EXTERNAL ASSESSMENT CENTRE REPORT:

Pipeline Embolization Device for the treatment of complex intracranial aneurysms

Produced by:	Cedar www.cedar.wales.nhs.uk
Home Unit	Cedar
Authors:	Kathleen Withers, Evaluation Scientist Dr Grace Carolan-Rees, Cedar Director Megan Dale, Evaluation Scientist Joelle L Williams, Evaluation Scientist Dr Judith White, Evaluation Scientist
Contribution of Authors:	KW wrote the clinical evidence section of this report. GCR and MD wrote the economic evidence section with support from KW and JW. JLW performed the quality assessment of the literature search
Correspondence to:	Kathleen Withers, Cardiff Medicentre, Heath Park, Cardiff, CF14 4UJ Email: Kathleen.Withers@wales.nhs.uk Tel: 029 20 744771
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None

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Alison Weightman, Director, Support Unit for Research Evidence (SURE), Cardiff University

Prof. Ceri Phillips, Professor of Health Economics and Deputy Head of School (Research), Swansea University

Dr Rob Lenthall, Consultant Neuroradiologist, Nottingham University Hospitals NHS Trust, Nottingham

Dr Tony Goddard, Consultant Diagnostic and Interventional Neuroradiologist, Leeds Teaching Hospitals NHS Trust, Leeds

Dr Phil White: Consultant Neuroradiologist, Lothian University Hospitals NHS Trust, Edinburgh

Dr Andy Molyneux, Consultant Neuroradiologist, North Bristol NHS Trust, Bristol.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the National Institute for Health and Clinical Excellence. Any errors are the responsibility of the authors.

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Table of Abbreviations

AE	Adverse Event
CARAT	Cerebral Aneurysm Rerupture After Treatment trial
CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
CVD	Cardiovascular Disease
DID	Delayed Ischaemic Deficiency
EAC	External Assessment Centre
EVT	Endovascular Treatment
FDA	Food and Drug Administration
HES	Hospital Episode Statistics
IA	Intracranial Aneurysms
ICA	Internal Carotid Artery
ICH	Intracranial Haemorrhage
ICER	Incremental Cost Effectiveness Ratio
ISAT	International Subarachnoid Aneurysm Trial
ISUIA	International Study of Unruptured Intracranial Aneurysms Investigators
KOL	Key Opinion Leader
MAUDE	Manufacturer and User Facility Device Experience
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NICE	National Institute of Health and Clinical Excellence
PED	Pipeline Embolization Device
PITA	Pipeline for Intracranial Treatment of Aneurysms study
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PUFS	Pipeline for Uncoilable or Failed Aneurysms trial
PVO	Parent Vessel Occlusion
QALYs	Quality Adjusted Life Years
QoL	Quality of Life
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
SAH	Subarachnoid Haemorrhage
SURE	Support Unit for Research Evidence
NICE	National Institute for Health and Clinical Excellence
NST	Neurosurgical Treatment
TNT	Treating New Targets

1 SUMMARY

The manufacturer, Covidien has submitted clinical and economic evidence to support the use of Pipeline Embolization Device (PED) in patients with complex, intracranial aneurysms, specifically large / giant wide necked and fusiform aneurysms.

1.1 Scope of Submission

Covidien have largely stayed within the scope outlined by NICE, however, NICE had not explicitly excluded ruptured aneurysms from the scope of the decision problem and Covidien included data on both ruptured and unruptured aneurysms within their submission. However, the manufacturer did not include ruptured aneurysms in the original notification of the device to the NICE Medical Technology Evaluation Programme. Patients with ruptured aneurysms pose significantly different treatment challenges to those with non-ruptured aneurysm and furthermore, PEDs are not recommended as a sole therapy for patients with acutely ruptured aneurysms. It was confirmed during discussions with NICE during the evidence critique period that this subgroup of patients is excluded from the scope of the submission.

1.2 Summary of submitted clinical evidence

The manufacturer has included 13 studies as part of their qualitative synthesis, and state that two of these (FDA 2011;Nelson 2011) have been included in quantitative synthesis. These are both based on trials designed to assess the safety and efficacy of PED. The PITA (Pipeline for Intracranial Treatment of Aneurysms) study was a prospective single-arm feasibility study in patients with unruptured wide necked intracranial aneurysms (IAs) with unfavourable dome/neck ratios (<1.5) or who had failed previous therapy. Data are available for 31 patients. Pipeline for Uncoilable or Failed Aneurysms trial (PUFS) is an unpublished, ongoing prospective single-arm open label interventional trial in 108 patients with wide neck, large and giant IAs. One year data are available for this study which is expected to end in July 2014. Data from this unpublished trial are available via the Food and Drug Administration (FDA 2011).

Both the PITA and PUFS studies achieved the primary objectives of their respective studies reporting 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). PITA also reported a 97.9% device placement success (target 80% minimum) while PUFS goal of a minimum 50% complete occlusion rate without parent artery stenosis at 180 days was also achieved (73.6%). Nelson (2011) also reported high complete aneurysm occlusion rates of 93.3% at 180 days in the PITA study.

The EAC feels that these studies are both appropriate to the submission, and the manufacturer has tabulated and discussed their findings in detail. The manufacturer excluded the remaining eleven studies from the data extraction process due to concerns regarding their quality. However, the EAC feels that data extraction from these studies provides important information relevant to the scope of the submission.

1.3 Summary of submitted economic evidence

Only one poor quality unpublished cost analysis was found in the literature search. The economic evidence therefore relies upon the *de novo* model produced by the manufacturer. On the basis of the model the manufacturer claims that:

1) PED is dominant compared with stent-assisted coiling
2) for a willingness to pay threshold of £30,000, PED is the most cost-effective option.

Sensitivity analysis showed that the model is particularly sensitive to the cost and numbers of PEDs and coils used. The EAC has identified some concerns with the model inputs, particularly with respect to the number of PEDs and coils used for large and giant aneurysms. The model was re-run with a more appropriate number of PEDs (2.4) and coils (25) and it was found that rather than being cost saving, PED was more costly. Particular uncertainty remains regarding the number of coils, whereas there is more confidence regarding the amended number of PEDs. The EAC has shown that for 2.4 PEDs, the model shows PED to become cost saving when the number of coils used is greater than or equal to 36. Therefore one could say based on the model that PED is found to be cost saving compared with stent-assisted coiling, if the number of coils used on average is greater than or equal to 36.

With respect to the second claim, the EAC found that the model deviated from the scope given by NICE by costing retreatment for each comparator using a retreatment technique that did not correspond to the scope. The incremental analysis was reworked and for a willingness to pay threshold of £30,000 neurosurgical clipping was found to be the most cost-effective option.

1.4 Commentary on the robustness of submitted evidence

Clinical Evidence

Covidien have identified 13 studies as being relevant to the decision problem. The EAC has identified one of these as inappropriate and has removed it from the clinical evidence section. Matouk (2010) presents data on ruptured aneurysms which were identified during the evidence critique period as being outside the scope of the decision problem. Of the remaining studies:

- One is an unpublished trial
- Seven are full length manuscripts published in peer reviewed journals
- One is a journal letter
- Three are conference abstracts

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. Additionally, three studies were identified which were not available at the time of the sponsors 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. A total of 16 references were included by the EAC in their clinical appraisal of evidence.

The studies included comprise of two trials (one published the other ongoing and unpublished), six case series (where n >5) and 8 case reports (where n ≤5). None of the studies included were comparative, as due to the nature of this disease, comparative studies are generally inappropriate. Much of the available data is weak in quality in the evidence hierarchy, and 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 as discussed later. However despite these issues, these studies are a useful source of data for complication rates and adverse events.

Economic Evidence

The robustness of the model results depends on the robustness of the inputs. The identification and selection of papers used as sources for the inputs was not described and therefore it is not possible to be confident that these are the most appropriate. The model was annotated with the sources used for each input but on investigation some of these were secondary sources. The model structure was reliant on extrapolation from intermediate outcomes and uncertainties were introduced at each stage of the pathway. Some parameters were derived from data combined from a number of papers. Some studies used were not directly relevant to the decision problem. The thorough sensitivity analysis highlighted the most critical areas.

1.4.1 Strengths

Strengths of the clinical evidence:

- The two primary studies were explained clearly and in detail
- The manufacturer provided a comprehensive overview of the condition requiring intervention
- The mechanism of action of the device was described clearly
- Advantages and disadvantages of current treatment options and their comparison to PED were clearly explained.
- Well described literature search strategy

Strengths of the economic evidence

- Competent modelling
- The model is well annotated with references for the data sources
- Extensive sensitivity analysis

1.4.2 Weaknesses

Weaknesses of the clinical evidence

- Relevant case report not identified via the literature search
- Poor quality of available studies

- Lack of comparator studies
- Incomplete data extraction from most of the identified studies
- Absence of adverse event data from sources including MAUDE and the manufacturer (data from the manufacturer was readily supplied on request)
- Data not available or available in insufficient quality / quantity to adequately address all areas of the outcome measures specified within the scope.

Weaknesses of the economic evidence

- Deviation from the scope
- Poor handling of complications and adverse events
- Uncertainty regarding the number of PEDs and coils used
- No justification for the choice of papers used as sources for inputs
- Complicated model structure

1.4.3 Areas of uncertainty

Areas of Uncertainty of the Clinical Evidence

- The number of patients suitable for treatment with PED, particularly those for whom no other treatment options are available.
- Minimal available data currently available on adverse events.
- Lack of long term follow up data.
- Low patient numbers and lack of comparator studies resulting in evidence gaps

Areas of Uncertainty of the Economic Evidence

- The average number of coils used in stent-assisted coiling when treating large and giant aneurysms
- The average number of PEDs used to treat large and giant aneurysms
- Numerous assumptions made in the economic model

1.5 Key Issues

As randomised controlled trials (RCT's) were not appropriate, there is a reliance on data from two trials, and a variety of low quality, small case series/reports. Patients included in some of the

studies reported overlap but the degree of data duplication is unclear making data extraction difficult. As a device in its infancy, statistics are scarce and there is no long term follow up data available. Two year data from the PUFS study will be available at the end of this year and other ongoing studies are likely to be published in the near future. However, while the clinical evidence is poor, the reports do provide useful data, showing high success rates; sometimes in patients for whom there are no treatment alternatives.

Uncertainty remains regarding the number of coils used to treat large and giant aneurysms in stent-assisted coiling. This is a critical parameter that could change the outcome of the model. Neither the manufacturer nor the EAC have undertaken a structured search for comparator technologies. The manufacturer has quoted a value based on opinion in an editorial. The EAC has consulted expert advisers, and considered the numbers reported in the selected papers in the clinical evidence but these may not be the most appropriate sources available. If using the numbers of coils and PEDs estimated by the EAC, there is a significant addition cost against PED.

2 BACKGROUND

This EAC report aims to provide an independent critique of the clinical and economic evidence provided by the manufacturer.

2.1 Critique of manufacturer's description of underlying health problem

Covidien have provided a thorough, well referenced overview of intracranial aneurysms, describing various types of relevant intracranial aneurysm, symptoms and complications.

Prevalence and Complications of Intracranial Aneurysms

The pathophysiology of IAs is clearly described and relevantly illustrated with appropriate references. These clearly define / describe:

- Overall prevalence rate for aneurysms = 2.8% ((Vlak 2011))
- Higher prevalence rate for women than men; prevalence ratio 1.57 (Vlak 2011)
- Symptoms of IAs; headache; seizures; visual disturbances; dizziness; facial paralysis or pain (Gonzalez NR 2006; NHS 2011)

- Most common presentation is mass effect on adjacent structures (Vega C 2002)

Untreated, large / giant and wide necked aneurysms carry high risks to the patient, causing compressive symptoms and a high risk of rupture. The ISUIA (Anon 1998) study found five year cumulative rupture rates of aneurysms in the anterior circulation of 2.6% for aneurysms sized 7-12mm; 14.5% for aneurysms sized 13-24mm and 40% for aneurysms sized 25mm or greater.

Estimate of patient population

Covidien have used HES (Hospital Episode Statistics) online as their basis to estimate the patient population with large, giant wide-neck or fusiform unruptured aneurysms who would be suitable candidates for treatment with the Pipeline Embolization Device. Discussions with the clinical experts suggested that the estimated figure of 460-580 patients with unruptured aneurysms in England and Wales eligible for treatment with PED was likely to be excessively high. This figure was calculated from a baseline of 2191 in-patient admissions in England and Wales during 2009 - 2010 of patients with a primary diagnosis of unruptured cerebral aneurysms. This was initially addressed by removal of Welsh patient to focus on NHS England patients as per NICE remit. As each patient may be admitted on more than one occasion with the same primary diagnosis, this was likely to have elevated the patient estimate. The EAC interrogated HES Online (Hospital Episode Statistics) to determine the number of *patients* admitted with a primary diagnosis of unruptured cerebral aneurysms in 2009 – 2010. This feature of HES is freely available to certain groups (such as the NHS), but would have only been available to the manufacturer via a commissioned, tailor made report. The EAC found that the total number of patients with unruptured cerebral aneurysms with finished admissions, treated in England was 1585 in 2009 – 2010. As per the manufacturers submission, the 1998 International Study of Unruptured Intracranial Aneurysms Investigators, reported data from two large cohort studies which found that 21 - 26.5% of aneurysms are large or giant, meaning that of these 1585 patients, approximately 333 to 420 patients treated in England will have large or giant aneurysms based on ISUIA data. While not all of these patients will be suitable candidates for treatment due to factors such as age and co-morbidity, most of these cases will require treatment if available. However, it is possible that until the safety and efficacy of Pipeline has been proven further, this figure may be

substantially lower with clinicians opting to utilise existing, proven treatment strategies where possible.

2.2 Critique of overview of current service provision

Covidien have provided a comprehensive and appropriately referenced overview of the considerations for patients with IAs, listing issues including current impact of aneurysm on quality of life, risk of rupture, potential risk of morbidity and mortality associated with treatments, long-term efficacy of treatment and patient related factors such as age, presence of co-morbidities.

While PED will not change the existing care pathway, it does offer an additional option. This is particularly relevant for patients with hard to treat aneurysms such as those within the scope of the decision problem which are often not amenable to treatment with currently available techniques. The difficulties in treating these aneurysms have been described and appropriately referenced in the submission.

The manufacturer lists current treatment strategies as:

- Reconstructive techniques
    - Embolic coiling (including balloon assisted coiling)
    - Stent assisted aneurysm coiling / multiple conventional stents
    - Neurosurgery (clipping or wrapping) and bypass procedures
    - SILK artery reconstruction device (with coiling)
- Deconstructive techniques
    - Parent vessel occlusion
- Other
    - Conservative management

The manufacturers have tabulated advantages and disadvantages to the above treatment options and have compared each option to PED to show the benefit of PED in relation to other treatment strategies. While all of the strategies described have been implemented in the patient population, comparisons to SILK within coils should be avoided under the scope of this assessment.

3 Critique of definition of decision problem

Covidien state that they made a single addition to the decision problem as specified by NICE, adding SILK artery reconstruct devices to the list of comparators. The EAC felt that this was appropriate, as both devices are referred to as flow diverters in the literature, are similar in concept and aimed at the same patient population. Several studies have directly compared the two devices. However, discussions with NICE during the evidence critique period made it clear that due to MHRA restrictions on SILK (specifying that the SILK device should not be used without coils) which are currently in place, and the different safety profiles of the two devices, all comparisons to SILK should be avoided at this stage.

No other changes to the scope of the decision problem are identified in part 4 of the submission. However, in parts 2.5 and 2.6 of the submission where current clinical practice is described and where main comparators are identified and justified, embolic coils (used alone) have been added and discussed and compared to PED. Coiling can be used effectively both with the aid of a supporting device and as a stand alone treatment (FDA 2011; van Rooij 2009), however, the size and type of aneurysms discussed under the scope of the report would be unlikely to be treated without additional measures; it has therefore been excluded from the decision problem.

EAC Amendments

The EAC identified an amendment to the decision problem as indicated below:

- Population: Patients with unruptured complex intracranial aneurysms, specifically large/giant, wide necked and fusiform aneurysms.
- Intervention: No change
- Comparator: No change
- Outcomes: *Altered* size of collective aneurysm thrombus mass
- Cost Analysis: No change
- Subgroups: Exclusion of patients with ruptured aneurysms
- Special Considerations: No change.

Pipeline Embolization Devices (PEDs) are not recommended as a sole therapy for patients with acutely ruptured aneurysms, and this subgroup of patients offer very different treatment challenges to those with non-ruptured aneurysms. Also, ruptured aneurysms were not in the original notification of the device to the NICE Medical Technology Evaluation Programme.

In the NICE scope, one of the outcomes is identified as “size of aneurysm thrombus mass” the EAC has modified this to “altered size of aneurysm mass” for clarity.

4 CLINICAL EFFECTIVENESS

4.1 Critique of manufacturer’s approach

Covidien have provided a table to illustrate the eligibility criteria for study selection. The inclusion and exclusion criteria for the studies were mainly felt to be appropriate with the exception of the language restriction as foreign language manuscripts are often available with English abstracts or even full manuscript translations. The literature search performed by Covidien was clear and well documented; the search strategy itself was reasonable if not fully robust.

