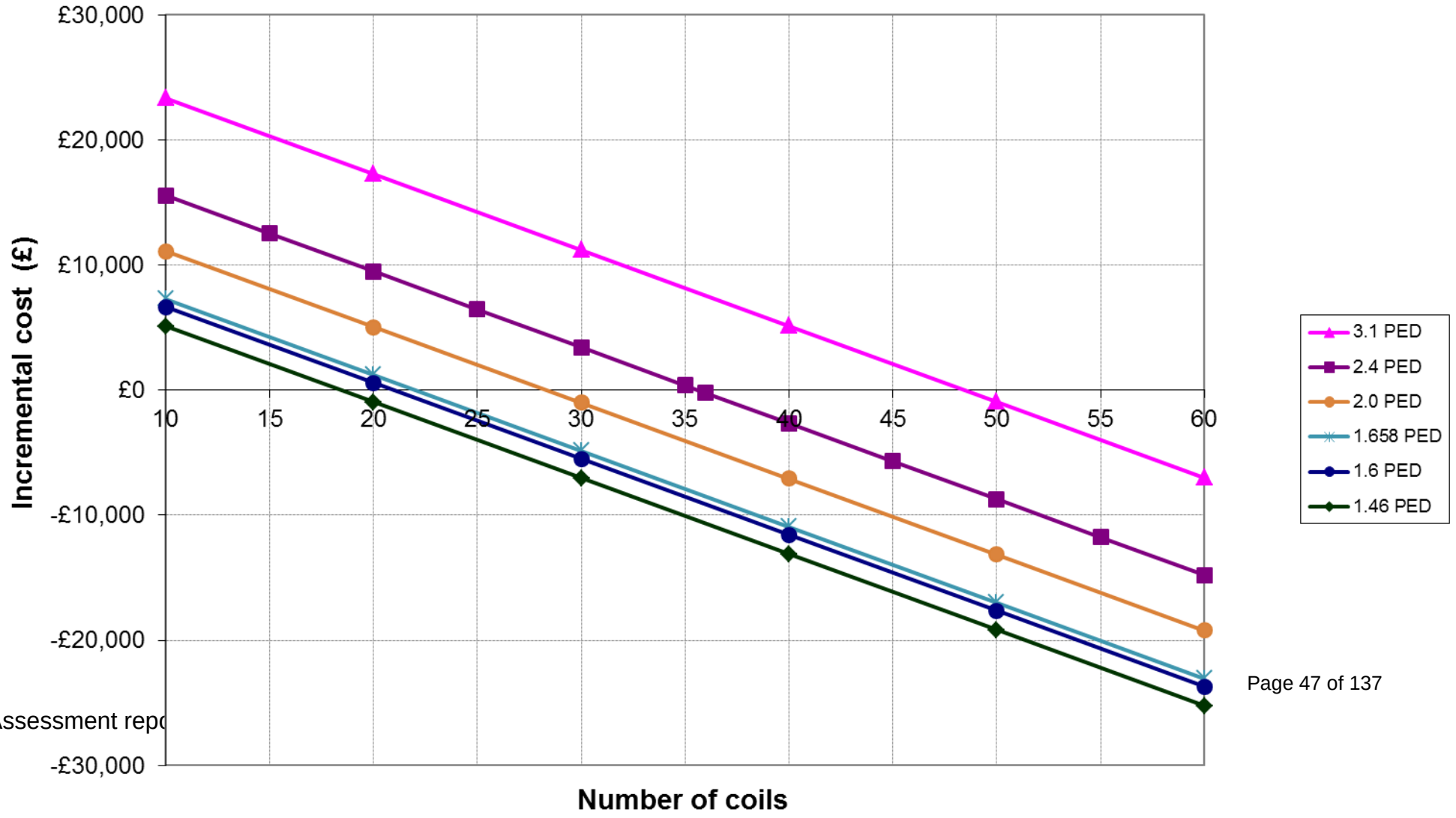
Number used		Total procedure cost		
Pipeline embolisation device	**Coils**	**Pipeline embolisation device**	**Stent-assisted coiling**	**Incremental costs**
1.46	40	£24, 341	£37,451	–£13,110 (base case)
1.46	19	£24, 341	£24,706	–£365
1.6	21	£25,900	£25,920	–£20
1.658	22	£26,546	£26,527	£19
1.658	23	£26,546	£27,134	-£588
2.0	28	£30,354	£30,168	£185
2.0	29	£30,354	£30,775	-£421
2.0	40	£30,354	£37,451	-£7,098
2.4	25	£34,807	£28,348	£6460 (judged by EAC as most appropriate estimate)
2.4	36	£34,807	£35,024	–£216
3.1	49	£42,601	£42,913	–£312

a Negative cost indicates cost saving for Pipeline embolisation device versus stent-assisted coiling.

b One stent used for each intervention.

Tabular format of data presented to MTAC while developing its provisional recommendations on the Pipeline embolisation device. Made available in this format for convenience and clarity.

Figure 1. Incremental cost of PED over Stent-assisted coiling, varying number of PED devices and coils per procedure



Assessment repo

Appendix E: Additional submission information

Pipeline embolisation device for the treatment of complex intracranial aneurysms

The purpose of this table is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the original sponsor submission. This is normally where the External Assessment Centre:

- become aware of additional relevant evidence not submitted by the sponsor
- need to check “real world” assumptions with NICE’s expert advisers, or
- need to ask the sponsor for additional information or data not included in the original submission

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is made available to MTAC. The table is presented to MTAC in the assessment report overview, and is made available at public consultation.

Submission Document Section/ Sub-section number	Question / Request to Manufacturer or Expert Adviser Indicate whether Manufacturer or Expert Adviser was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.	Response Attach additional documents provided in response as Appendices and reference in relevant cells below.	Action / Impact / Other comments
1.6	Expert Adviser: The Manufacturer states that the UK Neuro-Interventional Group is currently running an independent audit of all cases in the UK involving Pipeline. Do you feel that there is any data arising from this audit particularly regarding adverse events which may be relevant to our report? If so, would it be possible for me to access this?	Expert 1: I have not seen any data from the UKNG registry but I would like to ask the president of the UKNG about providing access (as the registry was not set up with this purpose in mind)	Enquiries found that the audit was set up at the request of the MHRA. NICE advised data from this audit not required at this stage of the

<table>
<tr><td>Submission Document Section/ Sub-section number</td><td>Question / Request to Manufacturer or Expert Adviser

Indicate whether Manufacturer or Expert Adviser was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.</td><td>Response

Attach additional documents provided in response as Appendices and reference in relevant cells below.</td><td>Action / Impact / Other comments</td></tr>
<tr><td></td><td></td><td></td><td>process.</td></tr>
<tr><td>Table A1.1</td><td>Expert Adviser: Are items listed below required per procedure or per PED?