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. The flow diagram indicates that 13 studies are included for qualitative synthesis and two of these are selected for quantitative synthesis but does not provide justification for these selections. The two chosen studies are relevant to the decision problem and data from these two studies is presented in detail over 30 pages of text including 11 tables. While this provides a great deal of information, the extensive use of numerous large tables leads to difficulty in finding and interpreting appropriate data. Weaknesses of the studies are poorly addressed.

The remaining eleven studies are poorly identified by the manufacturer. While table B5.3 references the authors of eleven studies it is not clearly stated that these are the studies identified for qualitative synthesis. Furthermore, information in this table is not extracted directly from the identified studies with a lack of reference to the sources of patient population and study descriptions cited. Little or no information has been extracted from these eleven studies with

information relevant to the scope of the decision problem being omitted in many cases. Strengths and weaknesses of the studies have not been discussed.

Other areas relevant to the scope have also been poorly addressed by the manufacturer with no adverse event data being presented other than from the two primary studies included. No appropriate medical device reports have been identified via the manufacturer or the Food and Drug Administration in the form of MAUDE (Manufacturer and User Facility Device Experience) data.

4.1.1 Description and critique of the manufacturer's identification and selection of studies.

Covidien carried out a clearly illustrated literature search using a good set of sources which included those suggested by NICE. The EAC commissioned assistance from SURE (Support Unit for Research Evidence), a specialist research group to identify weaknesses and suggest potential improvements in the manufacturers search strategy.

Criticisms

The lack of documentation explaining the criteria for excluding studies from qualitative synthesis means that it is not possible to critique these decisions.

The EAC felt that twelve of the thirteen studies included for qualitative synthesis were appropriate to the decision problem. The EAC disagreed on one selected study:

- Matouk C, O'Kelly C, Ellis M, Sarma D, Gray B, Spears J, et al. Pipeline embolization device reconstruction of ruptured intracranial aneurysms: Report of two cases. Proceeding of the 45th Annual Congress of the Canadian Neurological Sciences Federation (CNSF); 2010 Jun 8-11; Quebec, QC Canada. Canadian Journal of Neurological Science 2010;37 (3 Supplement 1):S88-9.

This conference abstract reports two cases of ruptured intracranial aneurysms. As ruptured aneurysms were identified as being outside of the scope of the decision problem, the EAC has removed this study from the report.

Enhancements

Adapting the Medline search strategy used by Li (2010) in the Cochrane Review Protocol, additional search terms were identified for inclusion and existing search terms were expanded to ensure relevant studies were not missed.

The EAC identified several studies where aneurysm was spelt “aneurism”. An 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. Relevant searches were also expanded to include the following additional sources:

- Web of science, Science Citation Index
- Stoke Centre Stroke Trials Registry
- Current Controlled Trials
- Clinicaltrials.gov

The search strategy used by the EAC is illustrated in Appendix 1. This led to the retrieval of 882 references once duplicates were removed, a substantial increase from the 168 studies identified by the manufacturer.

The EAC has provided a bibliography of studies excluded from the EAC qualitative synthesis with reasons for exclusion in Appendix 2

4.1.2 Table of identified studies. What studies were included in the submission and what were excluded. Include details of any relevant studies that were not included in the submission.

Included / excluded in the submission

It is unclear what studies were excluded from the submission. The manufacturer provided references to 13 included studies in tables B5.2 and B5.3 of the submission. One of these has been excluded by the EAC as identified above, the following studies were appropriately identified by the manufacturer for inclusion in the evidence submission:

- Nelson PK, Lylyk P, Szikora I, Wetzel SG, Wanke I, Fiorella D. The pipeline embolization device for the intracranial treatment of aneurysms trial. American Journal of Neuroradiology 2011;32(1):34-40.
- Food & Drugs Administration (FDA). Chestnut Medical Technologies. Pipeline Embolization Device Executive Summary P100018 [report online]. 2011 Feb 1 [accessed August 31st 2011]. Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/UCM247160.pdf
- Fiorella D, Woo HH, Albuquerque FC, Nelson PK. Definitive reconstruction of circumferential, fusiform intracranial aneurysms with the pipeline embolization device. Neurosurgery 2008;62(5):1115-20.
- Fiorella D, Kelly ME, Albuquerque FC, Nelson PK. Curative reconstruction of a giant midbasilar trunk aneurysm with the pipeline embolization device. Neurosurgery 2009; 64:212-7. (Fiorella 2009a)
- Fiorella D, Hsu D, Woo HH, Tarr RW, Nelson PK. Very late thrombosis of a pipeline embolization device construct: case report. Neurosurgery 2010; 67: ons E313-ons E314.
- Lylyk P, Miranda C, Ceratto R, Ferrario A, Scrivano E, Luna HR, et al. Curative endovascular reconstruction of cerebral aneurysms with the pipeline embolization device: the Buenos Aires experience. Neurosurgery 2009;64:632-42. (Lylyk 2009a)
- Szikora I, Berentei Z, Kulcsar Z, Marosfoi M, Gubucz I, Nelson PK, et al. Effect of flow modification on aneurysm induced mass effect. Proceedings of the 19th Symposium Neuroradiologicum - The World Congress of Diagnostic and Therapeutic Neuroradiology; 2010 Oct 4–9; Bologna, Italy. Neuroradiology Journal 2010;23(1):324. (Szikora 2010a)
- Szikora I, Berentei Z, Kulcsar Z, Marosfoi M, Vajda ZS, Lee W, et al. Treatment of intracranial aneurysms by functional reconstruction of the parent artery: the Budapest experience with

the pipeline embolization device. American Journal of Neuroradiology 2010;31(6):1139-47. (Szikora 2010b)

- Phillips T, Mitchell P, Dowling R, Yan B. Endovascular treatment of intracranial aneurysms with new generation flow diverting stents. Early experience in an Australian neurointerventional centre. Proceedings of the 61st Annual Scientific Meeting of the Royal Australian and New Zealand College of Radiologists (RANZCR); 2010 Oct 14-17; Perth, Australia. Journal of Medical Imaging Radiation & Oncolology 2010 Oct; 54(Supplement 1):A122.
- Hartmann M, Rohde S, Braun C, Hahnel S, Bendszus M. Endovascular treatment of cerebral aneurysms with the pipeline embolization device. Proceedings of the Jahrestagung der Deutschen Gesellschaft fur Neuroradiologie (DGNR); 2010 Sept 22-25; Mannheim Germany. Clinical Neuroradiology 2010 Aug;20(3):190-1.
- Klisch J, Turk A, Turner R, Woo HH, Fiorella D. Very late thrombosis of flow-diverting constructs after the treatment of large fusiform posterior circulation aneurysms. American Journal of Neuroradiology 2011; 32(4):627-32.
- van Rooij WJ, Sluzewski M. Perforator infarction after placement of a pipeline flow-diverting stent for an unruptured A1 aneurysm. American Journal of Neuroradiology 2010;31:E43-E44.

Although the manufacturer has identified thirteen studies above, they have excluded eleven of these from further discussion. The excluded studies have not been clearly identified at any point, and only the PITA study published by Nelson (2011) and the PUFS study (FDA 2011) are included in further discussions. The manufacturer has acknowledged that case reports and case series are relevant, and while the data they contain may be of relatively poor quality, they are still useful to identify issues such as adverse events. Some of the studies initially included describe relatively large patient numbers and useful outcome and complication data. Although in some cases poorly reported or with some duplication of data between studies, the EAC felt that these should be utilised more effectively as useful data sources in the absence of more robust studies.

Studies identified by the EAC for inclusion

The EAC identified a further four studies for inclusion as appropriate to the evidence submission. These comprise of three case reports and one conference abstract discussing a large case series (n=96 patients).

- O'Kelly C; Spears J; Chow M; Wong J; Silvaggio J; Boulton M; Weill A; Willinsky R; Kelly M; Marotta T. Canadian experience with the pipeline embolization device for repair of unruptured intractranial aneurysms. Canadian Journal of Neurological Sciences Conference: 46th Annual Congress of the Canadian Neurological Sciences Federation, 2011; 38(3) supp 1: S31
- Hampton,T.; Walsh,D.; Tolias,C.; Fiorella,D. Mural destabilization after aneurysm treatment with a flow-diverting device: A report of two cases. Journal of NeuroInterventional Surgery 2011;3 (2):167-171
- Sararols L;Castillo L;Graell X;Macho J;San-Roman L;Macaya J;Goi F. Right giant internal carotid artery bifurcation aneurism: Presentation with homonymous left hemianopsia and successful treatment with intraneurismatic bypass. Neuro-Ophthalmology Conference: 10th European Neuro-Ophthalmology Society, EUNOS Meeting Barcelona Spain. Conference Publication 2011; 35: S65
- Fiorella D, Albuquerque F, Gonzalez F, McDougal CG, Nelson PK. Reconstruction of the right anterior circulation with the Pipeline embolization device to achieve treatment of a progressively symptomatic, large carotid aneurysm. *Journal of NeuroInterventional Surgery* 2009; 2:31-37 (Fiorella 2009b)

A full table of studies with details is available below:

Table 1 - Study overview

Study reference	Study details	Patient population	No of patients (P) & aneurysms (IA)	Comments
Included by the Manufacturer				
Nelson *et al* (2011) (PITA study)	• Prospective single arm feasibility study • 4 centres • 180 day duration	Wide neck IAs unsuitable for treatment with coils	31 (P) 31 (IA)	Unclear if consecutive patients
FDA (2011) (PUFS Study)	• A prospective single-arm open label interventional trial • 10 centres • 180 day duration • Up to 5 year follow up	Wide-neck, large and giant IAs	108 (P) 110 (IA)	Follow up is on-going Expected end date July 2014 Data available via FDA reference
Fiorella *et al* (2008a)	• Case report (n=2)	Large symptomatic circumferential fusiform intracranial vertebral artery aneurysms	2 (P) 2 (IA)	Limitations due to type of report – high risk of bias
Fiorella *et al* (2009a)	• Case report (n=1)	Giant circumferential midbasilar aneurysm	1 (P) 1 (IA)	Limitations due to type of report – high risk of bias
Fiorella *et al* (2010)	• Case report (n=1)	Large symptomatic circumferential fusiform intracranial vertebral artery aneurysms	1 (P) 1 (IA)	This patient was also reported in previous publication Fiorella et al (2008)
Lylyk *et al* (2009a) *	• Prospective, single-centre study • All-inclusive case series • 12 month follow up	Large and giant wide necked nonsaccular and recurrent intracranial aneurysms	53 (P) 63 (IA)	The manufacturer reports this study now has data on 180 patients with 217 IAs Six of these patients also enrolled in PITA study
Szikora *et al* (2010a) Conference abstract	• Study to demonstrate the effect of flow modification of mass effect caused by large and giant aneurysms • Minimum 6 month follow up	Large and giant aneurysms causing mass effect	NK (P) 42 (IA)	Unclear if any of these patient are included in journal publication below
Szikora *et al* (2010b)**	• Single centre study • Case series to find an effective treatment technique for difficult to treat aneurysms • 6 month angiographic follow up	Difficult to treat large, giant, fusiform or wide neck aneurysms	18 (P) 19 (IA)	Nine of these patients were also enrolled in the PITA study

Study reference	Study details	Patient population	No of patients (P) & aneurysms (IA)	Comments
Phillips *et al* (2010) Conference abstract	• Single centre case series • 8 month duration • 6 month follow up planned	Aneurysms assessed as difficult to treat with coiling or stent assisted coiling.	10 (P) NK (IA)	
Hartmann *et al* (2010) Conference abstract	• Case series illustrating initial experiences with PED	Non-ruptured large and giant wide necked aneurysms	8 (P) 9 (IA)	
Matouk *et al* (2010) Conference abstract	The EAC recommends removal of this study from the evidence submission for the following reason: • This study contains data from cases of small, ruptured aneurysms and is therefore outside the scope of the decision problem			
Klisch *et al* (2011)	• Case report (n=2) • 12 month follow up	Very large fusiform basilar trunk aneurysms	2 (P) 2 (IA)	Limitations due to type of report – high risk of bias
Van Rooij (2010)	• Case report (n=1)	Large dumbbell aneurysm	1 (P) 1 (IA)	Limitations due to type of report – high risk of bias
Included by the EAC				
O'Kelly *et al* (2011) Conference abstract	• Prospective data collection, retrospective data pooling and analysis • 7 treatment centres • Minimum 3 month follow up	Unruptured aneurysms Mean diameter 18mm	96 (P) NK (IA)	The author advises that they hope to publish this data in full in the near future
Hampton *et al* (2011)	• Case report (n=5)	Unclear	5 (P) 5 (IA)	Limitations due to type of report – high risk of bias
Sararols *et al* (2011)	• Case report (n=1)	Giant unruptured right carotid-ophthalmic segment aneurysm	1 (P) 1 (IA)	Limitations due to type of report – high risk of bias
Fiorella *et al* (2009b)	• Case report (n=1)	Large unruptured right internal carotid artery bifurcation aneurysm	1 (P) 1 (IA)	Limitations due to type of report – high risk of bias

* Six of these patients also enrolled in the PITA study
** Nine of these patients also enrolled in the PITA study

Patient duplication and data clarity within identified studies

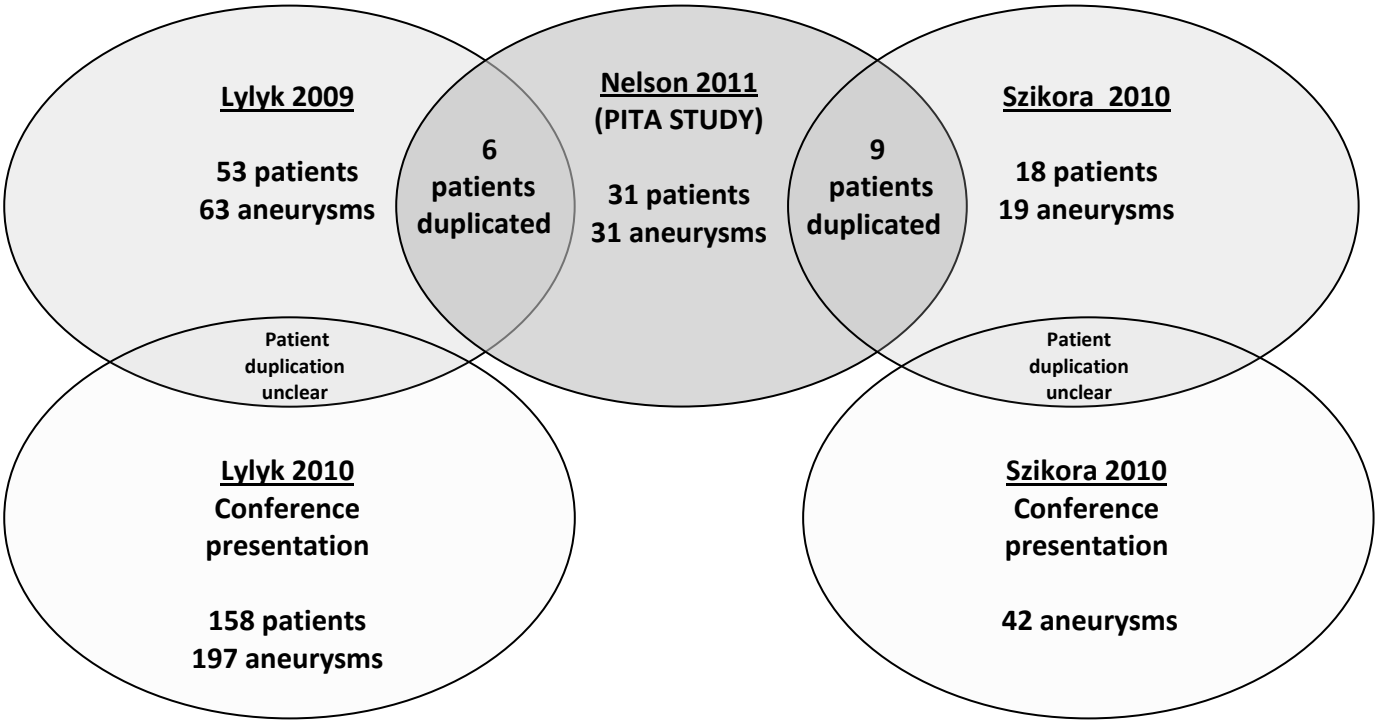
Issues arose around the clarity of relevant literature regarding one of the main studies involving PED due to a degree of patient duplication. PITA was a multi-centre trial with patients treated at medical centres in Germany (4 patients), Austria (12 patients), Budapest (9 patients) and Buenos Aires in Argentina (6 patients). In total 31 patients were treated in this trial reported by Nelson (2011). The 9 patients treated at the Budapest centre were also reported in an earlier publication by Szikora (2010b) who treated a total of 19 aneurysms in 18 patients. Szikora subsequently presented data at the 2010 World Congress of Diagnostics and Therapeutic Neuroradiology Conference in a session discussing treatment of 42 aneurysms with Pipeline (Szikora 2010a). It is unclear if any duplication of patients exists within this study although it is highly likely there will be at least a degree of replication.

A case series of patients treated with PED was reported by Lylyk in a 2009 paper entitled Curative Endovascular Reconstruction of Cerebral Aneurysms with the Pipeline Embolization Device: the Buenos Aires Experience (2009a). This study of 53 patients with 63 aneurysms included the six patients treated in Buenos Aires as part of the PITA study. Data from this study was also presented at conferences in 2008 and 2009. Lylyk presented new data in May 2010 at the American Association of Neurological Surgeons (AANS) Annual Meeting. This abstract has data on 158 patients with 197 aneurysms treated with Pipeline. While this report primarily aimed at assessing technical feasibility, safety and efficacy of treating ruptured aneurysms with PED, most aneurysms treated were unruptured. As no relevant data is available from this abstract it has not been included in the list of relevant studies.

It is unclear what degree of patient duplication has occurred throughout these presentations, although this is likely to be very high. The manufacturer reports in the submission that the Buenos Aires experience with PED study has data on 180 patients with 217 aneurysms.

The manufacturer has not clarified the duplication in patient populations between the 13 studies identified for qualitative analysis. The EAC has contacted the authors to try to clarify this for the papers identified in the manufacturers' submission and for the additional papers identified by the EAC. The relationship between the studies is illustrated in Figure 1 below:

Figure 1



Other data sources

The Flow Diversion in Intracranial Aneurysm Trial (FIAT (Raymond J 2011)) is currently recruiting patients with an estimated enrolment of 344 patients. This study aims to compare flow diversion to best standard treatment e.g. conservative management, coiling, surgical clipping parent vessel occlusion in the context of a randomised controlled trial. Some patients will be entered into a registry where no alternative treatments are available, with all enrolled patients being followed up for 12 month. While this trial is not specific to Pipeline, all flow diverters are eligible (personal communication) and it is likely to be well represented in the study. Two other ongoing multi-centre studies are also reported in the literature; the UK flow diverter audit and the Hong Kong registry for safety and effectiveness (Wong).

The EAC has also identified sources of information on adverse events via the Food and Drug Administration website in the form of MAUDE (Manufacturer and User Facility Device Experience) reports. Medical Device Report data was also sought from the manufacturer. These are tabulated in Appendices 3 and 4. MAUDE held 25 reports of adverse events related to Pipeline: three of

these events were reported in patients who subsequently died. Seven events were potentially linked with adverse patient outcomes while the remainder led to no reported patient injury.

The manufacturers have data on 18 Medical Device Reports received since FDA approval was gained in April 2011. Four patients died following adverse events, 12 reports resulted in no patient injury, and in two reports patient injury was unknown.

4.1.3 Description and critique of manufacturers approach to validity assessment and details of the quality assessment of studies.

Covidien applied a structured quality assessment to PITA and PUFS (FDA 2011; Nelson 2011), the two primary studies discussed in their submission. The manufacturer felt that the remaining studies were not robust enough to include in data extraction and therefore they were not quality assessed. Consequently, strengths and limitations of these studies were not identified. No other part of the submission addressed quality of the studies. The quality assessments used for PITA and PUFS was based on Carey TS, Boden SD. A critical guide to case series reports. Spine 2003; 28(15):1631-4. This provides an appropriate checklist of characteristics which should be addressed to determine the quality of case series. The paper by Carey identifies eight features which should be covered:

- Clearly defined question
- Well described study population
- Well-described intervention
- Use of validated outcome measures
- Appropriate statistical analyses
- Well-described results
- Discussion/conclusions supported by data
- Funding source acknowledged

The manufacturer included the first seven of these points, however the final point “funding source acknowledged” was omitted from the quality assessment. The manufacturer appraised both studies positively against all identified quality criteria, with the exception of “appropriate statistical analyses” for PITA which as a feasibility study was not powered by statistical analyses. The EAC has identified an issue with the quality assessment carried out in regard to the PITA study

regarding the first point. The manufacture has positively assessed the PITA study in the critical appraisal in regard to providing a clearly defined question. Data from the manufacturer and from the FDA Executive Summary illustrate that the PITA study did address a well defined question and was designed to assess the safety and performance of PED in the minimally invasive endovascular treatment of PED. However, the primary study reference for the PITA trial is Nelson (2011) and this paper fails to clearly address a defined question. As the remaining eleven studies met the inclusion criteria developed by the manufacturer they should have automatically been included for critical appraisal, this leads to a significant omission. The EAC has provided a quality assessment table to encompass all studies included as clinical evidence section which is available in Appendix 5.

4.1.4 Description and critique of manufacturers outcome selection

Covidien provided extensive evidence regarding the primary and secondary outcome measures for the two primary studies and clearly specified the measures used to asses these. Both studies are highly relevant to the decision problem although relevance to the decision problem was inferred rather than explicit. Outcome measures including successful device placement, target aneurysm occlusion, neurological death and ipsilateral stroke and were therefore highly appropriate. In common within other areas of the submission the remaining studies were not analysed. The EAC has provided a fully inclusive table of outcome measures to include those specified in the scope in Appendix 6. Results from Fiorella 2008 and 2010 have been combined as they contain data on the same patient. Many of the selected studies did not pre-specify outcome measures with many concentrating their reported outcome data on adverse events and rates of occlusion.

Successful device deployment

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 2010b
- Balloon dilation was needed to open the distal section of one device (Szikora 2010b)
- One device shortened more than expected requiring an additional PED to be placed telescopically (van Rooij 2010).

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

Successful occlusion

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 was 3-30 months.

Altered size of aneurysm mass

This area 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.

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). Szikora (2010b) reported improvements in 61% of patients (n= 18).

Resource use

Resource use outcomes were not specifically discussed as an outcome measures in any of the studies included although the PUFS study found a mean procedure time of 124 minutes (range 39 – 427), this was not described in relation to cost savings or length of procedure for alternative treatments. Fiorella (2009a and 2010) also alluded to basic resource use, describing a procedure time of 90 minutes and 40 minutes total fluoroscopic time in two reports.

Stroke

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

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 C 2011) reported respective rates of 5.6% and 4.2%.

Delayed parent vessel occlusion

Three reports of delayed occlusion were identified in the literature by Fiorella (2010) and Klisch (2011) with parent vessel occlusion 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.

Subarachnoid haemorrhage

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 2010b) (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.

Device related ADRs

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.

Discussion of Adverse Events / Complications

A summary of adverse events is tabulated in Table 2 below. The data within this table falls into two broad categories:

- Category 1 – Serious but expected adverse events
- Category 2 – Serious unexpected adverse events

Concerns arise when excessive reports are received involving category 1 events or when any category 2 events occur. Regarding the adverse events, two clinical advisors responded, one felt that due to the patient population and past experience with other treatment options, the adverse events reported were not unusual. Another advisor felt that some of the serious but expected adverse events occurred in a higher proportion than might be expected. The issues surrounding adverse events with Pipeline from the literature are detailed below.

Table 2 - Adverse events

Study	Adverse Event / Complication
Nelson (2011) (n=31)	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. • Iatrogenic rupture of the distal ICA with large left hemisphere stroke
	Patient 2 • Periprocedural stroke manifest as right sided hemiparesis and motor aphasia
	Patient 3 • Mild asymptomatic stenosis
FDA (2011) (PUFS Study) (n=108)	21 adverse events (15 serious) were judged to be probably or definitely related to PED Major ipsilateral stroke / neurological death occurred in 6 patients:
	Patient 1 • Ischaemic event (due to non compliance with antiplatelet therapy)
	Patient 2 • Ischaemic event with stenosis in target aneurysm's parent vessel and in a collateral vessel treated with stent-assisted coiling
	Patient 3 • Suspected non-response to antithrombotic treatment leading to ipsilateral stroke & death
	Patient 4 • Haemorrhagic event (unspecified)
	Patient 5 • Haemorrhagic event (unspecified)
	Patient 6 • Event of unknown cause
Fiorella (2008 & 2010) (n=2)	Patient 1 23 months post treatment (cessation of antiplatelet therapy at 18 months) • Blurred vision & diplopia • Right sided weakness • Complete occlusion of the left vertebral artery • Thrombus extending into basilar artery • Brainstem stroke 29 months post treatment • Severe dysarthria, • Progressive right sided hemiplegia • New areas of brainstem infarction • Fatal brainstem infarction
Lylyk (2009a) * (n=53)	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
Szikora (2010b) ** (n=18)	Patient 1 • Mild post procedural 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).

Study	Adverse Event / Complication
Phillips (2010) (n=10)	Patient 1 • Post operative transient ischaemic event (resolved completely)
	Patient 2 • Post operative seizures
Hartmann (2010) (n=8)	Patient 1 • Ipsilaterlal parenchymal haemorrhage 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.
Klisch (2011) (n=2)	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.
	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
Van Rooij (2010) (n=1)	Patient 1 • Apathetic and hemiparetic on right side • Infarction in the left basal ganglia; occlusion of perforator arteries
O'Kelly (2011) (n=96)	Patient 1 • Delayed aneurysm rupture
	Patients 2,3 and 4 • Distal territory haemorrhage
Hampton (2010) (n=5)	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 subarachnoid and intraventricular haemorrhage • Death
	Patient 3 • Worsening short term memory 3 months post procedure • Interval enlargement of the aneurysm
n = no of patients * Six of these patients also enrolled in the PITA study ** Nine of these patients also enrolled in the PITA study	

4.1.5 Describe and critique the statistical approach used

The manufacture has provided a summary of statistical analyses in the two primary studies. As a feasibility study PITA was not powered by statistical analyses and therefore statistical tests were not applied. The manufacturer does state that confidence intervals for continuous outcomes were calculated using standard methods however while the author does provide basic outcomes

statistics, confidence intervals have not been provided for these data. The information regarding the PUFS study was accurate and thorough.

The remaining studies have not been discussed by the manufacturer in regard to statistical analyses, however, the design of the studies and lack of controls led to a lack of relevant statistics in these studies.

4.1.6 Summary statement about the review of clinical effectiveness

Covidien appropriately identified thirteen studies relevant to the decision problem defined by NICE. On the whole these studies were of a poor quality in regard to the evidence hierarchy due to the predominance of case reports and case series. The inclusion of conference abstracts without full length manuscripts also reduced the amount of available data. However, these studies are relevant to the decision problem and held a range of useful data which between them covered a large proportion (although not all) of the outcomes identified within the scope. Some of the identified studies were based on trials providing a more robust data source. The EAC added to the studies identified by the manufacturer with a further four relevant manuscripts which also contained pertinent data.

In the manufacturers' submission, only two of the identified studies were presented as being robust enough to offer supporting evidence to the submission. This led to loss of substantial amounts of relevant information from the remaining studies which had been originally identified for inclusion. These omissions are considerable and led to a paucity of data regarding negative aspects such as adverse events, and also positive outcomes such as high occlusion rates which were seen throughout the studies.

4.2 Summary of submitted evidence

The EAC has indentified a total of 16 studies as being pertinent to the decision problem. These comprise of:

- One unpublished trial
- Ten full length manuscripts published in peer reviewed journals
- One journal letter

- Four conference abstracts

There are several concerns regarding the quality of relevant data:

- Absence of control group in any study: During the development of PED comparator studies have been impractical for several reasons including small patient numbers; the lack of a single comparator and patients in whom no other treatment option was available.
- Lack of clarity in reporting: For several of the included studies many details are unclear, for example it is unclear what inclusion/exclusion criteria were applied, whether consecutive patients were enrolled and if studies were prospective or retrospective.
- Lack of data: Several of the studies although relevant to the decision problem contain very limited data as they are only available in abstract form. This reduces the quality of the study as essential data is condensed or omitted.
- Study design limitations: Many of the included studies are case reports or case series which are low in the evidence hierarchy.
- Overlap of patients between studies and inability to separate data from these patient duplications.

Strengths of the submitted evidence include:

- The included studies address outcome measures relevant to the scope of the decision problem
- There is a high rate of clinical success within the studies

4.2.1 Summary of results

- **Successful device deployment**: There was a high rate of successful device deployment with only one single case report with a success rate of less than 95%
- **Successful occlusion:** More than half (7 out of 12) of the studies reporting occlusion rates described 100% occlusion success. The lowest occlusion rate reported was 69%.
- **Stroke:** Only two case series reported strokes with rates of 6.5% (n=31)and 5.6% (n=108)
- **Delayed parent vessel occlusion:** There were three reports from two papers of patients developing delayed parent vessel occlusion. Two of these patients died.

4.2.2 Critique of submitted evidence syntheses

No meta-analysis or systematic reviews were identified by the manufacturer or the EAC as being relevant to the decision problem. Lack of high quality data regarding inconsistent reporting and lack of clear statistical outcomes meant that meta-analysis is inappropriate.

In general the EAC feels that the synthesis of data by the manufacturer from the two primary studies was adequate but at times confusing. The remaining studies would have benefitted from a more in-depth data extraction process to utilise useful data within them.

5 ASSESSMENT OF COST ANALYSIS

5.1 Overview of manufacturer's economic assessment

5.1.1 Methods

This section of the report assesses the economic analysis submitted by the manufacturer regarding the use of PED for treatment of unruptured large and giant IAs. The manufacturer submission comprises:

- a search strategy for economic studies
- a description of a *de novo* economic model
- a functional model in excel

Table 3 - Reference table for areas of cost analysis in manufacturer's evidence

Area of cost analysis evidence	Section in submission document	Tables/Figures in submission document
Review of literature	Section 6.1	Table B6.1
Model structure	Section 6.2.3	Figure B6.1
Comparator		
Subgroups	Section 6.8	
Perspective and time horizon	Section 6.2.7	Table B6.2
Resource use and costs	Section 6.3.6 Section 6.4	Tables B6.11-6.14
Adverse event costs	Section 6.4.7 Section 6.6.6	Table 6.15 Table B6.31
Discount rates	Section 6.2.7	Table 6.2
Sensitivity analysis	Section 6.5	Tables B6.26-6.30 Chart B6.7-6.11
Results	Section 6.6	Tables B6.17-6.25
Validation	Section 6.7	Table B6.33

5.1.2 Identification of studies

The manufacturer provided details of the search strategy for economic studies. This looked for any economic literature concerning intracranial aneurysms; however none were identified that analysed PED. One unpublished study, a simple cost calculation model, was identified. This was produced by the previous manufacturer of pipeline, and was supplied to the EAC. There was very little information on the assumptions used in this model. The search strategy appeared comprehensive, both in the search terms included and the databases searched. The EAC has not repeated the submitted search, but did not identify any economic studies in the literature search for clinical evidence. The manufacturer did not provide details of search or selection criteria for papers that were used as data sources for the costs and clinical outcomes extrapolated beyond study follow up periods as described in section 6.3.7. It was therefore not possible for the EAC to quality check study selection.

5.1.3 Quality assessment of identified studies

Quality assessment using the supplied checklist was not undertaken by the manufacturer as it was considered to be of insufficient relevance to the decision problem. The EAC agreed a quality assessment was not possible given the lack of information accompanying the model, and that it would not add to the evidence available. The EAC carried out a quality assessment of the manufacturer model (Appendix 7).

5.1.4 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. A schematic diagram (Figure B6.1 of the manufacturer's submission) describes the model structure, which 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.

In the model, there are six interventions which can be selected as either the comparator or the intervention:

- PED;
- stent-assisted coiling;
- neurosurgical clipping;
- endovascular PVO;
- neurosurgical PVO;
- conservative management.

For the purposes of this report, the treatment selected is PED, and the comparators are the remaining five interventions.

5.1.5 Assumptions

Section 6.3.8 of the manufacturer submission lists the model assumptions identified by the manufacturer as:

- Occlusion rates for neurosurgical clipping
- Neurovascular and endovascular PVO occlusion rates
- Rupture and retreatment rates
- SAH occurs in 100% of ruptured aneurysms
- Anaesthetist time, one hour greater than procedure length

Four of the five assumptions identified concern the secondary outcomes that are used in the model to extrapolate beyond the study length of the clinical PUFS trial that is used as the main source of data on PED (FDA 2011). It is not clear how the references given as sources of the secondary outcome data were identified and selected as details of selection criteria and methods are not given. The majority are papers primarily concerning the comparator technologies and therefore would not have been identified in the original search.

5.1.6 Data sources

The manufacturer has provided model inputs across several tables in their report. Clinically-relevant inputs were presented in Tables B6.3 – B6.10, and resource-use and cost inputs are presented in Tables B6.11-B6.15. The data sources used in the model are listed in Table 4 together with comments from the EAC. There is no information on why particular sources were chosen, or how they were identified.

5.1.7 Resources and costs

The key drivers in the model were identified as the numbers and costs of PED's and coils (section 6.6.8 of the manufacturer submission). The sources for the costs are referenced in Table B6.12 of the manufacturer's submission. The number of PED devices used is taken from data held by Covidien, and is significantly different from that quoted in PUFS (FDA 2011) which is used as the main source of information for most other aspects of PED within the model. The number of coil devices used comes from an opinion in an editorial review (Wehman 2006).

Clinical experts were not used to provide evidence of effectiveness within the model, but six clinical experts provided data on duration of stay for PED. The method used was stated to be by key opinion leader (KOL) questionnaire, but neither this nor the full responses are included in the submitted evidence. The declarations of interest from each expert are not included in the submission.

5.1.8 Time horizon

The time horizon of the model is 10 years as given in the NICE guidance for manufacturers. This is appropriate for the technology and patient group.

5.1.9 Discounting

Discounting for costs and QALYs is applied at a rate of 3.5% as given in the NICE guidance for manufacturers and this is appropriately applied.

5.1.10 Results

The base case results for the six treatment options are presented in Table B6.22 of the manufacturer submission and are also presented on a cost-effectiveness plane (Chart B6.6 of the manufacturer submission). The incremental analysis is presented in three tables (B6.23 to B6.25 of the manufacturer submission) in the form of columns of costs, QALYs and ICER.