<table><tr><td>Consumables (if applicable) Per consumable:</td><td>Marksman catheter (1)</td></tr></table></td><td>Expert 1: The consumables listed are per-case</td><td>General information.</td></tr>
</table>

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	name, frequency: Guidewire (1) Distal Access Catheter (1) Guide Catheter (1)		
2.2	Expert Adviser: In the manufacturers submission, the following assumptions have been made: “We calculate that there are approximately 460–580 patients with unruptured IAs eligible	Expert 2: 2,191 patients in England and Wales are admitted with a primary diagnosis of unruptured IA. That is over 90 patients per annum per English/Welsh	Clarification from NICE that ruptured aneurysms not included the

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	for treatment annually with PED, based on the following assumptions: 2,191 patients in England and Wales are admitted with a primary diagnosis of unruptured IA. PED will be used primarily for large or giant aneurysms, of which the prevalence is approximately 21.0–26.5%. (ISUIA Cohort Study)E	INR centre. That sound high. They may deal with that many UIAs per annum by letter/image review/clinic review but nowhere near that many are admitted for Rx per annum PED will be used primarily for large or giant aneurysms, of which the prevalence is approximately 21.0-26.5%. (ISUIA Cohort Study) That cohort is probably unrepresntative of current practice where increasingly UIA are found incidentally on MRI (mostly small, nowhere near 25%	scope

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	All patients with large or giant aneurysms require interventional treatment. All large and giant aneurysms have wide necks and/or are fusiform. In practice, approximately 80% of PED cases will involve unruptured IAs, and 20% ruptured IAs (based on expert opinion); therefore the total number of patients eligible for treatment annually in England and Wales is estimated	large/giant)or as a result of screening or additional to a ruptured aneurysm (again mostly small or medium) All patients with large or giant aneurysms require interventional treatment. -Some will not be treated due to age/co-morbidity. -Parent vessel occlusion will remain a real choice for some patients as proven and relatively safe if pass occlusion testing	

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	at 575–725." What are your opinions on the assumptions regarding the 20% which has been added for the ruptured IA's and is this a realistic estimate?	-Surgical bypass will be required in a small % of cases & other surgical approaches may be appropriate in some cases due to anatomy & location of aneurysm -In 10-15mm size range, stent assisted coiling often still a good option All large and giant aneurysms have wide necks	

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		and/or are fusiform. Not all, though most. In practice, approximately 80% of PED cases will involve unruptured IAs, and 20% ruptured IAs (based on expert opinion); therefore the total number of patients eligible for treatment annually in England and Wales is estimated at 575-725. -Difficult at this stage in learning curve with PED to know that for UK.	

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		-Personally I suspect the true figure based on current knowledge/practice regarding PED indications/use is likely to be half that eligible - 250-350. Certainly only a fraction of that use is occurring at present!! -However, if PED use takes off in retreatment of previously coiled aneurysms that are large/giant then the use of PED would be augmented I am able to verify the number of patients with a primary diagnosis of unruptured IA in England and Wales and have access to the data from the ISUIA	

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		study estimating 21 - 26.5% of these are large or giant. I would however, be interested in your opinions on the assumptions regarding the 20% which has been added for the ruptured IA's and whether this is a realistic estimate. -Excessively high I think, for reasons given, mainly as assumes all Rx = PED. For some considerable time - pending RCT evidence in particular- treatment of large/giant aneurysms won't be so FD weighted, especially with ongoing safety concerns.	

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		Expert 3: Figures seem high for total numbers of unruptured aneurysms treated (more like 50 per annum in a larger centre). Figures for de novo large aneurysms are also high and not all of these will be treated. 575-725 potentially eligible patients is a very high figure. Large aneurysms 10-15mm in size would still be treated with coiling with or without stent assistance in the majority of cases unless flow diversion is shown to be	

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		as safe, efficacious and cost effective. I would estimate figures at around 200-300 maximum that may be eligible and this would included re-treatments. Small recurrences after coiling may not be treated due to risk of procedure and low risk of haemorrhage. Expert 4: I feel that the data re number of eligible patients is high. Although the referenced studies	

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		suggest 20 – 26% of unruptured IA patients will have large or giant aneurysms, due to the good safety profile of coiling treatment and unknown issues re safety with pipeline, at this stage he feels only about 5 – 10% of total large giant unruptured aneurysm patients will be considered for treatment with pipeline.	
2.2	Expert Adviser: Would it be possible to provide an idea of a typical patient pathway (if indeed there is one)?	Expert 3: As regards pathways, none exist in reality. In most INR centres, cases will be discussed with neurosurgical colleagues and often our peers as well for complex cases.	No action required

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General	Expert Adviser: In your opinion are the adverse events / complications in patients treated with Pipeline reported in the literature are acceptable in this patient population. (See table 1 below) I would be particularly interested to know your thoughts on the three patients with late	Expert 2: There are 2 distinct groups of complications/adverse events to consider: Category 1) Serious but expected AEs (at a certain rate &/or in a certain time frame) even if incident rate is very low Category 2) Serious but unexpected (type or timing)	Comments required to interpret clinical evidence in clinical.