The EAC have included additional results in Tables 7 - 10, using alternative inputs for PED and coil use and alternative treatment options to meet the NICE scope requirements.

5.1.11 Sensitivity analysis

There is no sensitivity analysis on structural assumptions and the manufacturer reports that this is because of lack of data. Extensive one-way sensitivity analysis exploring the impact of a large number of model inputs was undertaken (Tables B6.26 – B6.30 and Tornado plots in charts B6.7 – B6.11 of manufacturer's submission). The selected ranges used in the sensitivity analysis were different for each parameter, which may be appropriate, but no explanation was provided for the

choice of values. The EAC also ran the model with sensitivities set uniformly at twenty per cent, but did not find any significant differences.

Two-way sensitivity analysis of the number of PEDs and number of coils used was presented in Tables B6.34 – B6.36, however the EAC does not support the sensitivity ranges, or base case figures used in these cases.

Probabilistic sensitivity analysis was not undertaken. An additional scenario analysis (Table B6.31) included the consequences of some adverse events, which had not been included in the base case analysis. Another scenario analysis considered short term outcomes only, excluding conservative management, (Table B6.32).

The base case results need to be considered with the sensitivity analyses in Tables B6.26 and B6.27 respectively of the manufacturer submission, and a consideration of the range of values used, with the Tornado diagrams (chart B6.7 and B6.8). The tornado diagrams highlight the parameters that most affect the outcome of the model and the numbers and costs of PEDs and coils (where used) are clearly important parameters in the model. If an inappropriately narrow range were used in sensitivity analysis its importance in the model may not be evident from the tornado diagram. Therefore the EAC also checked the ranges used for all parameters in the sensitivity analysis.

5.1.12 Model validation

The model was internally validated (Table 6.33 of the manufacturer submission) by undertaking 'stress tests' which test the model to see if it performs as expected for particular inputs. No unexpected results were obtained. These tests help to confirm that the model functions as intended. No formal external validation is presented but the manufacturer compares the results of the *de novo* model with the unpublished cost analysis (section 6.9.1 of the manufacturer submission) and found that the results differed substantially, with the *de novo* model being more conservative. The difference was identified as being due to the previous model assumption that retreatment costs for stent assisted coiling are considerable, but PED patients requiring no additional treatment. The manufacturer considered this assumption to be inappropriate

5.2 Critique of approach used

5.2.1 Scope

The manufacturer's model has deviated from the scope in respect of cost analysis in a number of areas. The scope specified three separate analyses:

Analysis 1

Population: Patients with complex intracranial aneurysms for whom stent-assisted coiling is considered feasible (*de novo* or repeat treatment).

Intervention: Pipeline Embolization Device

Comparator: Percutaneous interventional techniques including stent-assisted coiling and parent vessel occlusion

Analysis one is implemented as described in the scope, except that patients who undergo Endovascular PVO are stated in the manufacturer's report to be retreated by neurosurgical clipping whereas the scope indicates that stent-assisted coiling is considered feasible for retreatment. In fact the model does apply retreatment by stent-assisted coiling and not as indicated in Table B6.14 of the manufacturer submission. The effect of these inputs is shown in Section 5.3 of the EAC report.

Analysis 2

Population: Patients with complex intracranial aneurysms for whom stent-assisted coiling is not considered feasible (*de novo* or repeat treatment).

Intervention: Pipeline Embolization Device

Comparator: Neurosurgical techniques (including bypass)

Neurosurgical techniques are sub-divided into neurosurgical PVO and neurosurgical clipping, but it is not clear if bypass is included with PVO in the model, although this was included in the scope. Table B6.14 in the manufacturer submission shows that the model assumes retreatment for the neurosurgical clipping case is costed as stent-assisted coiling, whereas the scope indicates that the population comprises patients for whom stent-assisted coiling is not feasible for treatment or retreatment.

Analysis 3

Population: Patients with complex intracranial aneurysms for whom stent-assisted coiling and neurosurgical techniques are not considered feasible (*de novo* or repeat treatment).

Intervention: Pipeline Embolization Device

Comparator: Conservative treatment.

Whilst the model does include a comparison of PED with conservative treatment this was not applied to the population defined in the scope. So, for example, the model incorporates costs for retreatment using stent assisted coiling in the conservative management group (Table B6.14 in the manufacturer submission) and this is the largest element of cost in conservative management. Removing this element makes conservative management even less costly compared with PED.

5.2.2 Underlying assumptions

There are a number of assumptions underlying the model that were not identified by the manufacturer:

- It is assumed that the outcomes for patients with unruptured aneurysms are the same as those for ruptured aneurysms, since occlusion rates for comparators are taken from studies of ruptured aneurysms, whereas occlusion rates for PED were taken from the PUFS study of predominantly unruptured aneurysms.
- It is assumed that the link between intermediate and final outcomes based on occlusion categories (section 6.3.4) is the same for PED as for the comparator technologies. However, this is likely to underestimate the benefit of PED.
- There is an assumption in the sensitivity analysis that the number of PEDs and coils required for giant aneurysms is greater than for small or large aneurysms (described as inappropriate comparisons in Tables B6.34, B6.35 and B6.36). 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
- It is assumed that conservative treatment outcomes can be modelled as residual aneurysms, although there has been no treatment to the aneurysm, which would remain at its original size. The likelihood for residual aneurysms to rupture is used to model the likelihood of rupture of an untreated aneurysm. This is a conservative assumption within the model.

- The retreatment rate is related to the initial outcome (level of occlusion) rather than the procedure. The source of the retreatment rate (Campi 2007) was for stent-assisted coiling.

5.2.3 Model structure

The model follows the following steps:

Step 1. Treatment, followed by survive / die

The model starts with a treatment, depending on the user selection. For each treatment other than conservative management there is a percentage risk of perioperative mortality. There are no other inputs at this stage.

Step 2. Initial Outcome for surviving patients

Patients are split into three initial outcome groups:

- complete occlusion,
- residual neck, and
- residual aneurysm.

The model used inputs directly reported in this way for PED (PUFS trial (FDA 2011)) and stent-assisted coiling (Murayama 2003). For the other comparators, complete occlusion is reported and the remaining two outcomes are deduced. In the case of neurosurgical clipping, a ratio of 2:1 is used, calculated from another trial (Molyneux 2003). For the remaining treatments the manufacturer submission states an assumption that patients without complete occlusion will be divided equally between residual neck and residual aneurysm; there is no evidence to support this assumption.

For conservative treatment all patients are in the residual aneurysm category. This may be a flawed approach unless it is known that a residual aneurysm i.e. one that has previously been treated, and has been reduced in size, behaves in the same way as one that has been untreated. This assumption may overestimate the effectiveness of conservative treatment. The quality of life (QoL) utility for all surviving patients at this stage is 0.73 (Bor 2010).

Step 3 Prediction of ongoing outcomes

The degree of occlusion is used to predict the subsequent outcomes; in this model they are defined as no:

- complication;
- retreatment; or
- rupture

which either results in death or a reduced QoL utility (0.64). This step relies on the assumption that the degree of occlusion is related to the retreatment and rupture rate, and that it will be similar regardless of the initial treatment technique.

Retreatment – this incurs a treatment cost again, but doesn't have any other impact on how the patient is modelled. The retreated patient remains in the model, subject to the same possibilities of no complication, rupture or retreatment. The treatment assumed is dependant on the initial treatment, as stated in the EAC Table 5. It is not necessarily the same as the initial treatment. Retreatment costs are assumed to be the same as initial treatment costs for that procedure.

Rupture – this carries a 58% probability of death (Johnston 2008), with survivors having a reduced quality of life (0.64) and a cost of rehabilitation and care that is greatest in the first year, but continues throughout the model.

For the time period set, the risks stated are used every six months to give an accumulating number of cases of rupture, retreatment and death (including normal mortality). The associated QoL utilities and costs are also accumulated, discounted over time, and then calculated to give a per patient value.

Step 4: Results

The main cost areas are summarised in the results table for the treatment and comparator. The *incremental cost* incurred by using the selected treatment rather than the comparator is also given. Thus a negative incremental cost means that the treatment is cost saving compared to the comparator in this model.

Quality adjusted life years (QALYS) are presented for both the treatment and comparator, together with the incremental difference. In this case a positive incremental QALY value means that the treatment has a greater benefit than the comparator.

The *incremental cost effectiveness ratio (ICER)* is the incremental cost divided by incremental QALY, or the additional cost for one additional QALY. If the treatment is dominant, then it is both cheaper and results in increased quality adjusted life years.

EAC comments on the results are provided in Section 5.3

The model also lists some additional results not discussed in the manufacturer submission:

- Life years, and cost per life year
- Total number of ruptures, and cost per rupture averted
- Years free from event, and cost per event free year

Additional option: Include adverse events

There is an option of including "adverse events", although most of the results are reported without this selected. In the model "adverse events" are interpreted as non-fatal events resulting in a reduced quality of life and additional cost, occurring during or soon after the initial treatment.

The data sources are:

- comparators - complications of treatment (Darsaut 2011)
- Pipeline – adverse events (PUFS trial (FDA 2011))

The adverse events included are SAH or stroke. No other events are included in the model, although PUFS reports several more and not all types of stroke are reported from Darsaut.

The majority of the comparator adverse events from Darsaut are double counted when this option is selected, since they contribute to the perioperative mortality figures used in step 1. 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.

5.2.4 Comparators

All relevant comparators were included in the analysis, but some were not included in the same sense as in the scenarios requested by NICE.

- Neurosurgical bypass was not explicitly included in the neurosurgical PVO category

- Conservative treatment was not modelled appropriately for the scenario where all other comparator treatments were unusable
- Neuroclipping was not modelled appropriately for retreatment (stent assisted coiling, but this should have been clipping).

5.2.5 Literature search

The literature search is thorough and well recorded in Appendix 1 of the submission, but the process for selection of papers is less clear. Summing the number of papers identified in each search gives 1031 papers. Duplication would account for a reduction in this figure, but it is not stated how this is reduced to the 368 papers identified in section 6.1.2. No cost analyses relating to Pipeline were identified from these published papers.

5.2.6 Data Sources

A total of 17 papers are referenced as the source of inputs for the model. The majority of these give clinical information on comparator techniques. There is no information about how these papers were selected.

Table 4 - Table of studies used in as data sources in the economic model

How reference is used in model	Author	Title	Study details	Intervention	Population	Exclusions	Main Outcomes	Notes
• Age • Mortality and initial outcome for PED • length of procedure for PED • PED adverse event rates	**(FDA 2011) PUFS Trial**	Pipeline for Uncoilable or Failed Aneurysms (PUFS trial)	• Multicenter, US, Europe, Middle East • Prospective, single-arm • n=108 (100 at 180days) • 30 day, 180 days, 1 year follow-up	• Pipeline Embolization Device (PED)	• Large or giant AND wide-necked aneurysms • Petrous, cavernous, or paraopthalmic location • 89% female • Mean age 57.0	• SAH in last 60d • Intracranial haemorrhage in last 42d • >1 IA • Worsening clinical condition in last 30d • Intra- and extra- cranial stenosis	• IA occlusion 73.6% • Major stroke or neurological death 5.6% • 2.8% death rate at 180d • Device-related AEs 19.6% • From 99 patient at 180d, 81.8% complete occlusion; 8.1% residual neck; 7.1% residual aneurysm; 3.0% cannot determine	• Mean no. PEDs 3.1 (1-13) • 21 related adverse events at 180 days, 15 serious (14%). • Procedure length 124 minutes
• Mortality rate/ coil, clip and PVO • Initial outcome/ clip and PVO • AE rates (all except PED)	**(Darsaut 2011)**	Predictors of clinical and angiographic outcome after surgical or endovascular therapy of very large and giant intracranial aneurysms	• Single centre, US • Retrospective medical records review • n=183 • At least 31 days clinical follow-up • 1984-2008	• Neurosurgical clipping • Neurosurgical PVO • Endovascular PVO • Endovascular coiling	• ≥20mm IA • Treated • Unruptured	• Not treated • <31 day follow-up	• Aneurysm and treatment characteristics • Complication rate: clipping 16.7%; surg. PVO 13.3%; coiling 11.1%; endovascular PVO 18.3%. • Further retreatment • Mortality: clipping 13.1%; surg. PVO 17%; coiling 19%; endovascular PVO 21% • Complete occlusion rate: clipping 85%; surg PVO 59%; coiling 26%; endovascular PVO 41%	• Not explained why model uses occlusion rates from Darsaut (2011) for clipping and PVO, but uses Murayama (2003) for coiling • Model does not use complete data from AEs, omitted hemodynamic and surgical trauma strokes. • Only included SAH in first 31 days. Omitted SAHs after this. • Model spreads non-occluded rates over "residual neck" and "residual aneurysm" categories
• Initial outcomes/ coiling/ complete occlusion, residual neck and aneurysm. (Weighted average of groups A & B)	**(Murayama 2003)**	Guglielmi detachable coil embolization of cerebral aneurysms: 11 years experience	• Single centre, US • Retrospective medical records review • n=818 patients • 11 year follow-up (5 years & 6 years) • 1990-2002	• Coil embolization	• Aneurysm • 30% large or giant aneurysms • 41.8% patients unruptured	• Not reported	• Complete occlusion for aneurysm sizes: 55%; neck remnant: 35.4% • Clinical outcome, recanalization rate 20.9% • Procedural complications 8.4%	• Reporting is broken into subgroups by A and B and also aneurysm size.
Effectiveness: • Initial outcomes, Clipping. 2:1 ratio to calculate number of residual neck and aneurysm.	**(Molyneux 2003)**	ISAT trial of neurosurgical clipping vs endovascular coiling in 2143 patients with ruptured intracranial aneurysms	• Multicentre (42), mainly UK & Europe • RCT • n=2143 • 2 month & 1 year follow-up	• Endovascular coiling EVT (n=1063) • Neurosurgical clipping (NST) (n=1055)	• Ruptured IA • SAH • Treatment needed and suitable for either EVT or NST • Clinical uncertainty as to best treatment option	• SAH > 28 days ago • Inclusion criteria not met • Participating in another trial	• Dead or dependant at 1 year (EVT: 23.5%, NST 30.9%) Angiographic follow-up: • Complete occlusion (EVT 66%, NST 82%) • Subtotal occlusion/neck remnant (EVT 26%, NST 12%) • Incomplete occlusion (EVT 8%, NST 6%)	• Population of ISAT trial is different to PED model scope. Most importantly ISAT includes only ruptured aneurysms. Also, 52% of aneurysms ≤5mm, and 92% ≤10mm.

How reference is used in model	Author	Title	Study details	Intervention	Population	Exclusions	Main Outcomes	Notes
• Health state utilities for no complications and SAH. Also for part of adverse event disutilities calculation	**(Bor 2010)**	Optimal screening strategy for familial intracranial aneurysms: a cost effectiveness analysis	• Economic evaluation • Markov model and Monte Carlo simulations • No clinical data • The Netherlands (Euros)	• Screening using magnetic resonance angiography	• Family history of SAH, defined as =<2 affected first-degree relatives.	• Not reported	• Cost effectiveness of screening. • Reports QoL utilities, as one of inputs: QoL of positive result after screening 0.73; QoL after SAH: 0.64; QoL of resident in nursing home: 0.31 • Also reports costs/ICERs for screening and treatment.	• Costs based on Dutch health care system. • Negative effect of a positive screening outcome based on small untreatable aneurysm. • Model uses 0.73 as utility for no complications after treatment for IA. This may not be appropriate. • Sources of utilities not adequately described, some from Dorman (2000) and Wemer (2005)
• Utility following stroke – part of calculation for adverse event disutilities	**(Rosen 2010)**	Cost effectiveness of intensive lipid-lowering treatment for patients with congestive heart failure and coronary heart disease in the US	• Markov model • Cost-effectiveness comparison between two treatments for CHF/CHD • Used patient-level data from statin trial • USD$	• High vs low dose statins for congestive heart failure (CHF) & coronary heart disease (CHD)	• Patients with a history of both CHF and CHD from TNT (Treating New Targets) trial.	• Not reported	• QALYS / ICERs • Also reports: probability of related events and utilities for different conditions. • Stroke: 0.57	
• Rupture rate of three types of aneurysm • Death rate following rupture	**(Johnston 2008)**	Predictors of rehaemorrhage after treatment of ruptured intracranial aneurysms: the cerebral aneurysm rerupture after treatment study (CARAT)	• Multicentre (9), US • Ambidirectional retrospective cohort study • Medical records review • CARAT study • n=1001 • 1996-1998 • Mean 4 years follow-up	• Coil embolization • Surgical clipping for ruptured IA	• 1° diagnosis of ruptured intracranial aneurysms and treated with coil or clip	• Intracranial arteriovenous malformation or fistula present; • Vessel occlusion used to treat the aneurysm; • Endovascular balloon used • No information on degree of aneurysm occlusion after treatment.	• Re-rupture rates by degree of occlusion: complete occlusion 1.1%; small residual neck 2.9%; residual neck 5.9%; partial occlusion 17.6%. • Degree of aneurysm occlusion after treatment strong predictor of risk of rerupture • Risk of rerupture greater after coil compared to clip • reports patient characteristics, related to re-rupture rate	• Technique used for treatment of ruptured aneurysm has impact on risk of rerupture. • Population includes ruptured aneurysms only. • Not specifically large/giant aneurysms.