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	thrombosis occurring shortly after cessation of anti-platelet therapy reported in the papers by Fiorella (2010) and Klisch (2011)	AEs It is any events in category 2 &/or a perceived excess of category 1 events that concern people about FDs. In the papers you listed my opinion largely coincides with that of the authors and is as follows:	

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		Fiorella: Both were very late stent thrombosis events not related to antiplatelet medication = Category 2 (serious & unexpected adverese events) Hampton: cases 1 & 3 expected complication but at a higher rate than expected. Case 2 falls into unexpected serious AE (delayed bleed post coiling of unruptured aneurysm)	

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		Hartmann: case 1 is probably best classed as an UNEXPETCED serious AE (unexplained haemorrhage remote from target aneurysm). Case 2 is probbaly expected serious AE Hauck: EXPECTED SAE	

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		Klisch: case 1 EXPECTED SAE (early thrombosis after stopping antiplatelet) but case 2 is more delayed thrombosis after stopping antiplatelet & I would regard as UNEXPECTED SAE Lylyk: all expected SAE Nelson: all EXPECTED SAE O'Kelly: both UNEXPECTED SAE	

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		Phillips: both EXPECTED SAE PUFS: 2 UNEXPECTED SAE (2%) - unexplained haemorrhage in unrutptured aneurysms, 1 uncategorised and 3% symptomatic stroke rate (acceptable but towards high end of recent literature) Szikora: all explained	

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		So quite a few category 2 events and a suggestion of more often than expected category 1 events. Also Lylyk/Nelson/Szikora all have significant links to Chestnut Medical now taken over by eV3. If you look at it without their studies it looks more worrying still Expert 3: A lot of the US patients had aneurysms with a very poor prognosis left untreated. They were also	

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		by and large, patients for whom other treatment was not deemed possible or had very high morbidity/mortality attached. So they are a select and unusual patient population from a wide geographic area in the US. These aneurysms are thankfully rare. Late occlusions occurred in large aneurysms with multiple devices. Occlusions have been reported with other devices including SILK, Onyx (when this was used more commonly for large aneurysms- now fallen	

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		out of favour), and even standard stent-assisted coiling. So, for the population, this is probably not unusual. Most patients will remain on lifelong aspirin after treatment.	
2.2	Expert Adviser: The manufacturers of Pipeline make the following assumptions in the submission: All patients with large or giant aneurysms	Expert 2: All patients with large or giant aneurysms require interventional treatment.	Comments support data regarding potential patient

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	require interventional treatment All large and giant aneurysms have wide necks and/or are fusiform Are these fair assumptions?	-Some will not be treated due to age/co-morbidity. -Parent vessel occlusion will remain a real choice for some patients as proven and relatively safe if pass occlusion testing -Surgical bypass will be required in a small % of cases & other surgical approaches may be appropriate in some cases due to anatomy &	numbers assumptions made in EAC report. No action required.

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		location of aneurysm -In 10-15mm size range, stent assisted coiling often still a good option All large and giant aneurysms have wide necks and/or are fusiform. Not all, though most. Expert 3: These are firm assumptions.	

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		The decision to treat an aneurysm depends on the patient harbouring it (some are elderly, have other health problems that are more important etc - i.e. short life expectancy, or poor quality of life), the risks of treatment and the wishes of the patient. So no all of these aneurysms require treatment. It is generally true that large aneurysms have large necks but this does not mean the Pipeline is the only suitable treatment. Fusiform aneurysms are rare - we	

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		see perhaps 2 to 3 a year. The exception is that most cavernous aneurysms have no definable neck and can be very large, but often these do not require treatment and if they do then parent vessel occlusion can be very effective in selected cases. So - perhaps the majority of patient with large or giant aneurysms will be considered for treatment.	

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		Pipeline offers an alternative to coils or stent and coils and it will be helpful to have this available to suitably trained individuals. Most large aneurysms have large necks but this does not preclude successful treatment with existing devices. Expert 4: In respect of the questions below. The simple answer is No and No. These are assertions	

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		which are far too generalised. Question 1: Some may need surgery, some may not be treated e.g. Cavernous aneurysms, Age and co morbidity may make it inappropriate. Qu2: No: some have narrow necks, many large aneurysm can be treated by coiling, sometimes surgery. Giant aneurysm are relatively rare.	

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		Expert 1: Agree with comments from Experts 3 and 4	
Tables B6.11 and B6.29	Expert Adviser: One of the tables in the economic submission has been partly reproduced below. We are currently searching the literature to verify these data but are trying to establish the number of PEDs and coils used in an average treatment. Our data is suggesting an average number of PEDs at approximately 2.4 per patient, and	Expert 2: Highly selective data! Limited experience at my centre with PED but that has been that usually 2+ PEDs required. Coils used - since starting to coil in 1997 I've never put 40 coils in an aneurysm at one sitting and even with retreatments <10 patients I've treated have	Comments support costings made in economic model. No action required.

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	while we would be interested in your opinions on this figure, we would be especially interested in your thoughts on the estimated number of coils. (See Table 2 below)	received >40 coils total (after 2-3 procedures). To some extent eV3 may be assuming that only small diameter coils (10 one thousandths of an inch) are used to get to that figure; whereas most people will use larger diameter coils (18/14) at first in very large/giant aneurysms. Some also use coils that swell up to fill space & may use less as a result.	

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		Even for giant aneurysms 40 coils is borderline high. These are often treated by PVO or surgery where anatomy allows - need far less coils than that. Most PED use would not be in giant saccular aneurysms as uncommon. Coiling (+/- stent) probably not regarded by most INRs as a good option for truly giant aneurysms. Most relevant comparison for coil use would be in 15-25mm aneurysms. Here stent + coil is used relatively	

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		more commonly as first choice Rx - median coil used might be nearer 20-25 versus with 1 stent or balloon versus 2 PED. The latter is considerbaly more expensive. Marksman microcatheter needed for PED also costs 2.5x as much as standard microcatheter cost. I don't accept that anything like 50% of patients undergoing stent assisted coiling require a BOT. In	

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		the group we've done PED in we've done BOT first in most though - i.e. the opposite to the company suggestion. Either to confirm unsuitable for PVO so PED only option, or as a precaution in case any major problems experienced using a new device with limited experience. In my centre BOT pre neurosurgery is very uncommon.	

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		Expert 3:. I would just echo Expert 2's comments. Some interventionists are using PED for recurrent aneurysms where re-coiling or stent-assisted coiling will be potentially more cost effective. Balloon occlusion test is used much more selectively than suggested/assumed in the table.	

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		'Average' aneurysm will take 4-5 coils Medium aneurysms will require c 10-15 coils. Large aneurysms 15-35 or very occasionally more. Stents cost from £1,800-2,300 Expert 4: 40 coils is very excessive.	

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Table B6.12	Expert Adviser: Regarding the cost of coils for the economic assessment. So far we have been unable to determine any cost details and wondered if you would be able to assist in any way, or suggest where we can find this data.	Expert 2: Coil costs depend on: Type; Size; Length Plus any individual centre negotiation around volume usage and unit cost!! There is no single answer! Cheapest controlled detach coils in UK around 325 per coil (but not a commonly used coil), up to 995 for most expensive (hydrocoils - but these swell up potentially to 12 times	Comments support assumptions made in economic model. No action required.