How reference is used in model	Author	Title	Study details	Intervention	Population	Exclusions	Main Outcomes	Notes
Effectiveness: • retreatment rate	**(Campi 2007)***	Retreatment of ruptured cerebral aneurysms in patients randomized by coiling or clipping in ISAT	• Multicentre, mainly UK & Europe • Retrospective medical record review from ISAT • 1994-2002 • Sub-group of pts requiring retreatment • n=230 • 7-years	• Retreatment after endovascular coiling (EVT) (n=191) • Retreatment after neurosurgical clipping (NST) (n=39)	• Subgroup of ISAT population • AND pts who had undergone more than procedure to target aneurysm	• Subgroup of ISAT population • No further exclusions	• Retreatment rate (EVT 17.4%, NST 3.9%) • Late retreatment >3months (EVT 9%, NST 0.9%) • Mean time to retreatment: 20.7 months • HR for retreatment after EVT 6.9	• Retreatment rates in paper only relate to EVT-treated aneurysms. • Population issues of ISAT trial.
Resource use: • Length of procedure: • Coils • Clipping Cost: • angiogram • endovascular equipment • neurosurgery equipment	**(Wolstenholme 2008)***	Treatment pathways, resource use, and costs of endovascular coiling vs surgical clipping after a SAH	• Costing from ISAT • Prospectively collected • n=1644 • 22 UK centres	• Endovascular coiling (n=809) • Neurosurgical clipping (n=835)	• As described in Molyneaux (2005) • UK treated patients only	• As described in Molyneaux (2005) • Non-UK patients	• Costs include – staff – equipment – hospital stay – consumables – imaging • Resource use for 1st treatment • Costs for 1st 12 months • Appendix has – breakdown of costs – resources for subsequent treatments	• Has very full cost and resource information • SAH/ruptured aneurysms only • Hospital based, rather than full care costs.
Resource use: • microcatheter • coils (for coiled and endov. PVO)	**(Wehman 2006)incorrectly cited as Hopkins (2006)**	Giant cerebral aneurysms: Endovascular challenges	• Review of clinical experience • Opinion-based • Literature review (not systematic)	• A range of endovascular techniques	• Giant aneurysms >25mm	• Not applicable	• Review describes evaluation, treatment planning and procedure options and techniques	• "Upward of 40 to 50 coils can be required to fill a giant aneurysm" quoted in reference to balloon assisted coil embolization. No reference provided – opinion of author.
Resource use: • aspirin dose • Clopidrogel dose	**(Nelson 2011)**	The pipeline embolization device for the intracranial treatment of aneurysms trial.	• PITA trial • Multicentre: Europe (3), Argentina (1) • Single-arm • n=31 • January – May 2007	• PED	• Wide-neck IAs (neck<4 mm or dome /neck ratio of <1.5) OR • IAs that had failed previous endovascular attempts.	• SAH within 60 days • Unstable neurologic deficit • <50% stenosis of the parent artery	• 47 devices were placed (mean 1.52 devices per aneurysm) • 97.9% device-placement success • 48.4% treated with PED alone, remainder PED+coils	• See clinical evidence section for more info • Length of time for medication with aspirin and clopidrogel longer in Nelson (2011) than model.

How reference is used in model	Author	Title	Study details	Intervention	Population	Exclusions	Main Outcomes	Notes
Cost: • staff (various) • cost of rupture (ambulance use)	**(Curtis 2010)**	PSSRU, unit costs of health care and social care	Widely used as economic evidence. Standard reference					
Cost: • operating room • Coil • Clip	**(Rivero-Arias 2009)***	The costs and prognostic characteristics of ischaemic neurological deficit due to subarachnoid haemorrhage in the UK: evidence from the MRC ISAT	• Resource use data collected during ISAT trial • UK NHS perspective • n=1644	• Delayed Ischaemic Deficit (DID) • Non-DID	• As described in Molyneaux (2005) • UK treated patients only	• As described in Molyneaux (2005) • Non-UK patients	• Mean health care costs at 24 months(SD):DID £28175 (£26773);no DID £ 18805 (£17287) • Effect on employment • Death at 1 and 2 year • Resource use for **imaging**, theatre time, **coils,** clips, ward stay	
Cost of stroke – acute and ongoing	**(National Collaborating Centre for Chronic Conditions 2006)**	Hypertension: Management in adults in primary care: pharmalogical update	Update of CG34, focusing on pharmacological management of hypertension. Based on systematic literature review	• Antihypertensive drugs	• RCTs comparing any combination of five antihypertensive drug classes	• Placebo-controlled trials • Non-RCTs	• Mortality • Stroke • Myocardial infarction • Heart failure • New-onset diabetes • Vascular procedures • Unstable angina • Study drug withdrawal • Cost-effectiveness	• In Table C9 cost of stroke: £8,046 (from HTA statins), in turn taken from Youman (2003). • Also report: utility of stroke 0.63 from HTA statins
Indirectly, cost of stroke	**(Ward 2007)**	A systematic review and economic evaluation of statins for the prevention of coronary events	• Systematic review • Clinical and cost effectiveness of • Markov model for costs and health outcomes • UK NHS perspective	• Statins in the 1° & 2° prevention of CHD & CVD • Lifetime of statin treatment	• Patients using statins for CHD and CVD in the UK.	• Methodologically unsound studies • Multi-interventional therapies where the effect of the statin could not be separated	• Effectiveness of statins • Cost-analysis of statin therapy	Table 55 reports: • Cost of treating stroke in 1st year £8046 (Youman 2003) weighted by severity and inflated to 2004 • Subsequent year £2163 (Youman 2003) weighted by severity and inflated to 2004 • Fatal event £7041 (Youman 2003) inflated to 2004
Indirectly, cost of stroke	**(Youman 2003)**	The Economic Burden of Stroke in the United Kingdom	• Burden-of-illness model • Based on clinical data from RCT (Kalra 2000) • Markov model • n=457 • UK	• Treatment for Stroke in UK	• Patients recruited from a population-based stroke register. • Included at time of presentation, ≤72 h after stroke onset.	• Mild stroke, • V. severe stroke, • Institutionalised or severe disability prior to stroke	• Mild/moderate/severe stroke, and discharge to home / nursing home. • Gives resource use and cost. Also cost for long term care and informal care.	

How reference is used in model	Author	Title	Study details	Intervention	Population	Exclusions	Main Outcomes	Notes
Indirectly, cost of stroke	**(Kalra 2000)**	Alternative strategies for stroke care: a prospective randomised controlled trial.	• Multi-centre and multi-agency, UK • Single blind RCT • n=1206 • April 1995 – Oct 1999	• Stroke unit • General wards with stroke team support • Domiciliary stroke care	• Patients recruited from a population-based stroke register. • Included at time of presentation, ≤72 h after stroke onset.	• Mild stroke, • V. severe stroke, • Institutionalised or severe disability prior to stroke	• Mortality or institutionalised at 1 year • Severe disability	

*International subarachnoid aneurysm trial (ISAT) was a multicentre RCT (mainly UK & Europe) with 2143 patients with ruptured intracranial aneurysms. ISAT compared endovascular detachable-coil treatment with craniotomy and clipping.

AE: adverse event; CARAT: cerebral aneurysm rerupture after treatment trial; CHD: coronary heart disease; CHF: congestive heart failure; CVD: cardiovascular disease; DID: delayed ischaemic deficiency; EVT: endovascular treatment; IA: intracranial aneurysm; ICER: incremental cost-effectiveness ratio; ISAT: International subarachnoid aneurysm trial; NST: neurosurgical treatment; PED: Pipeline embolization device; PITA: pipeline embolization device for the intracranial treatment; PSSRU: personal social service research unit; PUFS: pipeline for uncoilable or failed aneurysms; SAH: subarachnoid haemorrhage; TNT: treating new targets.

5.2.7 Model inputs

Clinical experts were not consulted by the manufacturer to assess the applicability of values in the model, although clinical experts were consulted on a specific question regarding length of time spent in the recovery ward post intervention. Given the assumptions that were made in the model it might have been prudent to also check other clinical parameters.

In the majority of cases the values used in the base case and range of inputs used in sensitivity analysis were appropriate. There were some cases where the EAC felt more appropriate values or ranges could have been chosen:

Quality of life data

Quality of life weights for the health states 'no SAH' or 'SAH' in Table B6.6 of the manufacturer submission were taken from Bor (2010). The utilities in this paper were derived from two studies in the literature, so the manufacturer did not reference the original source of the data. This is apparent throughout the submission and raises concerns that the data sources may not have been thoroughly researched or assessed for quality and relevance.

The utility for 'no SAH' is derived from Dorman (Dorman 2000), a validation study for a two question quality of life measure that reports EuroQol derived utilities. These are then weighted using a factor from Wermer (Wermer 2005) to account for the disutility in patients who have been told they have untreatable IA. The weighting is inappropriate for patients in the model who have just had successful treatment for IA. The utility for 'SAH' is for patients being cared for at home according to Bor. The utility for patients cared for in a nursing home is much lower in Bor (2010) (0.31) but this has been neglected in the model. This utility is derived from Dorman (2000)) where it is presented as a EuroQol utility for 'dependent' patients. Dependency, based on response to the question 'Do you need help from anybody with everyday activities?' is likely to be more frequent than care in a nursing home, since many dependent patients may be cared for at home. It would be reasonable to expect a significant proportion of patients after SAH to be dependent by this definition. This demonstrates the uncertainty introduced into the model by the use of secondary data sources.

Adverse event disutilities for thrombo-embolic stroke and remote ICH stroke are derived from Bor and Rosen (Bor 2010; Rosen 2010) in Table B6.8 of the manufacturer submission. Rosen takes data

from Sullivan (2005) which reflects the USA population and uses a panel to assign preference weights to a whole range of conditions, and is not primary data.

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.

Mortality rates

Mortality rates (section 6.3.2) were not gender specific, whereas the condition is known to be much more prevalent in females (PR = 1.57 (Vlak 2011)). Using the dichotomised male and female rates would be more appropriate; however the impact of this would be small within the model.

5.2.8 Resources and costs

In the majority of cases the values used in the base case and range of inputs used in sensitivity analysis were appropriate. There were some cases where the EAC felt more appropriate values or ranges could have been chosen.

Number of Pipeline devices used

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). 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.

Cost of Pipeline Embolization Devices

The manufacturer is best placed to determine the cost of the equipment and consumables required for PED placement. These are given as current list prices.

Number of coils used

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

Cost of coils

The cost of coils, stents and equipment required for comparator interventions are either list prices where available from manufacturers or taken from a single UK based publication (Rivero-Arias 2009) and inflated to current prices.

Length of procedure and length of recovery

Clinical expert opinion was used to determine length of stay in recovery post procedure for PED, but no declaration of interest was provided for the experts consulted (section 6.4.4 of the manufacturer submission). Procedure times for neurosurgical clipping and stent assisted coiling were determined from the ISAT study (Wolstenholme 2008) whose patient population comprises patients with ruptured aneurysms. These are not restricted to large or giant aneurysms. It is possible that procedure time could be different (longer) for unruptured large or giant aneurysms. Whilst this is a large trial, it is possible that there is a better source for this data, but the manufacturer has not described or justified selection of this source. The range of procedure times for PED and comparators considered in the sensitivity analysis was appropriate (1 to 5 hours). The range of days in recovery for PED and comparators was also appropriate (1 to 10).

Costs associated with health states

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 (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 factors 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

Cost of retreatment

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.

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

5.2.9 Adverse events

The submission would have benefitted from a clear definition of complications and adverse events. The main model includes:

- mortality at 31 days
- rupture
- retreatment

There is a separate scenario analysis (section 6.6.6 manufacturer submission) which is intended to include adverse events. The inputs in the model are shown in the manufacturer submission table B6.7, and reproduced in EAC Table 6

Table 6 - Adverse events inputs to model, from Manufacturer Table B6.7

Event	PED	Stent-assisted coiling	Neurosurgical clipping	Endovascular PVO	Neurosurgical PVO	Conservative management
SAH	0.9%	3.7%	1.2%	0.0%	0.0%	0.0%
Thrombo-embolic stroke	3.7%	3.7%	6.0%	18.2%	6.7%	0.0%
Remote ICH stroke	3.7%	3.7%	1.2%	0.0%	0.0%	0.0%

Adverse event rates for comparators are taken from Darsaut (Darsaut 2011) where they are described as treatment related complications. The events included are:

- SAH
- Thrombo-embolitic stroke
- Remote ICH stroke

Other reported events are excluded, although a rationale is not given. These are:

- Hemodynamic stroke
- Surgical trauma stroke

The same table of treatment related complications also gives a mortality rate at 31 days, which is used as the procedural mortality rate for the submitted model. Many of the complications used for adverse events data also resulted in death within 31 days. This means that many complications are being counted twice when the option for adverse events is selected.

Pipeline adverse events cover the first year after treatment and are taken from those reported in PUFs (FDA 2011), and replicated in Table B5.16, manufacturer submission. The model has included 6 serious adverse events in the categories:

- cerebral haematoma (1 entered in model as *remote ICH stroke*)
- haemorrhage intracranial (1 entered in model as *SAH*, 2 entered as *remote ICH stroke*)
- ischaemic stroke (3 entered in model as *thrombo-embolic stroke*)
- thrombotic stroke (1 entered in model as *thrombo-embolic stroke*)

In total, 44 serious adverse events were reported in PUFS (FDA 2011) in the first year, of which 15 were judged to be probably or definitely related to a pre-existing condition. For the remainder, 15 were judged to be probably or definitely related to PED, 8 to be probably or definitely related to PED placement, and 10 to be probably or definitely related to the use of antithrombotic

medications. It is unclear as to what overlap there is between these categories, and thus which adverse events should be included.

Ideally all serious adverse events related to the treatment would be reported, and used together with an appropriate QoL utility with those that occur at a later stage being present throughout the cycling of the model. The information for this is not available in Darsaut (2011) (Darsaut 2011). The EAC is not aware if it is available from other suitable sources; this would require a further literature search.

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.

5.3 Results included in manufacturer's submission

5.3.1 Analysis 1

Population: Patients with complex intracranial aneurysms for whom stent-assisted coiling is considered feasible (*de novo* or repeat treatment).
Intervention: Pipeline Embolization Device
Comparator: Percutaneous interventional techniques including stent-assisted coiling and parent vessel occlusion

PED vs stent assisted endovascular coiling

The main driving factors in this scenario, within the model are:

- Number of coils used
- Cost of coils
- Number of PED devices used
- Cost of PED devices
- Number of stents used

These are followed by:

- Lengths of procedure
- Recovery time
- Cost of retreatment for coiling

- Complete occlusion rate for coiling
- Retreatment rate for residual neck

Within the constraints of the model, the number and cost of PED and coil devices has by far the biggest impact in this scenario, and the EAC has little confidence that the model inputs reflect clinical practice, or that the sensitivity analysis captures a realistic range of possibilities.

The EAC suggest that more appropriate values would be:

- Number of coils = 25
- Number of PEDs = 2.4

These figures are based on clinical expert opinions and EAC findings (Appendices 8 and 9)

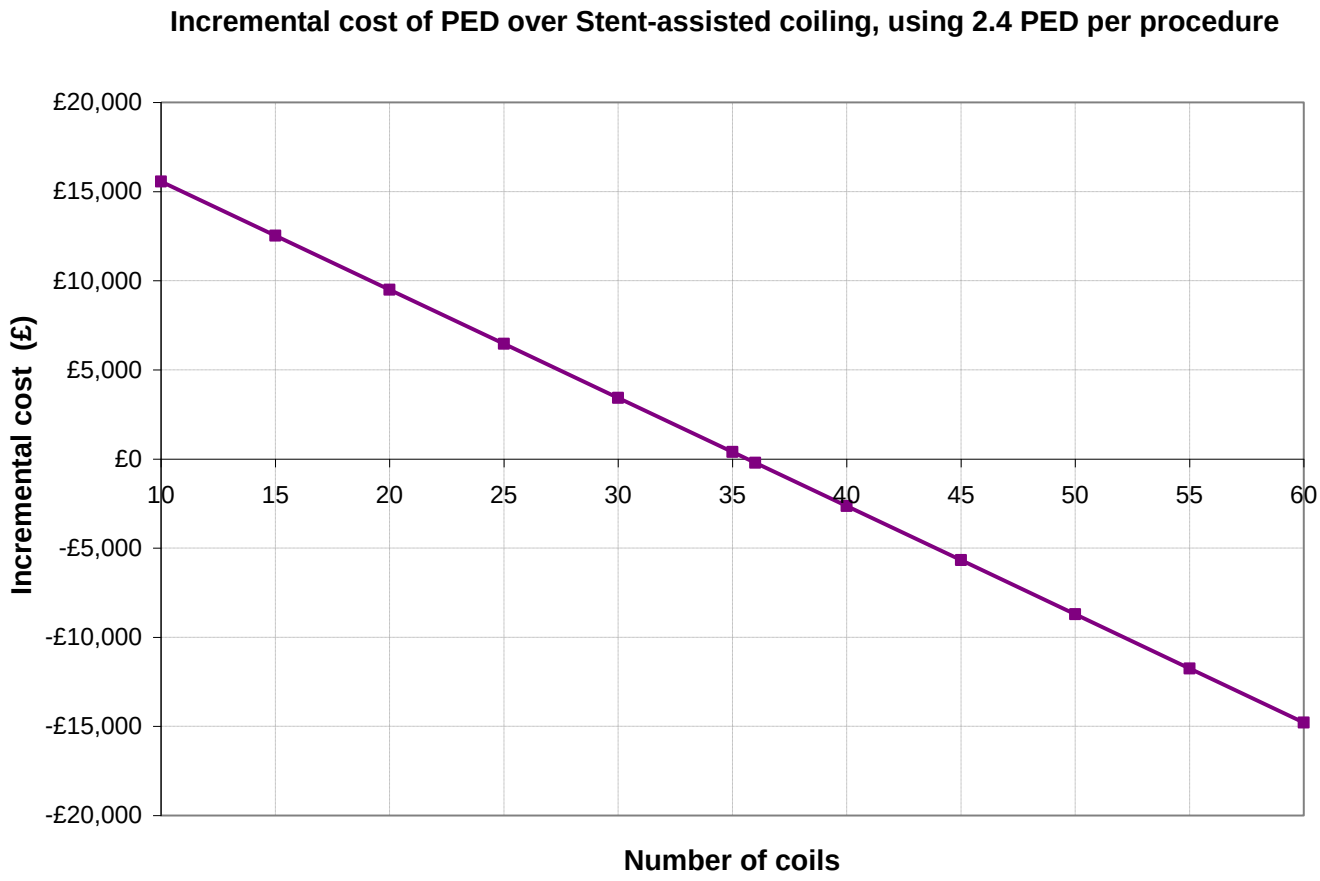
Adjusting the number of coils in the model does not change the number of stents used.

Table 7 - PED vs stent assisted coiling, base case and EAC inputs

		PED	Stent-assisted coiling	Incremental
Base case (1.46 PEDs, 40 coils)	Equipment costs	£16,830	£26,660	-£9,830
	Retreatment costs	£2,076	£4,956	-£2,880
	Total cost	**£24,341**	**£37,451**	**-£13,110**
EAC inputs (2.4 PEDs, 25 coils)	Equipment costs	£26,390	£18,770	£7,621
	Retreatment costs	£2,982	£3,743	-£761
	Total costs	**£34,807**	**£28,348**	**£6,460**

This shows that a change of device numbers, within realistic possibilities, results in the use of pipeline changing from a cost saving of £13,110 per patient, to an additional cost of £6,460 per patient in this scenario. It also has an affect on the cost per QALY, and cost per rupture averted. The effect of changing the numbers of coils (using no of PEDs =2.4) is shown in Figure 2.

Figure 2



PED vs endovascular PVO

All the drivers are very similar to scenario 1.1.

The manufacturer reports that endovascular PVO retreatment assumes the full cost of neurosurgical clipping (Table B6.14 in the manufacturer submission), however the model assumes the cost of stent-assisted coiling, which is the correct assumption according to the NICE scenario. Therefore the results reported in the manufacturer's submission reflect the NICE assumptions, and not those in table B6.14 of the manufacturer's submission.

Table 8 - PED vs endovascular PVO, base case and EAC inputs

		PED	Endovascular PVO	Incremental
Base case (1.46 PEDs, 40 coils)	Equipment costs	£16,830	£6,833	£9,996
	Retreatment costs	£2,076	£4,309	-£2,233
	Total cost	**£24,341**	**£16,893**	**£7,448**
EAC inputs (2.4 PEDs, 25 coils)	Equipment costs	£26,390	£6,833	£19,557
	Retreatment costs	£2,982	£3,254	-£273
	Total costs	**£34,807**	**£15,838**	**£18,969**

5.3.2 Analysis 2

Population: Patients with complex intracranial aneurysms for whom stent-assisted coiling is not considered feasible (de novo or repeat treatment).
Intervention: Pipeline Embolization Device
Comparator: Neurosurgical techniques (including bypass)

The option of neurosurgical bypass is not explicitly included in the model. There are two neurosurgical comparators considered separately in the model:

- neurosurgical clipping
- neurosurgical PVO

Neurosurgical clipping

Again, by far the biggest driver is the number and cost of PED devices. The next greatest influences come from length of procedure, time in recovery and cost of retreatment. The manufacturer's model assumes that retreatment would be by stent-assisted coiling, however the scope specifies a population where stent-assisted coiling is not feasible. The effect of changing the retreatment type to neurosurgical clipping would be a decrease in retreatment costs from £2,765 to £738. This also removes any sensitivity to the number or cost of coils or stents.

Table 9 - PED vs neurosurgical clipping, base case and EAC inputs

		PED	Neurosurgical clipping	Incremental
Base case (1.46 PEDs, 40 coils, retreat with stent-assisted coiling)	Equipment costs	£16,830	£1,087	£15,742
	Retreatment costs	£2,076	£2,765	-£689
	Total cost	**£24,341**	**£11,658**	**£12,684**
EAC inputs (2.4 PEDs, 25 coils, retreat with neurosurgical clipping)	Equipment costs	£26,390	£1,087	£25,303
	Retreatment costs	£2,982	£738	£2,243
	Total costs	**£34,807**	**£9,631**	**£25,177**

Neurosurgical PVO

The driving factors are the same as for scenario 2.1

Table 10 - PED vs neurosurgical PVO, base case and EAC inputs

		PED	Neurosurgical PVO	Incremental
Base case (1.46 PEDs, 40 coils, retreatment by neurosurgical clipping)	Equipment costs	£16,830	£3,067	£13,762
	Retreatment costs	£2,076	£998	£1,078
	Total cost	**£24,341**	**£11,654**	**£12,687**
EAC inputs (2.4 PEDs, 25 coils, retreatment by neurosurgical clipping.)	Equipment costs	£26,390	£3,067	£23,323
	Retreatment costs	£2,982	£998	£1984
	Total costs	**£34,807**	**£11,654**	**£23,153**

5.3.3 Analysis 3

Population: Patients with complex intracranial aneurysms for whom stent-assisted coiling and neurosurgical techniques are not considered feasible (de novo or repeat treatment).
Intervention: Pipeline Embolization Device
Comparator: Conservative treatment.

The change of PED numbers takes the incremental cost incurred per PED treatment from £13,989 to £26,062. The model assumes that any retreatment in the conservative arm would be using stent assisted coiling, however the scope specifies a population where other treatments are not possible. Therefore the EAC have rerun the model using a retreatment cost of zero. This further increases the incremental cost per PED treatment to £31,021. It also removes any sensitivity to coil numbers and costs.

Again the largest driver is the number and cost of PEDs used. Following this (for the conservative retreatment model), is length of procedure and days in recovery. Although it isn't highlighted by the tornado diagram, the costs of stroke will also be a significant factor. The EAC consider that there is a risk the model underestimates the cost of all aspects of stroke treatment. The model may underestimate the occurrence of stroke. Increasing these costs would decrease the incremental cost of PED. The utility values given to quality of life post stroke are not very robust, and decreasing the utility post stroke would favour treatment by PED.

The model assumes that all aneurysms treated conservatively will have the same risk of rupture and retreatment as a residual aneurysm. An untreated aneurysm may be larger, and at greater risk of rupture than the treated, residual aneurysm. Any increase in the probability of rupture for conservative treatment in the model would decrease the incremental cost of PED.

Table 11 - PED vs conservative, base case and EAC inputs

		PED	Conservative	Incremental
Base case (1.46 PEDs, 40 coils, retreatment with coils)	Equipment costs	£16,830	£0	£16,830
	Retreatment costs	£2,076	£6,566	-£4,489
	Total cost	**£24,341**	**£10,352**	**£13,989**
EAC inputs (2.4 PEDs, 25 coils, conservative retreatment)	Equipment costs	£26,390	£0	£26,390
	Retreatment costs	£2,982	£0	£2,982
	Total costs	**£34,807**	**£3,787**	**£31,021**

5.3.4 Cost-effectiveness analysis

According to the model PED is more costly than some of the comparators, but health benefits have been identified for PED and therefore a cost-effectiveness analysis was undertaken in addition to the cost analyses in the scope. It is difficult to see from the results presented in tables B6.23 and B6.24 and the accompanying text how these relate to the three analyses required in the scope. Table B6.23 shows an incremental analysis of all of the technologies considered. Table B6.24 is an incremental analysis of patients not suitable for neurosurgical clipping, which does not correspond to the population in Analysis 1, 2 or 3 of the scope. Table B6.25 is an incremental analysis of PED against each comparator. The results relevant to Analysis 1 can be found from PED versus stent-assisted coiling and PED versus endovascular PVO in this table. The results from the model for Analysis 2 are PED versus neurosurgical PVO and neurosurgical clipping, and the results for Analysis 3 are PED versus conservative management (Table 12 below).

Table 12 - Incremental analysis, PED against alternatives. Reproduced from B6.25, manufacturer submission. Using 1.46 PEDs and 40 coils (where relevant).

Scope	Technology	Incremental costs £	Incremental QALYs	ICER
Analysis 1	PED vs endovascular PVO	£7,448	1.265	£5,887
Analysis 1	PED vs stent-assisted coiling	-£13,110	1.003	Dominant
Analysis 2	PED vs neurosurgical PVO	£12,687	0.954	£13,297
Analysis 3	PED vs conservative management	£13,989	0.863	£16,202
Analysis 2	PED vs neurosurgical clipping	£12,684	0.574	£22,079

The main drivers for all three scenarios are the number and costs of PEDs and coils (where used). Other important factors are the Quality of Life utility, procedural mortality and the time horizon. The time horizon's importance is shown taking PED vs conservative as an example. Treatment with PED will have a procedural mortality rate, but lower residual aneurysms, and thus fewer ruptures over time. Conservative treatment has no procedural mortality rate, by definition, but over time will result in an increased number of ruptures. Thus a longer time horizon has more emphasis on the rupture rate and retreatment rate, and the procedural mortality's impact is reduced. The model takes 10 years as a base case which is appropriate.

Analysis 1

The results of the model show that PED is dominant (more effective and less costly) over stent-assisted coiling, and that there is an ICER of £5,887 for PED versus endovascular PVO. This result would imply that PED should always be used in preference to stent-assisted coiling, and that additional health benefits from using PED compared with endovascular PVO are accompanied by a modest additional cost.

The EAC re-ran the model with some changes to the input parameters where they were not considered to be the best available values. The inputs chosen were those expected to have the greatest influence on the result, and those where the sensitivity analysis was considered to be across a range that was too narrow. For Analysis 1, the numbers of PEDs and coils were modified as indicated in Tables 13 and 14.

Table 13 - PED vs stent-assisted coiling

	Incremental costs	Incremental QALYs	ICER	Comparator retreatment
Base case (1.46 PEDs, 40 coils)	-£13,110	1.003	Dominant	Stent-assisted coiling
EAC inputs (2.4 PEDs, 25 coils)	£6,460	1.003	£6,437	Stent-assisted coiling

Table 14 - PED vs endovascular PVO

	Incremental costs	Incremental QALYs	ICER	Comparator retreatment
Base case (1.46 PEDs, 40 coils)	£7,448	1.265	£5,887	Stent-assisted coiling
EAC inputs (2.4 PEDs, 25 coils)	£18,969	1.265	£14,993	Stent-assisted coiling

The effect of changing the number of PEDs and coils as described is that PED is no longer dominant over stent-assisted coiling. The increased QoL and length of life claimed incurs an additional cost of £6,437. When compared to endovascular PVO the ICER increases from £5,887 to £14,993.

Analysis 2

The results of the model in Table 14 above show that PED is more costly than neurosurgical interventions, but offers an improved outcome in terms of QoL and length of life. As discussed earlier the model includes retreatment by stent-assisted coiling rather than neurosurgical clipping. Therefore the EAC re-ran the model with the costs of retreatment by neurosurgical clipping as in the scope:

Table 15 - PED vs neurosurgical clipping

	Incremental costs	Incremental QALYs	ICER	Comparator retreatment
Base case (1.46 PEDs, 40 coils)	£12,684	0.574	£22,079	stent-assisted coiling
EAC (2.4 PEDs, 25 coils)	£25,177	0.574	£43,826	neurosurgical clipping

Analysis 3

The results of the model show that PED is more costly than conservative management but offers improved QoL and length of life. For conservative management the model includes cost of retreatment by stent-assisted coiling, which is not in the scope. Therefore the EAC re-ran the model without the costs of retreatment for conservative management. For conservative treatment, the rupture rate for residual aneurysms and QoL with no complications were also key drivers, with greater impact than cost and number of PEDs.

Table 16 - PED vs conservative management

	Incremental costs	Incremental QALYs	ICER	Comparator retreatment
Base case (1.46 PEDs, 40 coils)	£13,989	0.863	£16,202	stent-assisted coiling
EAC (2.4 PEDs, 25 coils)	£31,021	0.863	£35,928	no retreatment

The amendments to the model described in this section of the EAC report alter the outcome of the analysis in section 6.6.3 of the manufacturer submission. At a willingness to pay threshold of £30,000 per QALY, PED is no longer the most cost-effective option Table 17. Neurosurgical clipping is the most cost-effective option at the £30,000 threshold.

Table 17 - Incremental analysis using EAC inputs to update table B6.23, manufacturer submission. PED=2.4, Coils=25

Technology	Total costs	QALYs	ICER	Comparator retreatment
Endovascular PVO	£15,838	4.241		Stent-assisted coiling
Stent-assisted coiling	£28,348	4.503	£47,748	Stent-assisted coiling
Neurosurgical PVO	£11,654	4.552	Dominant	Neurosurgical clipping
Conservative management	£3787	4.643	Dominant	Conservative
Neurosurgical clipping	£9,631	4.932	£20,221	Neurosurgical clipping
PED	£34,807	5.506	£43,860	PED

5.4 Comment on validity of results presented with reference to methodology used

There are significant assumptions underlying the model that could affect its validity. Lack of data on long term outcomes of PED means the modellers have extrapolated using rather complicated methods from studies that have many differences from the scope. The selection of these particular studies has not been described or justified and further undermines the reliability of the results. Relationships between final outcomes and initial outcomes are tenuous and justification is inadequate.

The handling of complications and adverse events is confusing and inadequate. The definition of the terms is not clear from the submission and seems to differ from definitions in references used. The costs and consequences of complications and adverse events were not well researched and not derived from primary data. A more rigorous search for appropriate data would give more confidence in the model. The EAC has provided a quality assessment of the manufacturers' economic model in Appendix 7.

5.5 Summary of uncertainties and issues

Data sources are not justified and therefore doubt remains regarding the validity and quality of model inputs. The numbers of PEDs and coils remain uncertain and there was inadequate sensitivity analysis on the number of PEDs. Changing the values of these key drivers of the model alters the final result of the analysis. Methods chosen for retreatment in the model did not match those given in the scope. Changing the retreatment methods to match the scope alters the final result of the analysis. 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.

6 Additional work undertaken by the External Assessment Centre

- The EAC commissioned the Support Unit for Research Evidence (SURE) to identify improvements in the manufacturers search strategy. The EAC used these suggestions to amend and re-run the search. The identified studies were subject to a systematic selection process which was independently checked for quality.
- The EAC contacted organisers of the conferences at which relevant abstracts been presented to identify contact details for the appropriate authors. These authors were e-mailed to determine if full length manuscripts were available or if further data could be access
- Attempts were made to contact the authors of the studies where patient duplication had occurred.
- The HES database was interrogated and their analysts contacted to determine the most accurate patient population.
- The Department of Health NHS reference costs were contacted to ascertain costs for angiograms within the NHS.

7 DISCUSSION

7.1 Summary of clinical effectiveness issues

The available studies show encouraging data which reflect many of the outcome measures within the scope of the decision problem. High success rates regarding device placement and aneurysm occlusion are reported throughout the studies. However there are numerous difficulties in

accurately comparing some data fields due to lack of clarity in reporting. This is particularly relevant for adverse events. Problems in transparency of data also occur due to the patient duplication which has occurred across several of the studies.

A lack of systematic reviews and meta-analysis leads to a reliance on relatively poor quality data and a low level evidence base. Absence of comparator studies means that assessment against alternative treatments are impossible; however, as recognised in the scope, there are patients for whom no other treatment alternatives are available for whom there will be no comparators.

7.2 Summary of cost issues

The economic analysis relies on the *de novo* model. The following concerns are highlighted in this report:

- The key drivers of the model were identified in the manufacturer submission as the number and costs of PED and coils. There are uncertainties regarding the number of PEDs and coils used for the defined patient population in analysis 1 of the scope.
- Retreatments included in the model for neurosurgery and for conservative management differed from those required in the scope.
- The inclusion and treatment of complications and adverse events within the model is unsatisfactory.
- For PED versus conservative treatment the costs of long term care may have been underestimated.
- Throughout the model the selection of sources for inputs was not justified.

7.3 Implications for guidance and research

Identify Comparator studies - In order to directly compare PED with alternative treatments, comparator studies would need to be undertaken. Due to the nature of the disease however, this is not feasible. Alternatively a comprehensive literature search on the comparators should be carried out in order to gather comparable data. This would allow attempts to be made to compare efficacy and safety of PED to other available treatment options. Furthermore, identification of studies involving similar patient groups treated with coils would enable a more accurate

estimation of the number of coils used in this patient population. This would give clarification to the estimated costs involved in the two treatment groups.

Long term outcomes of PED – Two year data for the PUFS study will soon be available, and as the use of PED becomes more established there will be more long term data available. This will help to determine the long term outcomes of the device.

Other ongoing studies – The UK flow diverter audit and the Hong Kong Registry for safety and efficacy are two potential future sources of useful data. The FIAT trial although not PED specific will also provide a source of further information which may help clarify some areas of uncertainty.