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		the size of a similar length Platinum 10 coil). Pt18 coils occupy twice the volume in aneurysm per cm than 10 coils. 14 coils occupy 150% of volume of a 10 coil. Some coils are very long and so on ..... vERY SOFT FINISHING COILS USUALLY MORE EXPENSIVE THAN STANDARD FILLING COILS - SAY 425-550 each Framing coils more expensive than filling coils - say	

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		450-650 Any individual operator may treat an aneurysm with differing proportions of framing/filling/finishing coils and use coils of different manufacturers so that a common coiling cost cannot sensibly be derived.	

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		Best estimate might be to take a best guess median coil value but it won't be very accurate. If I had to pick one it would be somewhere around 500-550 median coil cost. Number of coils used per aneurysm of a certain size is extremely user dependent relating to coil mix and technical approach adopted. There is no simple answer	

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		Expert 3: Costing should be possible. Average number of coils per aneurysm overall is 4.5 Coils cost between £350- £500. Trusts tend to negotiate separately for price depending on usage etc. Microcatheters are c£ 200-250 Wires £150	
	Manufacturer: Can we get access to the	Thank you very much for your Email. I make sure that	Document

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	unpublished document refered to on page three which discusses costs of PED. While you state that this data is not used in the submission, it would be helpful for us to have it so we can comment appropriately.	you will receive the document. Markus	received
	Would it be possible to clarify what the “MDR Date Due” refers to on this table please as I am unclear whether this is related to the incident or the investigation.	No response	

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	Manufacturer: I haven't been able to locate reference 13 from the pipeline economic submission. Hopkins et al (2006) Endovascular treatment of giant aneurysms. Neurosurgery 59 (5; November supplement). I have checked this journal supplement and it's not there. There are some papers in	Attached you will find the piece of evidence that you inquired. Markus	Information received

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	Neurosurgery that include Hopkins in the list of authors. I need to identify the correct paper as it's given as the source for the number of coils used in giant aneurysms, which is important in the model. Can you check and give me the correct reference?		

Table 1

Study	
Fiorella (2010) [redacted]	Adverse Event / Complication
Hampton (2010) [redacted]	Patient 1 Post procedural, perforator territory (pontine) infarct Patient 2 Worsening headache developed 5 days post procedure Partial thrombosis of the aneurysm found on repeat CTA Subsequent aneurysm rupture with aubarachnoid and intraventricular hemorrhage Death Patient 3 Worsening short term memory 3 months post procedure Interval enlargement of the aneurysm
Hartmann (2010) [redacted]	Patient 1 Ipsilaterlal parenchymal hemorrhage within 24 hours of treatment (remote from targeted aneurysm) Patient 2 Patient death due to mass effect and SAH from treated giant basilar aneurysm after 72 hours.
Hauck (2010) * [redacted]	Patient 1 Subarachnoid haemorrhage Temporary hydrocephalus Slight weakness of the right hand
Klisch (2011) [redacted]	Patient 1 12 months post treatment (5 days after cessation of antiplatelet therapy) Flu-like symptoms Progressive headache Complete occlusion of the aneurysm and basilar artery trunk over the entire reconstructed segment.

Study	
	Patient 2 12 months post treatment (2 weeks after cessation of antiplatelet therapy) Basilar occlusion syndrome consisting of tetraparesis progressing to coma Complete occlusion of the sital right vertebral artery at the level of the construct. Complete occlusion of the entire reconstructed segment of the basilar artery. Large posterior circulation infarction Death
Lylyk (2009) *** [redacted]	3 patients developed temporary headache and exacerbation of their cranial nerve palsies 3 patients with mild non symptomatic in-stent stenosis 2 patients with moderate non symptomatic in-stent stenosis 2 patients with severe non symptomatic in-stent stenosis
Nelson (2011) [redacted]	Patient 1 Unsuccessful PED placement – diminished flow in parent ICA following PED deployment. During angioplasty to correct attenuated flow, the ICA beyond the implant ruptured. Carotid artery ultimately ligated. Patient 2 Iatrogenic rupture of the distal ICA with large left hemisphere stroke Patient 3 Periprocedural stroke manifest as right sided hemiparesis and motor aphasia Patient 4 Mild asymptomatic stenosis
O'Kelly (2011) [redacted]	Patient 1 Delayed aneurysm rupture Patients 2,3 and 4 Distal territory hemorrhage

Study	
Phillips (2010) [redacted]	Patient 1 Post operative transient ischaemic event (resolved completely) Patient 2 Post operative seizures
Szikora (2010) ** [redacted]	Patient 1 Mild postprocedural hemiparesis lasting 2 days (thought to be due to contrast overload) Patient 2 Embolic occlusion of a retinal artery branch resulting in a small visual field deficit Patient 3 Acute intraprocedural in-stent thrombosis within the ICA leading to transient hemiparesis (this patient found to have been non-compliant with antiplatelet medication) Patient 4 Death due to diffuse SAH within 5 hours of procedure. (Autopsy showed rupture of a small coexisting bifurcation aneurysm).
Van Rooij (2010) [redacted]	Patient 1 Apathetic and hemiparetic on right side Infarction in the left basal ganglia; occlusion of perforator arteries
*This patient was also included in the PUFS study ** Nine of these patients also enrolled in the PITA study *** Six of these patients also enrolled in the PITA study	

Table 2

	PED	Stent-assisted coiling	Neurosurgical clipping	Endovascular PVO	Neurosurgical PVO	Conservative Management	Reference
Procedure time (hours)							
Equipment/ consumables							
PED	1.46	0	0	0	0	0	Data on file (Covidien).
Marksman catheter	1	2	0	1	0	0	One per procedure (other than neurosurgical clipping and neurosurgical PVO), although stent-assisted coiling also requires additional microcatheter.
Guidewire	1	1	0	1	1	0	One per procedure (other than neurosurgical clipping).
Distal access catheter	1	0	0	0	0	0	Assumed one use for PED.
Guide catheter	1	1	0	1	1	0	One per procedure (other than neurosurgical clipping)
Coil	0	40a	0	6b	0	0	aHopkins et al. (2006). bPersonal communication (Covidien).
Stent	0	1.00	0	0	0	0	Assumes one stent for stent-assisted coiling.
Clip	0	0	5	0	2	0	Assumed five clips for neurosurgical clipping and two for neurosurgical PVO.
Balloon	0	0.5	0	0	0	0	Assumes that 50% of patients receiving stent-assisted coiling require a balloon.
Balloon test	0	0	0	1	1	0	Assumed all patients undergoing endovascular and neurosurgical PVO require one balloon

							test.
Endovascular equip (per hour)	0.00	2.29	0.00	0.00	0.00	0.00	Based on procedure time (above)
Neurosurgical equip (per hour)	0.00	0.00	3.56	0.00	0.00	0.00	Based on procedure time (above)