Upcoming publications – The available literature contained a number of conference abstracts. At least one of these ((O'Kelly C 2011)) is planned to be published in the near future. As more experience is gained with PED, so its value as a treatment option can be determined.

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Wong, G.K.C., Kwan, M.C.L., Ng, R.Y.T., Yu, S.C.H., & Poon, W.S. (2011) Flow diverters for treatment of intracranial aneurysms: Current status and ongoing clinical trials. *Journal of Clinical Neuroscience.18 (6) (pp 737-740).*

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Appendix 1 – EAC Search Strategy

Introduction

As a comparatively new device, aimed at a small, specific patient population, it was anticipated that experience with and therefore literature relating to the Pipeline Embolization Device would be relatively limited. An initial search of the available relevant literature suggested that even using broad search terms, the number of references identified would be manageable (<1000). Therefore search terms were kept wide in order to capture all relevant citations.

EAC Search Strategy

The manufacturer's search strategy was adapted and expanded to reflect search terms included by Li (2010). Changes were also made to incorporate alternative spellings (i.e. aneurysm, aneurism). Modified searches were applied to the following sources:

Medline (including Medline 1948 - Present and Medline In-Process and other non-indexed citations)

EMBASE (1980 to 2011 week 31)

Cochrane Library (CENTRAL, CDSR, DARE, HTA, EED)

Web of Science (SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, 2000 – 2011)

Current Controlled Trials (all registers)

Clinicaltrials.gov

All literature searches were carried out between the 11th and 18th of August 2011. The following search terms were used:

Medline and Medline in Process:

1. Intracranial Aneurysm/
2. Aneurysm/ or aneurysm, unruptured/
3. exp brain/ or exp meninges/ or exp cerebral arteries/
4. 2 and 3
5. ((anterior communicating or posterior communicating or anterior cerebral or middle cerebral or posterior cerebral) adj5 artery adj5 aneur$).ti,ab.
6. (cerebral adj5 aneur$).ti,ab.
7. (intracerebral adj5 aneur$).ti,ab.
8. (cranial adj5 aneur$).ti,ab.
9. (intracranial adj5 aneur$).ti,ab.
10. (brain adj5 aneur$).ti,ab
11. (berry adj5 aneur$).ti,ab.
12. (basilar adj5 aneur$).ti,ab.

13. (saccular adj5 aneur$).ti,ab.
14. (fusiform adj5 aneur$).ti,ab.
15. or/1-14
16. pipeline.ti,ab.
17. PED.ti,ab.
18. (chestnut or EV3 or covidien).ti,ab.
19. (flow diverter$ or flow diversion$).ti,ab.
20. emboli?ation device$.ti,ab.
21. or/16-20
22. 15 and 21
23. (PUFS or (pipeline adj6 uncoilable adj2 failed aneur$)).mp.
24. (PITA or (pipeline adj6 intracranial treatment adj2 aneur$)).mp.
25. (Complete Occlusion and Coilable Aneur$).ti,ab.
26. or/22-25
27. animals/ not (humans/ and animals/)
28. 26 not 27

EMBASE:

1. exp intracranial aneurysm/
2. Aneurysm/ or aneurysm, ruptured/
3. exp brain/ or exp meninges/ or exp cerebral arteries/
4. 2 and 3
5. ((anterior communicating or posterior communicating or anterior cerebral or middle cerebral or posterior cerebral) adj5 artery adj5 aneur$).ti,ab.
6. (cerebral adj5 aneur$).ti,ab.
7. (intracerebral adj5 aneur$).ti,ab.
8. (cranial adj5 aneur$).ti,ab.
9. (intracranial adj5 aneur$).ti,ab.
10. (brain adj5 aneur$).ti,ab.
11. (giant adj5 aneur$).ti,ab.
12. (berry adj5 aneur$).ti,ab.
13. (basilar adj5 aneur$).ti,ab.
14. (saccular adj5 aneur$).ti,ab.
15. (fusiform adj5 aneur$).ti,ab.
16. or/1-15
17. pipeline.ti,ab.
18. PED.ti,ab.
19. (chestnut or EV3 or covidien).ti,ab.
20. (flow diverter$ or flow diversion$).ti,ab.
21. (emboli?ation adj2 device$).ti,ab.
22. or/17-21
23. 16 and 22
24. (PUFS or (Pipeline adj6 Uncoilable adj2 Failed Aneur$)).mp.
25. (PITA or (Pipeline adj6 Intracranial Treatment adj2 Aneur$)).mp.
26. (Complete Occlusion and Coilable Aneur$).ti,ab.
27. or/23-26
28. Animal/ or Animal Experiment/ or Nonhuman/

29. (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,sh.
30. 28 or 29
31. exp Human/ or Human Experiment/
32. 30 not (30 and 31)
33. 27 not 32

Cochrane Library:

1. MeSH descriptor Intracranial Aneurysm explode all trees
2. Aneurysm/ or aneurysm ruptured/
3. Exp brain/ or exp meninges/ or exp cerebral arteries/
4. (#2 AND #3)
5. ((anterior communicating or posterior communicating or anterior cerebral or middle cerebral or posterior cerebral) adj5 artery adj5 aneur*)
6. (cerebral NEAR/5 aneur*):ti,ab,kw
7. (intracerebral NEAR/5 aneur*):ti,ab,kw
8. (cranial NEAR/5 aneur*):ti,ab,kw
9. (intracranial NEAR/5 aneur*):ti,ab,kw
10. (brain NEAR/5 aneur*):ti,ab,kw
11. (giant NEAR/5 aneur*):ti,ab,kw
12. (berry NEAR/5 aneur*):ti,ab,kw
13. (basilar NEAR/5 aneur*):ti,ab,kw
14. (saccular NEAR/5 aneur*):ti,ab,kw
15. (fusiform NEAR/5 aneur*):ti,ab,kw
16. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)
17. (pipeline)
18. (ped)
19. (chestnut or EV3 or covidien)
20. "flow diverter*" or "flow diversion*"
21. (emboli?ation NEAR/5 device*)
22. (#17 OR #18 OR #19 OR #20 OR #21)
23. (#16 AND #22)
24. (PUFS or (Uncoilable near/2 "Failed Aneur*"))
25. (PUFS or (Uncoilable near/2 "Failed Aneur*"))
26. (Pipeline NEAR/6 "Intracranial Treatment" NEAR/2 Aneur*)
27. "Complete Occlusion" and "Coilable Aneur"
28. (#23 OR #24 OR #25 OR #26)

Web of Science:

#1. (TS=(cerebral SAME aneur*) OR TS=(intracerebral SAME aneur*) OR TS=(cranial SAME aneur*) OR TS=(intracranial) OR TS=(brain SAME aneur*) OR TS=(berry SAME aneur*) OR TS=(basilar SAME aneur*) OR TS=(saccular SAME aneur*) OR TS=(fusiform SAME aneur*))
#2. (TS=(pipeline) OR TS=(PED) OR TS=(chestnut) OR TS=(EV3) OR TS=(covidien) OR TS=(flow diverter*) OR TS=(flow diversion*) OR TS=(emboli?ation device?))

#3. (TS=(PUFS) OR TS=(pipeline * uncoilable * failed aneur*) OR TS=(PITA) OR TS=(pipeline * intracranial treatment * aneur*) OR TS=(complete occlusion * coilable aneur*))
#4. #1 AND #2
#5. #4 OR #3

Stoke Centre Stroke Trials Registry, Current Controlled Trials and Clinicaltrials.gov

1. Pipeline OR flow diversion OR flow diverter

Results

The numbers of references retrieved at each stage are indicated below in Table 18. These results were imported into Reference Manager and duplicates removed. Two reviewers independently assessed each title and abstract with reference to the stated study inclusion criteria. This resulted in 69 publications, which were further assessed using the full text where available. One abstract from a German language journal was identified as potentially being relevant to the decision problem, however only the abstract was available in English and this held no relevant data and was therefore excluded.

Three of the identified publications (Lylyk 2008;Lylyk 2009a;Lylyk 2009b) were based on a single study, with two of the three only available as abstracts. Therefore as a fully inclusive manuscript Lylyk 2009a was identified as being most relevant to the decision problem.

Table 18 - References retrieved by EAC

Source	References retrieved
Medline and Medline In-process	266
Embase	411
Cochrane Library (CENTRAL, CDSR, DARE, HTA, EED)	6
Web of Science	542
Stoke Centre Stroke Trials Registry	0
Current Controlled Trials	9
Clinicaltrials.gov	5
Ad hoc internet search	2
Total Before Duplicate Removal	1239
Total After Duplicate Removal	882
References selected for full-text assessment	55
Total number of studies for data extraction	16

Appendix 2 - Studies excluded from qualitative synthesis

Study	Reason for exclusion
Amar AP; Tummala RP; Hopkins LN; Lavine SD; Chen M; Connolly ES; Solomon RA; Meyers PM; Riina HA. Definitive reconstruction of circumferential, fusiform intracranial aneurysms with the pipeline embolization device – Comments. Neurosurgery 2008; 62 (5):1120-1121	Commentary on Fiorella (2008) publication
Armonda RA. Curative endovascular reconstruction of cerebral aneurysms with the pipeline embolization device: The Buenos Aires experience – Commentary. Neurosurgery 2009: 64 (4): 642	Commentary on Lylyk (2009a) publication
Augsburger L; Farhat M; Reymond P; Fonck E; Kulcsar Z; Stergiopulos N; Rufenacht DA. Effect of flow diverter porosity on intraaneurysmal blood flow. Clinical Neuroradiology 2009; 19 (3): 204-214	Unclear if Pipeline, primarily blood flow study
Aurboonyawat T; Schmidt PJ; Piotin Mabank R; Spelle Lemoore J. A study of the first-generation pipeline embolization device morphology using intraoperative angiographic computed tomography (ACT). Neuroradiology; 2011; 53:23-30	Primarily study of morphology, little patient data available.
Biondi A; Drier A; Sourour N; Di MF; Jean B; Dormont D. Endovascular procedure evaluation using 3 Tesla diffusion-weighted MR imaging in patients with intracranial aneurysms treated by Flow Diverter Stents. Neuroradiology Journal Conference: 19th Symposium Neuroradiologicum - The World Congress of Diagnostic and Therapeutic Neuroradiology Bologna Italy. The Neuroradiology Journal:2010; 23(1) :476	Data not individually presented for different treatments
Cebral JR; Mut F; Raschi M; Scrivano E; Ceratto R; Lylyk P; Putman CM; Aneurysm Rupture Following Treatment with Flow-Diverting Stents: Computational Hemodynamics Analysis of Treatment. American Journal of Neuroradiology; 201132(1):27-33	Study of velocity in aneurysm
Civelli V. Endoluminal approach with flow-diverter stents for treatment of intracranial aneurysms. Neuroradiology Journal Conference: 19th Symposium Neuroradiologicum - The World Congress of Diagnostic and Therapeutic Neuroradiology Bologna Italy. The Neuroradiology Journal:2010; 23(1) :476	Overview
Cloft HJ. Flow diversion for cerebral aneurysms: A cautionary tale. American Journal of Neuroradiology 2011; 32 (1):26	Unclear what type of flow diverter included
D'Urso PI; Lanzino G; Cloft HJ; Kallmes DF. Flow diversion for intracranial aneurysms: a review. Stroke 2011; 42:2363-2368	Review
Fiorella D; Lylyk P; Szikora I; Kelly ME; Albuquerque FC; McDougall CG; Nelson PK. Curative cerebrovascular reconstruction with the Pipeline embolization device: the emergence of definitive endovascular therapy for intracranial aneurysms. Journal of Neurointerventional Surgery 2009; 5:56-65	Overview
Food and Drug Administration H. Cardiovascular and neurological devices; reclassification of two embolization devices. Final rule. Dec 2004. Federal Register	Not Flow Diverters
Guimaraens L; Sola T; Vivas E; Casasco A; Diaz C. Aneurysms treatment using intracranial stent (large wide-necked and giant aneurysms). Neuroradiology Journal Conference: 19th Symposium Neuroradiologicum - The World Congress of Diagnostic and Therapeutic Neuroradiology Bologna Italy. The Neuroradiology Journal:2010; 23(1) :323	Data not individually presented for different treatments
Hauck EF; Hopkins LN. Curative endovascular reconstruction of cerebral aneurysms with the pipeline embolization device: The Buenos Aires experience – Commentary. Neurosurgery 2009;64 (4):643	Commentary on Lylyk (2009a) publication

Study	Reason for exclusion
Hauck EF; Natarajan SK; Langer DJ; Hopkins LN; Siddiqui AH; Levy EI. Retrograde trans-posterior communicating artery snare-assisted rescue of lost access to a foreshortened pipeline embolization device: Complication management. Neurosurgery 2010; 67(2);495-502	PUFS Patient, data already available
Hoh BL. Curative endovascular reconstruction of cerebral aneurysms with the pipeline embolization device: The Buenos Aires experience – Commentary. Neurosurgery 2009; 64(4): 642-643	Commentary on Lylyk (2009a) publication
Kadziolka K; Estrade L; Leautaud A; Fathi W; Pierot L. Silk versus Pipeline for reconstructive endovascular treatment of intracranial aneurysms. Technical differences, difficulties, advantages and disadvantages of two types of flow diverters. Neuroradiology Journal Conference: 19th Symposium Neuroradiologicum - The World Congress of Diagnostic and Therapeutic Neuroradiology Bologna Italy. The Neuroradiology Journal:2010; 23(1) :323	Insufficient data available on Pipeline
Kulcsar Z; Houdart E; Bonafe A; Parker G; Millar J; Goddard A; Renowden S; Gal G; Turowski B; Mitchell K; van den Berg R; Gruber A; Wanke I; Rufenacht D. Aneurysm rupture after flow diversion treatment: The role of intraaneurysmal thrombosis. Neuroradiology Journal Conference: 19th Symposium Neuroradiologicum - The World Congress of Diagnostic and Therapeutic Neuroradiology Bologna Italy. The Neuroradiology Journal:2010; 23(1) :245-246	Silk
Kulcsar Z; Houdart E; Bonafe A; Parker G; Millar J; Goddard AJP; Renowden S; Gal G; Turowski B; Mitchell K; Gray F; Rodriguez M; van den Berg R; Gruber A; Desal H; Wanke I; Rufenacht DA. Intra-aneurysmal thrombosis as a possible cause of delayed aneurysm rupture after flow-diversion treatment. American Journal of Neuroradiology 2011; 2 (1):20-25	Silk
Kulcsr Z; Houdart E; Bonafe A; Parker G; Millar J; Goddard T; Renowden S; Gal G; Turowski B; Mitchell K; van den Berg R; Gruber A; Desal H; Wanke I; Rufenacht D; ESNR - Founders award for interventional neuroradiology: Intraaneurysmal thrombosis as a cause of rupture after flow diversion treatment. Neuroradiology Journal Conference: 19th Symposium Neuroradiologicum - The World Congress of Diagnostic and Therapeutic Neuroradiology Bologna Italy The Neuroradiology Journal:2010; 23(1): 473	Unclear what type of flow diverter used (Likely to be Silk)
Lanzino G. Curative endovascular reconstruction of cerebral aneurysms with the pipeline embolization device: The Buenos Aires experience – Commentary. Neurosurgery 2009; 64 (4): 643	Commentary on Lylyk (2009a) publication
Lieber BB; Sadasivan C. Endoluminal scaffolds for vascular reconstruction and exclusion of aneurysms from the cerebral circulation. Stroke 2010; 41: S21-S25	Discussion of engineering issues
Lylyk P; Miranda C; Berez A; Nelson K; Scrivano E; Romero R; Ingino C. Initial experience and mid term follow up with intracranial endovascular reconstruction aneurysms treatment with a new stent pipeline. Circulation 2008; 118(12): e474	Pre publication abstract, same data as Lylyk (2009a)
Lylyk P; Miranda JC; Ferrario A; Ceratto R; Scrivano E. Intracranial endovascular reconstruction of cerebral aneurysms with a new stent Pipeline: Initial experience and mid term follow up. Stroke Conference: 2009 State-of-the-Art Stroke Nursing Symposium San Diego, CA United States. Conference Publication: 2009; 40 (4): 137)	Pre published conference abstract, same data as Lylyk (2009a)
Lylyk P; Pabon B; Ferrario A; Scrivano E; Lundquist J; Ceratto R; Nella R. Endovascular treatment of ruptured intracranial aneurysms with pipeline flow-diverter stent: Pros and cons. Journal of Neurosurgery Conference: 78th Annual Meeting of the American Association of Neurological Surgeons, AANS 2010 Philadelphia, PA United States Journal of Neurosurgery 2010; 113: A433-434	Included unruptured and unruptured aneurysms but data not individually presented for two