Appendix F: Sponsor's factual check of the assessment report and the External Assessment Centre's responses

Issue 1

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC Response
Section 1.2, p7: the EAC report describes that the manufacturer state that two studies have been included in quantitative synthesis (meta-analysis). This is an error in Figure B5.1 in the original submission. The main text in the submission document clearly states that two studies have been used for	Remove references to manufacturer having proposed a meta-analysis throughout document.	As the sponsor's submission describes, a meta-analysis has not been conducted, nor was it ever the intention of Covidien to meta-analyse the results of PITA and PUFS (most importantly because the trials enrol different patient populations). The actual analysis of these trials in a quantitative assessment is described clearly, and in Section 5.6, Covidien clearly state	Amendment accepted

the quantitative assessment (not a meta-analysis). Furthermore, this is clearly stated later in Section 5.6.		that meta-analysis is not applicable.	

Issue 2

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC Response
Section 1.2, p7: the report states that the PITA study was in patients with wide necked IAs unsuitable for treatment with coils.	The PITA study was in patients with wide-necked IAs or who had failed previous attempts at treatment.	Inclusion criteria of the PITA study (see Table B5.5 in sponsor's submission).	Amendment accepted

Issue 3

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC Response

Section 1.2, p7: the report states that the main studies have not been correctly identified throughout the submission document.	Deletion of this statement.	PITA and PUFS naming was used for clarity within the submission document, and have been referenced appropriately in Table B5.2. The EAC report itself refers to the studies by their acronyms in numerous places, as in these specific cases it is clearer and more appropriate to do so.	Amendment accepted

Issue 4

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC Response
Section 1.2, p8: the report states 'Nelson (2011) also reported high complete aneurysm occlusion rates of 93.3% in the	Addition of 'at 180 days' as follows: 'Nelson (2011) also reported high complete aneurysm occlusion rates of 93.3% at 180 days	Scientific accuracy of statement. The mechanism of action of PED is not to occlude intracranial aneurysms	Amendment accepted

PITA study'.	in the PITA study'.	acutely (after which reopening could occur) but rather to occlude an aneurysm chronically. Additionally, occlusion rates are known to increase with time, therefore the time frame is important to include.	

Issue 5

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC Response
Section 1.2, p8: the EAC report states that 'Both the PITA and PUFS studies achieved the hypothesis objectives of their respective studies reporting	Both the PITA and PUFS studies achieved the primary objectives of their respective studies.	PITA had no formal hypothesis testing because it was a feasibility study.	Amendment accepted

incidences of death and ipsilateral stroke at 6.5% and 5.6% respectively against targets of 10% or less at 30 days (PITA) and 20% or less at 180 days (PUFS)'. This is not accurate as PITA had no hypothesis because it was a feasibility study.			

Issue 6

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC Response
Section 1.4, p9: EAC identified Matouk (2010) as inappropriate and excluded it from the clinical	This study was excluded because it presents data on ruptured aneurysms. It should be made clear here that	The inclusion of Matouk (2010) was not the sponsor's error and the clarification of scope to exclude	Accept amendment but would like to note that the EAC contacted the author prior to clarification

evidence section.	exclusion of ruptured IAs (outside the scope of the submission) was confirmed after the sponsor's document was submitted (and therefore it was not an error in the original submission).	ruptured IAs should not affect the reader's interpretation of the robustness of the submitted evidence.	of removal of unruptured aneurysms from the scope. The author advised that the aneurysms included were small so therefore outside of the scope anyway.

Issue 7

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC Response
Section 1.4, p9: the report states that the four further studies identified were found due to an adapted literature search and more inclusive study selection criteria. One of	Change to state that an additional three studies have been identified after the date of the sponsor's literature search (conducted in early June 2011), However, despite this, the large case series (O'Kelly 2011), which	These studies were not identified because they were not available at the time of the sponsor's literature search, with the exception of Fiorella 2009. All	Changed to: Using an adapted literature search and more inclusive study selection criteria the EAC identified an additional manuscript: a case report not identified by the manufacturer.

these studies is a large case series.	describes the Canadian experience with the device was, in part, already identified in Table B5.3. There was a single manuscript that was not identified, which was a case report (n=1).	the publications are from congresses held in June 2011; the literature search was conducted at the beginning of June 2011. This should not be described as resulting from an adapted literature search and/or more inclusive study selection criteria. The Canadian experience (O'Kelly 2011) was identified in the sponsor's submission, described as 'Canadian special access patients' in Table B5.3.	Additionally, three studies were identified which were not available at the time of the sponsor's literature search Three of these additional studies are full length manuscripts from peer reviewed journals, another is a conference abstract discussing a large case series. No reference was made to the O'Kelly abstract in the Manufacturers submission.

Issue 8

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC Response
Section 1.4, p9: None of the studies included were comparative.	Add clarification in the main commentary of the report the reasons why comparative, high-quality studies were not practical or feasible during the development of PED.	The commentary on the robustness of the data should include the reasons for the lack of high-quality comparator studies (which are explained clearly within Section 5.2.3 of the sponsor's submission document). The EAC report acknowledges this in the summary on p70; however should be included up-front as well.	Agree: amended to "None of the studies included were comparative, as due to the nature of this disease, comparative studies are generally inappropriate."

Issue 9

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC Response
Section 1.4.2, p10 (weakness of clinical evidence): the report states that there was inadequate identification of studies chosen for data extraction via the literature search. This is stated again in Section 4.1.2, p20 of the report.	Deletion of comment, and removal of the term 'inadequate identification of studies' throughout the document.	The studies identified for data extraction were adequate - only one case report was not identified (n=1), see Issue 7. All the studies were clearly identified in Section 5.2.3 of the sponsor's submission.	Have amended this particular sentence to: "Relevant case report not identified via the literature search" Generally the EAC feels that the studies omitted from data extraction provided useful pertinent data relevant to the decision problem and should have been included. The studies are referenced in section 5.2.3, however, large amounts of

			data have been excluded from this table.