Study	Reason for exclusion
McDougall CM; O'Kelly C. Combined open and vascular approach for deployment of flow diversion stent. Canadian Journal of Neurological Sciences Conference: 46th Annual Congress of the Canadian Neurological Sciences Federation. The Canadian Journal of Neurological Sciences 2011; 38(3) S36	Open and endovascular use of Pipeline in single patient
Mustafa W; Kadziolka K; Anxionnat R; Pierot L. Direct carotid-cavernous fistula following intracavernous carotid aneurysm treatment with a flow-diverter stent: A case report. Interventional Neuroradiology2010; 16 (4):447-450	Silk
Pierot L. Letter by Pierot regarding article 'Flow-diverter stent for the endovascular treatment of intracranial aneurysms: a prospective study in 29 patients with 34 aneurysms. Stroke 2011; 43: e38-e39	Silk
Pierot LP. Flow diverter stents in the treatment of intracranial aneurysms: Where are we? Journal of Neuroradiology 2011; 38: 40-46	Review
Raymond J; Darsaut TE; Guilbert F; Weill A; Roy D. Flow Diversion in Aneurysms Trial: the Design of the FIAT study. Interventional Neuroradiology 2011; 17: 147-153	Study design paper, no patient data
Richling B; Al-Schameri AR. Implants for endovascular neurointervention: From Serbinenko's balloon to flow diverters. Journal fur Neurologie, Neurochirurgie und Psychiatrie 2010; 11 (3):65-68	In German with English abstract. Unclear if Pipeline
Seibert B; Tummala RP; Chow R; Faridar A; Mousavi SA; Divani AA. Intracranial aneurysms: review of current treatment options and outcomes. Frontiers in neurology July 2011; 2: article 45	Review
Senturk C; Casasco A; Guimaraens L. Flow diverter stents: The ultimate solution for untouchable aneurysms or a weapon too dangerous to use. Neuroradiology Journal Conference: 19th Symposium Neuroradiologicum - The World Congress of Diagnostic and Therapeutic Neuroradiology Bologna Italy The Neuroradiology Journal:2010; 23(1): 476-477	Unclear what type of flow diverter used
Shlomovitz E; Jaskolka JD; Tan KT. Use of a Flow-Diverting Uncovered Stent for the Treatment of a Superior Mesenteric Artery Aneurysm. Journal of Vascular and Interventional Radiology 2011; 22(11): 1052-1055	Silk
Stienen MN; Seule MA; Weber J; Gautschi OP. An uncommon reason for facial hypoesthesia. Schweizerische Rundschau fur Medizin - Praxis 2011; 100 (11):653-657	In German with English abstract. Unclear if Pipeline
Walcott BP; Pisapia JM; Nahed BV; Kahle KT; Ogilvy CS. Early experience with flow diverting endoluminal stents for the treatment of intracranial aneurysms. Journal of Clinical Neuroscience 2011; 18:891-894	Review
Wong GKC; Kwan MCL; Ng RYT; Yu SCH; Poon WS. Flow diverters for treatment of intracranial aneurysms: Current status and ongoing clinical trials. Journal of Clinical Neuroscience 2011; 18 (6):737-740	Review
Wong GKC; Tan HB; Yu SCH; Poon WS. Use of the pipeline embolization device for the treatment of recurrent intracranial aneurysm after previous stent-assisted embolization. Surgical Practice 2011; 15: 29-30	Small aneurysms
Wong JH; Goyal M; Hudon ME; Morrish WF. Prospective evaluation of early use of SILK versus pipeline flow-diverting stents. Stroke Conference: 1st Canadian Stroke Congress Quebec City, Canada. Stroke 2010; 41 (7):e490	Data not individually presented for different treatments

Appendix 3 - Adverse events with Pipeline from the Food and Drug Administration MAUDE database (Accessed 09.08.11)

Event Date	Patient Outcome	Event Description
07.06.11	Disability	Following implantation, the patient returned for diagnostic angiogram and was found to have developed a carotid cavernous fistula. This was treated with onyx and the patient discharged.
31.05.11	Death	Patient treated with three PEDs without complications. During the night the patient had a perforator occlusion infarct which resolved with integrilin. Afterwards the patient was brought in for a 24 hour angio and expired from what was thought to be a brain stem infarct.
26.05.11	Malfunction *	The pipeline was deployed and found twisted during the procedure. The twist was removed with wire manipulation. No patient injury reported.
25.05.11	Disability	During the procedure it was reported that the pipeline was delivered under tension, thus it necked after deployment. Several attempts were made to open the pipeline, but without success. At attempt was then made to retrieve the pipeline but it resulted in a cavernous fistula. Consequently the parent vessel was sacrificed. No complications were reported with the patient as a result of the event.
24.05.11	Malfunction *	During the procedure the pipeline was deployed but the proximal section did not open completely. The issue was resolved by manipulation of the catheter. No patient injury reported.
24.05.11	Disability	Two pipelines were successfully deployed. Two hours post procedure, the patient experienced an ischaemic event.
17.05.11	Malfunction *	During procedure it was reported that the pipeline could not be disengaged from the capture coil. An attempt was made to withdraw the pipeline, but it stuck inside and enterprise stent. After several manipulations, the pipeline released from the capture coil. No patient injury reported.
17.05.11	Malfunction *	Approximately 8mm of the distal end of the pipeline did not open during delivery. As the physician attempted to retrieve the pipeline with an alligator, the pipeline fully opened. No patient injury reported.
13.05.11	Malfunction *	Treatment of an aneurysm previously treated with an enterprise stent. It was reported the pipeline was delivered into the previous enterprise stent with the distal end deployed. When coming around the bend, the pipeline had dense mesh over the stenotic region, giving the appearance of twisting. Several attempts were made and eventually the distal end deployed; however the stenotic region remained in the device. The physician was able to use a guide wire and balloon to open the stenotic region and the pipeline. No patient injury reported.
12.05.11	Malfunction	It was reported during pipeline delivery the distal section opened, but the rest was slow to open. The procedure was paused to remove the pipeline from the patient. No patient injury reported. (A large amount of blood was found on the pipeline which possibly caused the pipeline not to open).
09.05.11	Malfunction *	After the pipeline was deployed, the distal end would not dislodge from the capture coil (on the push wire). After approximately 40 minutes of manipulation, the pipeline released. No patient injury reported.
06.05.11	Disability	Two pipelines were deployed and one was possibly prolapsed and the other with some constriction. Balloon angioplasty was performed and both pipelines completely opened. End of procedure right a1 is noted very slow collateral filling. Previous run reviewed and show right a1 is occluded with simultaneous blood pressure increase as evident. Patient administered heparin and awoke with left side paralysis. Ct scan shows a small frontal infarct and areas of ischemia. Reported the patient has a mild weakness left side and has recovered. The patient was discharged from hospital.

Event Date	Patient Outcome	Event Description
04.05.11	Malfunction *	It was reported during delivery, the distal section of the pipeline could not be released from the capture coil. After several attempts, the rest opened but the distal tip is still inside the capture coil. Another pipeline was used to compress the distal tip between the two pipelines. No patient injury reported.
04.05.11	Death	It was reported 4 pipeline and 20 axiom coils were implanted. An hour later, the patient experienced a massive sah. The cause of haemorrhage was suspected distal wire perforation. Subsequently the patient expired.
04.05.11	Disability	It was reported after the pipeline was deployed during angiography run, a small dissection of the p1 proximal to the aneurysm was noted. No complications were reported with the patient as a result of the event.
03.05.11	Malfunction	The pipeline did not open during delivery. The system was removed from the patient and another one was used to complete the procedure. No patient injury was reported. (A large amount of blood was found inside the catheter and pipeline which possibly caused the pipeline not to open).
03.05.11	Malfunction *	After the pipeline was implanted, a balloon had to be used to open the distal section of the pipeline. No patient injury reported.
03.05.11	Malfunction *	After the pipeline was implanted, the physician had difficulty getting full wall opposition. A hyperglide balloon was used to inflate inside the pipeline to achieve full wall opposition. No patient injury reported.
29.04.11	Malfunction *	During delivery, the distal section of the pipeline opened but the midsection did not open. The entire system was removed from the patient and another one was used to complete the procedure. No patient injury reported. (A large amount of blood found on the catheter likely prevented the pipeline from fully opening).
22.04.11	Malfunction *	It was reported the pipeline could not be opened during deployment. Upon attempted removal, the distal end opened. The pipeline was implanted against the ica wall. No patient injury reported.
14.04.11	Death	Two pipelines were deployed successfully. During delivery of the third pipeline, the physician was uncomfortable with the device and decided to retrieve the whole system (first two pipelines left implanted). The patient was fine post procedure. Two weeks later the aneurysm ruptured and the patient expired.
13.04.11	Malfunction *	Resistance encountered during pipeline deployment and the device twisted on itself. A balloon was used to open the pipeline. No complications were reported with the patient as a result of the event.
12.04.11	Disability	It was reported after the pipeline was deployed, the mid section did not open. Several attempts were made, but without success. On the last attempt the proximal end of the pipeline collapsed inside the aneurysm and the distal section stayed in the vessel wall. Post procedure, it was reported the flow inside the ica was slower. No complications were reported with the patient as a result of the event.
05.04.11	Disability	It was reported that the proximal end of the pipeline did not open after deployment. Multiple attempts were made to open the proximal end and an alligator was used to retrieve the pipeline but without success. It was reported the patient experienced right hemiparesis with visual trouble and is recovering day after day.
30.03.11	Malfunction *	It was reported that the pipeline was implanted. While removing the pushwire, the distal section separated. The physician was able to retrieve the broken segment with an alligator. No patient injury reported.

* Indicates MAUDE reports reclassified as “Malfunction” as all specify that no patient injury was reported

Appendix 4 - MDR's (Medical Device Reports) received by the manufacturer since FDA approval of Pipeline

MDR Date Due	Patient Outcome	Event Description
02.09.2011	No patient injury	PED opened but not fully opposed to vessel wall. Balloon used with excellent radiographic result.
01.09.2011	Patient died.	PED placement in setting of multiple aneurysms plus recent rupture of arteriovenous malformation, treated with "Gluebran" in lipiodol. Patient had stroke and died.
31.08.2011	No patient injury	Failure of PED to fully open. Device removed.
31.08.2011	No patient injury	Difficulty positioning microcatheter. Attempt to use catheter pull-back technique after deploying distal end of PED just distal to a giant aneurysm. PED did not open, so technique did not work. PED removed.
19.08.2011	No patient injury	Difficulty opening proximal end of PED.
18.08.2011	No patient injury	PED kinked during deployment, requiring balloon to fully open.
12.08.2011	No patient injury	PED kinked during deployment, requiring balloon to fully open.
12.08.2011	No patient injury	Carotid-cavernous fistula approximately 2 weeks after PED placement. Patient underwent additional procedure without problems.
10.08.2011	No patient injury	Balloon used to fully open proximal end of PED.
30.07.2011	Patient died.	Post-procedure ipsilateral parenchymal haemorrhage.
30.07.2011	No patient injury	Balloon used to fully open proximal end of PED.
22.07.2011	Patient died.	Intraparenchymal and intraventricular haemorrhage at unknown point after PED placement.
17.07.2011	No patient injury	Difficulty opening distal end of PED.
15.07.2011	No patient injury	Could not retract delivery wire into catheter after successful PED delivery.
14.07.2011	No patient injury	Construct separation during placement of 3rd PED.
09.07.2011	Patient recovered well, unclear whether injury.	Clot on PED at end of procedure.
30.06.2011	Patient died.	Perforator infarction in basilar artery aneurysm treatment with PED.
23.06.2011	Unknown	Increased visual dysfunction postoperatively. No further details available.

Appendix 5 - Quality assessment of studies included in Clinical Evidence

Study	Clearly defined question?	Well described study population?	Well described intervention?	Use of validated outcome measures?	Appropriate statistical analyses?	Well-described result s?	Discussion/ Conclusion supported by data?	Funding source acknowledged?
Nelson (2011) (PITA study)	N	Y	Y	Y	Y	Y	Y	Y
FDA (2011) (PUFS Study)[a]	Y	Y	N	Y	Y	Y	Y	N
Fiorella (2008)	N	Y	Y	Y	N	Y	Y	NA
Fiorella (2009a)	N	Y	Y	Y	N	Y	Y	NA
Fiorella (2010)	N	Y	Y	Y	N	Y	Y	NA
Lylyk (2009a)	N	Y	Y	Y	Y	Y	Y	N
Szikora (2010a) Conference abstract	Y	N	N	Y	N	Y	Y	N
Szikora (2010b)	N	Y	Y	Y	Y	Y	Y	Y
Phillips (2010) Conference abstract	N	Y	N	N	N	Y	N	N
Hartmann (2010) Conference abstract	N	Y	N	Y	N	Y	Y	N
Klisch (2011)	N	Y	Y	Y	N	Y	Y	Y
Van Rooij (2010)	N	Y	N	N	N	Y	N	N
O'Kelly (2011) Conference abstract	N	N	N	N	N	N	N	N
Hampton (2011)	N	Y	N	Y	N	Y	Y	N
Sararols (2011)	N	Y	N	N	N	Y	N	N
Fiorella (2009b)	N	Y	Y	Y	N	Y	Y	N

a = As this study is unpublished, FDA paper has been used as source for qualitative assessment

Appendix 6 - Study Outcomes Measures

Study	No of patients (P) & aneurysms (A)	Average follow up (weeks)	Successful device placement	Occlusion rate in assessed patients	Altered size of aneurysm mass	Resolution of symptoms	Resource use outcomes	Stroke	Neurovascular death	Delayed parent vessel occlusion	Subarachnoid haemorrhage	Device related ADRs	Total number of Complications
Nelson (2011) (PITA Study)	31 (P) 31 (A)	26	96.8%	93.3%	-	-	-	6.5%	-	0	-	-	4
PUFS Study [c]	108 (P) 110 (A)	26	97.7%	73.6%	-	34%	-	5.6%	5.6%	-	-	1	21
Fiorella (2008 & 2010)	2 (P) 2 (A)	>52	100%	100%	-	-	-	50%	0	50%	0	0	1
Fiorella (2009a)	1 (P) 1 (A)	10	100%	100%	-	100%	-	0	0	0	0	0	0
Lylyk (2009a) *	53 (P) 63 (A)	>26	97%	93%	-	-	-	0	0	0	0	0	7
Szikora (2010a)	NK (P) 42 (A)	>26	-	89%	-	-	-	-	-	-	-	-	-
Szikora (2010b) **	18 (P) 19 (A)	26	95.1%	100%	-	61%	-	-	-	-	5.3%	-	4
Phillips (2010)	10 (P) NK (A)	NK	100%	100%	-	-	-	-	-	-	-	0	2
Hartmann (2010)	8 (P) 9 (A)	8	100%	-	-	-	-	-	12.5%	-	12.5%	-	2
Klisch (2011)	2 (P) 2 (A)	>52	100%	100%	-	-	-	0	0	100%	0	0	2
Van Rooij (2010)	1 (P) 1 (A)	NK	50%	-	-	-	-	100%	0	-	-	0	1
O'Kelly (2011)	96 (P) NK (A)	>13	-	69%	-	-	-	-	4.2%	-	1%	0	>4
Hampton (2011)	5 (P) 5 (A)	NK	-	-	Increase in 1 patient	-	-	-	20%	-	20%	-	3
Sararols (2011)	1 (P) 1 (A)	26	100%	100%	-	100%	-	0	0	0	0	0	0
Fiorella (2009b)	1 (P) 1 (A)	18	100%	100%	-	100%	-	0	0	0	0	0	0

[c] data taken from FDA Executive summary
* Six of these patients also enrolled in the PITA study
** Nine of these patients also enrolled in the PITA study

Appendix 7 - Quality Assessment of Pipeline Manufacturer's Economic Model

Study question	Grade	EAC Comments
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	No	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	NHS/PSS (Table B6.2)
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Treatment options are listed (footnote to Figure B6.1)
5. Were the alternatives being compared clearly described?	No	
6. Was the form of economic evaluation stated?	Yes	Described in section 6.2.3 and a schematic is given in Figure B6.1.
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	Section 6.2.4
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Quality of life weights for health states Table B6.6
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	No	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	No	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	No	Two papers are referenced Bor et al 2010 and Rosen 2010
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes/No	Papers are referenced but there is no description of the method of selection of the papers.
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	Yes	
20. Were details of any model used given?	Yes	

Study question	Grade	EAC Comments
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes/No	Choice of model was justified. Justification for key parameters was incomplete.
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	Yes	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	N/A	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	

Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination

Appendix 8 - Number of PED's used in treated patients

Report	Number of treated patients	Number of aneurysms	Total number of PEDs used
Included in literature review (where relevant data available)			
Nelson (2011) (PITA study)	31	31	47
PUFS	107	109	349
Fiorella (2008)	2	2	6
Fiorella (2009a)	1	1	7
Lylyk (2009a)*	53	63	84 [a]
Szikora (2010b)**	18	19	39
Hartmann (2010)	8	9	22
Klisch (2011)	2	2	13
Van Rooij (2010)	1	1	2
Hampton (2011)	5	5	6
Fiorella (2009b)	1	1	6
Other relevant studies			
Cebral (2011)	7	7	10
Aurboonyawat (2011)	6	6	9
Total	**242**	**256**	**600**
Average PEDs/Patient = 2.48		**Average PEDs / aneurysm = 2.34**	

* Six of these patients also enrolled in the PITA study

** Nine of these patients also enrolled in the PITA study

[a] Total number of PED's stated in this paper as 72. However, breakdown of PEDs per patient specified on two occasions totals 84 PED's.

Appendix 9 - Expert opinion for number of coils used

Clinical Expert	Comment
1	"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 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. 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 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 considerably more expensive. Marksman microcatheter needed for PED also costs 2.5x as much as standard microcatheter cost."
2	"40 coils is very excessive"
3	"Average' aneurysm will take 4-5 coils Medium aneurysms will require c 10-15 coils. Large aneurysms 15-35 or very occasionally more."