Issue 10

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC Response
Section 1.4.2, p10 (weaknesses of clinical evidence): the report states that there was inadequate data extraction from most of the identified studies. This is referenced to throughout the report.	Remove references to 'inadequate data extraction', and rephrase to inform the reader that the data was not extracted due to the poor quality of the data.	There were several concerns over the quality of the data within the 11 case reports/case series identified which led to the exclusion of these in the sponsors report. This was clearly stated in Section 5.2.4 of the submission. These concerns are also stated on p34 of the EAC report. Moreover, the	The EAC feels that the studies omitted from data extraction provide useful pertinent data relevant to the decision problem and should have been included in a more thorough data extraction, but concedes that this may be rephrased to allow for the manufacturers concerns re quality. Now reads: The

		report criticises the sponsor's assessment for not extracting AE data from these papers; however, critical information concerns the rates of events: rates cannot be assessed from case reports.	manufacturer excluded the remaining eleven studies from the data extraction process due to concerns regarding their quality. However, the EAC feel that data extraction from these studies provides important information relevant to the scope of the submission. Section 4.2.2 has been amended to: The remaining studies would have benefitted from a more in-depth data extraction process to utilise

			useful data within them. Elsewhere “Inadequate data” has been changed to “Incomplete data”

Issue 11

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC Response
Section 1.4.2, p10 (weaknesses of clinical evidence): the report states that there was absence of AE data from MAUDE and the manufacturer.	Delete sentence, and future references.	Although these were not available in the submission, they were readily provided upon request. The initial absence of AE data should not be considered as a weakness, as it was readily provided by the sponsor upon request for consideration.	The EAC feel that information on adverse events is relevant to the decision problem and should be included. Have updated to acknowledge the cooperation of the manufacturer. Amended to: “Absence of adverse event

		Moreover, although MAUDE data are of interest, they cannot be used to estimate rates of events (requested in the NICE template) as denominators are not calculated.	data from sources including MAUDE and the manufacturer (data from the manufacturer was readily supplied on request)"

Issue 12

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC Response
In Section 1.5, p11, the EAC report states that 'A lack of high quality studies means that there is a reliance on data from two relatively small trials and a variety of small case	Because RCTs were not appropriate, there is reliance on data from two trials, and a variety of low quality small case series/reports. It should be noted that PITA was run in compliance with ISO14155 and was	The Submission document clearly states in Section 5.2.3 why a comparative study was not appropriate and details the numerous reasons why a concurrent	Agree that the trial size is relative. Have amended to: "As randomised controlled trials (RCTs) were not appropriate, there is reliance on data from two trials, and a variety of low

series/reports'. We disagree that PITA and PUFS were relatively small, given the size of the target population.	fully monitored and source verified. PUFS was run in compliance with US Investigational Device Exemption regulations and was fully monitored and source verified. The quality of these studies is far superior to that of other published cohorts.	control group was not practical or feasible. The PUFS trial was a PMA study and therefore required substantial follow-up and auditing, and was rigorous. Furthermore, the sample size in PUFS is equivalent to roughly a third of all UK patients with large/giant aneurysms anticipated to be treated annually.	quality small case series/reports."

Issue 13

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC Response

Section 2.1, p13: the report states that discussion with clinical experts suggested that the sponsor's estimate of the patient population was 575–725. The EAC also implies that Welsh patient data was omitted, but it is not clear if this is only initially or in the final estimate as well.	Revise statement to: The sponsor suggested an estimated figure of 460–580 patients. Clarify if Welsh numbers are included in EAC estimate.	The clinical experts only advised on the ratio of patients who had ruptured vs. unruptured IAs who were likely to be treated with IA in clinical practice. Within Section 2.2 of the sponsor's submission it clearly states that the estimate of patients with unruptured IAs is 460-580 patients – which was based on HES data as described in the EAC report. The NICE template specifies that the patient number should include patients eligible	Figure changed to 460-580 patients to reflect unruptured aneurysms only. Only English figures included as requested by NICE

		for treatment in Wales as well as England.	

Issue 14

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC Response
Section 2.2, p14: states that 'no disadvantages of PED in comparison to other treatment options have been identified'. This is not the case, and furthermore was not requested in this section of the NICE template.	Delete comment.	The NICE template requests any issues relating to current clinical practice (Section 2.5) and main comparators (Section 2.6). These were clearly described and explained in detail in the sponsor's submission, as has been commented on as a strength in Section 1.4.1, p10 of the EAC report. The	Amendment accepted

		disadvantages of PED are adequately described in the AE section of the sponsor's submission.	

Issue 15

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC Response
Section 4.1, p16: states that no reasons have been provided for inclusion/exclusion of studies.	Delete sentence.	Inclusion/exclusion criteria were described in Table B5.1 of the sponsor's submission.	The numbers of studies excluded at each stage has been identified but not reasons for exclusion. Amended to: "In figure B5.1 a flow diagram illustrated the number

			of studies included and excluded at each stage, however not all steps in the study selection were clear”

Issue 16

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC Response
In Section 4.1.1, p17, the EAC states ‘SURE identified an error in the manufacturers’ search of the Cochrane library in line #21, with an incorrect space between Intracranial Treatment and the inverted comma following this. It is	Delete comment as this minor syntactical error does not affect the search results.	The search strategy was copied directly from the search history, so “intracranial treatment “ is what was entered into the search engine. This is a minor syntactical error: the results of searching with or without the	Amendment accepted

unclear if this is an error in the report or in the search performed'.		space were and are the same in terms of final effect – the search engine is tolerant of this and returns the same results whether the space is included or not.	

Issue 17

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC Response
In Section 4.1.1, p18, the EAC states they identified several studies where aneurysm was spelt 'aneurism'. An initial search identified a small but not insignificant number of papers with this	Delete comment.	Adding 'aneurism' makes sense and increases the sensitivity of the search, but only when used as a textword. The EAC have added 'intracranial aneurism/' as a MeSH term: this is not a MeSH term. The EAC	Thank you. intracranial aneurism/' was not used as a MeSH term – this was an typographical error This term increases sensitivity. Have amended to: "An

spelling and so amendments were made to the search strategy to incorporate both spellings.		have added other search terms and tweaked the proximity and Boolean combinations of some search lines. This has increased the sensitivity of the search and yielded more records: there are always opportunities to enhance sensitivity in any search strategy, if there are the resources available to deal with the reduced precision (increased number of records to process). The EAC searched resources in addition to those specified by NICE	initial search identified a small but not insignificant number of papers with this spelling and so amendments were made to the search strategy to incorporate both spellings; this alternative spelling identified an additional relevant study.”

		– inevitably they have found more records to assess for relevance. Again it is always possible to search additional information resources, if resources are available to deal with the increased number of records to process. The key question in any search is, did the extra effort find additional relevant studies?	

Issue 18

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC Response
Section 4.1.2, p21: the EAC report it states	Change to the Fiorella (2009b) reference	Incorrect Fiorella 2009 full citation –	Thank you Amendment

that Fiorella 2009a [Curative reconstruction of a giant midbasilar…] was omitted from the identified studies. The incorrect citation has been supplied here.	[Reconstruction of the right anterior circulation…]	Fiorella 2009a was included in the sponsor's selection, but not Fiorella 2009b.	made

Issue 19

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC Response
Section 4.1.2, p22, Table 1: it states that the PITA study included a 2-year follow up – this is not correct.	Delete '2 year follow-up' from Table 1 in PITA row	A 2-year follow up for PITA was performed; however this was not part of the PITA study design.	Amendment accepted

Issue 20

Description of factual inaccuracy	Description of proposed	Justification for amendment	EAC Response

	amendment		
Section 4.1.3 p26: regarding the quality assessment of the 11 case studies/series.	Change to: the remaining studies were not considered robust enough to include and were therefore were not quality assessed.	Upon writing the submission the studies were assessed for inclusion, and the 11 cases studies/series were not considered to contain a robust enough evaluation, in terms of design and execution, to be included in the main body of supporting evidence – this is clearly stated in Section 5.2.4 of the sponsor's submission document and were excluded from further discussion. These concerns are also stated on p34 of the EAC	Amended to: "The manufacturer felt that the remaining studies were not robust enough to include in data extraction and therefore they were not quality assessed"

		report. The NICE template requests that each study that meets the criteria for inclusion is critically appraised – this was indeed carried out for the two studies that the sponsor considered robust enough for quantitative assessment and inclusion.	

Issue 21

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC Response
Section 4.1.4, p27: Reporting of unsuccessful device deployment in	It should be noted in the EAC document that a new microcatheter has been	This risk was identified by the sponsor and addressed appropriately by	The EAC is unable to determine if this issue has been addressed by

PITA (Nelson 2011).	developed and approved since the PITA trial – the Marksman catheter – which addresses this issue. PED successful deployment rates with the Marksman catheter are improved compared with prior commercially available catheters. Marksman catheter is now very commonly used to deliver PED.	the development of a new microcatheter. The microcatheter is now approved for use in both the EU and USA. This is noted in Table B5.14 of the sponsor's submission: 'the problems with PEDs, resulting in non-deployment in 13% of cases in PITA, were identified and resolved before PEDs were used subsequently'.	the development of the Marksman. Has been amended to: "Since the PITA trial reported by Nelson a new microcatheter (the Marksman catheter) has been developed and approved. This may facilitate device deployment of PED."

Issue 22

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC Response
Section 4.1.4, p28: the EAC report states	Change to: 51% of patients with symptoms at	The change of neurological symptoms	Amended to reflect number of patients

that PUFS (FDA 2011) reported symptom improvement in 34% of patients (n=108).	baseline and follow-up reported improvements or possible improvements in neurological symptoms (n=76).	outcomes was measured in 100 of the 108 patients, of which 24 had no symptoms at baseline and follow-up – therefore the number of patients is 76. 34 patients reported improvements and 5 reported possible improvements. This calculates a rate of 51% (39/76). The report doesn't accurately reflect the symptom improvement that was seen after PED placement.	asymptomatic throughout the study: "The PUFS study (FDA 2011) reported symptom improvement in 34% of patients (n=100) while 24 of these subjects were asymptomatic at baseline and follow up. Szikora (2010) reported improvements in 61% of patients (n=18). "

Issue 23

Description of factual	Description of proposed	Justification for	EAC Response

inaccuracy	amendment	amendment	
Section 4.1.4, p28: No time frame is provided for occlusion rate reported by O'Kelly.	Add time frame for occlusion rate in O'Kelly.	Scientific accuracy. Occlusion rates are known to increase with time, therefore the time frame (e.g. 180 days) is important to include from a scientific viewpoint.	Amended to include: The follow up for these patients ranged from 3 – 30 months.

Issue 24

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC Response
Section 3 and Section 4.1.4, p28: altered size of aneurysm mass.	Add sentence stating that alterations in aneurysm size, although not measured directly, are reflected in other outcomes such as resolution of symptoms.	The audience of this document should be aware that this measure is reflected in the other outcomes such as resolution of symptoms. During discussion	Section 3 is in relation to the scope of the decision problem as outlined by NICE. Section 4.1.4 – amended to include:

		around the NICE scope, the sponsor requested that this outcome be deleted with the rationale “This outcome is not an independent measure and should be excluded. The effects of the aneurysm size are reflected in other outcomes such as resolution of symptoms.”	Although there are few data directly related to the altered size of aneurysms, this may be reflected in other outcomes such as resolution of symptoms.

Issue 25

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC Response
Section 4.1.4, Table 2: Many of the AEs stated as	Combine Patient 1 and 2 in Nelson (2011): same patient. Change Patient 4	As mentioned in the EAC report on p30, the AEs reported were not	Patient 1 and 2 combined. Column on category of

'Category 2: unexpected SAE' are incorrect and should be redefined as 'Category 1: expected SAE'. There is also duplication of a patient in Nelson 2011.	and 5 in FDA (2011) to 'expected' – haemorrhagic events are in the list of ADEs in the protocol for this study. Moreover, haemorrhagic events can occur after stent-assisted coiling (Stroke 2010;41:110, J Neurosurg 2009;110:35, J NeuroIntervent Surg 2010:2:16) Change Patient in Fiorella (2008 and 2010) to 'expected'. This patient presented with spontaneous occlusion of the vertebral artery, and therefore another spontaneous occlusion of an artery after stopping antiplatelet therapy is not surprising or unexpected. Change Patient 1 in	unusual – and therefore not unexpected. This is further supported by literature that describes haemorrhagic events after stent-assisted coiling. (Stroke 2010;41:110, J Neurosurg 2009;110:35, J NeuroIntervent Surg 2010:2:16)	adverse event deleted

	Hartmann (2010) to 'expected' – haemorrhagic events are expected after this treatment (see above). Change Patient 1 in Klisch (2011) to 'expected' – late thrombosis of a stent-treated artery is not an unexpected event. Change Patient 1 in O'Kelly (2011) to 'expected' - delayed aneurysm rupture is not an unexpected event (see above).		

Issue 26

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC Response
Section 4.2.1, p35: the report states that 'reported occlusion rates	Change to: More than half the studies (7 out of 12) reported 100% occlusion rate	Proposed amend reflects data more accurately.	Have amended to:More than half the studies (7 out of 12) reported 100%

ranged between 69% and 100%'. It is also important to include the timeframe for which occlusion is measured (as detailed elsewhere).	success. The lowest reported occlusion rate was 69%. – and include time frame.		occlusion rate success. The lowest reported occlusion rate was 69%. Time frames not included as this is a summary and these details are included elsewhere.

Issue 27

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC Response
Section 5.2.2 states: "It is assumed that the link between intermediate and final outcomes based on occlusion categories is the same for PED as for the	Add a sentence to state: "However, this is likely to underestimate the true benefit of PED".	To date, there have been no recurrences after complete occlusion in patients enrolled in PUFS (2-year follow-up), PITA (more than 2-year post-study follow-up) and	Amendment accepted

comparator technologies.”		the Argentina studies (4-year follow-up). It appears that once an aneurysm is cured with PED, recurrence is not an issue. In contrast, many patients with complete occlusion immediately after coil embolisation experience aneurysm recurrence. Reducing aneurysm recurrence after coil embolisation has been an endpoint in some recent clinical trials.	

Issue 28

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC Response
Section 5.2.2 states: “This does not take into account of a giant aneurysm with a small neck… or conversely a smaller aneurysm with a wide neck”.	Delete entire paragraph.	Smaller aneurysms are out of the scope of this submission, whilst larger aneurysms with small necks are rare (and would further favour the analysis of PED).	Amended to: This does not take account of a giant aneurysm with a small neck that could require a large number of coils, but just one PED. This is likely to be quite rare and would favour PED.

Issue 29

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC Response
Section 5.2.3: “For	Add: “Although potentially flawed,	As acknowledged elsewhere in the	Added “This assumption

conservative treatment all patients are in the residual aneurysm category. This may be a flawed approach…"	this assumption is likely to overstate the effectiveness of conservative management".	document, 'residual aneurysm' patients following treatment, are likely to have a better prognosis than those who aneurysms are untreated.	may overestimate the effectiveness of conservative treatment."

Issue 30

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC Response
Section 5.2.3: "There is no scope within the model to include ongoing adverse effects for the entire duration of the model or to include any adverse effects other than stroke".	Delete or rephrase sentence.	The model is designed to show a one-off cost or disutility for adverse events. This is not limited to only the first six months, but could apply to any duration of time, based on an average lifetime cost or disutility. Further, the model	The EAC accepts that the model has capacity for additional events to be added, and that it is difficult to obtain good quality data to populate the model. However it is important when

		does include capacity for additional events, but these were not included because no consistent measurement of AE rates between treatments was identified.	looking at the results to understand that these are not present. The cost for adverse events in the model is the cost of an acute episode (£8,046). The disutility in the model is considered for the initial 6 months. This is in contrast to modelling for rupture that includes a cost of £1080 per 6 months following stroke, and a continual disutility. There is no capacity for a

			rate of adverse events that would be ongoing, however the EAC accepts that this would be difficult to populate. Ammended to: "The model, as submitted, does not include ongoing adverse effects for the entire duration of the model or include any adverse effects other than stroke. The model does have capacity for additional events to be added".

Issue 31

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC Response
Section 5.2.8: “A cost for fatal stroke of £7,041 is available from the same original source as the costs used for non-fatal stroke. It is not clear why this was not used and suggests that the value in the model may be an underestimate”.	Add: “This is a conservative assumption, and the use of that value would increase the cost of the comparator groups by a greater value than the cost of the PED arm.”	The cost from that source was not included, since it was unclear as to whether it also included non-hospitalised deaths (i.e. patients who died at home, at no cost to the NHS).	Although the impact is not always in favour of PED (neurosurgical clipping results in a slightly lower fatal rupture rate), it is clearly in favour of PED when the comparator is conservative treatment, and this is the case where the impact will be noticeable. Therefore the comment will be added: “This will have an impact in favour of PED when compared with

			conservative treatment. The impact is likely to be small in other cases”

Issue 32

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC Response
Section 5.5: “The treatment of complications and adverse events in the model is inadequate and it is difficult to assess the impact of this on the results of the model”.	Delete comment.	Sensitivity analysis within the model demonstrates that the cost and disutility of adverse events has only a marginal impact on the model’s outputs.	Sensitivity analysis shows marginal impact due to the structure of the model. Since the adverse events are not fully included, sensitivity analysis on the rate of adverse events will not be realistic. No action.

Issue 33

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC Response
Section 5.3.4: Various mentions of "…, but offers improved QoL".	Change to: "…, but improves QoL and length of life".	The QALY gains are a combination of both improved quality of life and length of life.	Amendment accepted

Issue 34

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC Response
Section 5.2.8: "The number of PED devices used in the model was taken from data on file at Covidien; however several other sources indicate that this is an underestimate."	Re-run model with current UK/Ireland data using 1.6 PEDs, and update relevant sections of the EAC report.	As part of the proctoring and clinical support process, ev3 has attended all UK/ Ireland placements of the Pipeline device to date. The sponsor's original estimate was based on these data. We are providing to	EAC unable to to incorporate new data at this stage. However results for a range of PED values, including 1.6, will be submitted in additional

		NICE the current copy (27 September 2011) of the case specific data providing details on the following: • Date PED placement • Associated hospital and city • Aneurysm location • Number of PED placed. Furthermore, we have recalculated the average to include the most recent cases. The current data show that in 154 cases treated with PED, 252 PED were used, giving an average of 1.64 per case. Approximately 10%	information requested by NICE.

		of the total cases do not currently have data on the number of PEDs: these are being investigated, and an update can be provided once the numbers have been obtained. We believe this to be the most accurate source of information available regarding the actual numbers of devices required to treat patients in the UK/Ireland. This information is identical to that afforded to [redacted] for the UK audit that is underway. We propose that these data are the most robust and appropriate data available for	

		economic modelling as it relates to the actual case utilisation of the PED device.	