NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE,

Medical Technologies Evaluation Programme

Specification for manufacturer/sponsor submission of evidence

(Economic Section Only)

(August 2011, Final version)

(March 2010 template)

This document should be read in conjunction with Sections 1 to 5, submitted on 29th July 2011

Contents

6 Cost impact

6.1 Published cost-effectiveness and cost impact evaluations

Identification of studies

6.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and identify all unpublished data. Health economics studies should include all types of economic evaluation and cost studies, including cost analyses and budget impact analyses. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 7.6, appendix 6.

A range of databases indexing published research were searched for studies about the cost-effectiveness of the pipeline embolization device (PED) for cerebral aneurysm. The databases searched were the NICE minimum required MEDLINE, MEDLINE In-Process, EMBASE, EconLit and the NHS Economic Evaluation database (NHS EED). No date or language limits were applied. Full details of the

Description of identified studies

6.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

Three hundred and sixty eight papers papers were identified in the searches. Howvever, no cost analyses of PED were identified.

One unpublished document was identified. This document compared the cost of PED with the cost of stent-assisted coiling. It demonstrated cost savings of £29,115 when using PED rather than stent-assisted coiling. This analysis assumed use of

one PED per patient and did not provide a detailed breakdown of hospital costs or reflect the uncertainty around the parameters used, such as the number of coils used per patient. As such, this analysis was not incorporated into the current study.

Table B6.1 Summary list of all evaluations involving costs

Study	Year	Country where study was performed	Summary of model	Patient population (average age in years)	Costs (currency) (intervention, comparator)	QALYs (intervention, comparator) (when referred to in the study)	ICER (per QALY gained) (if applicable)
ev3 Treatment Cost Comparison Model	2010	Based on the UK setting	A simple cost calculation model	Not stated	Total cost for coiling was estimated at £54,610. The total cost for PED was estimated at £25,495,	Not calculated.	Not calculated.
ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life year(s)							

6.1.3 Please provide a complete quality assessment for each health economics study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[1] or Philips et al. (2004)[2]. For a suggested format based on Drummond and Jefferson (1996), please see section 7.7, appendix 7.

The one paper identified was not peer-reviewed and was not of sufficient detail for use in the current analysis. No clear references were provided for data sources. The model also appears to assume that all patients treated with coiling will require retreatment, whilst no patients treated with PED would require retreatment. As such, the model was not deemed to be of sufficient relevance to the decision problem scoped by NICE and, therefore, it was decided that a new model should be designed.

[1] 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.

[2] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

6.2 De novo cost impact analysis

6.2.1 Please provide the rationale for undertaking further cost analysis in relation to the decision-problem.

There is currently no published data available on the cost-effectiveness of PED reflecting the decision problem set out by the NICE scope. Economic decision analytic modelling is an appropriate method for this purpose as the long-term, as well as the short-term outcomes, are of interest.

Patients

6.2.2 What patient group(s) is(are) included in the cost impact analysis?

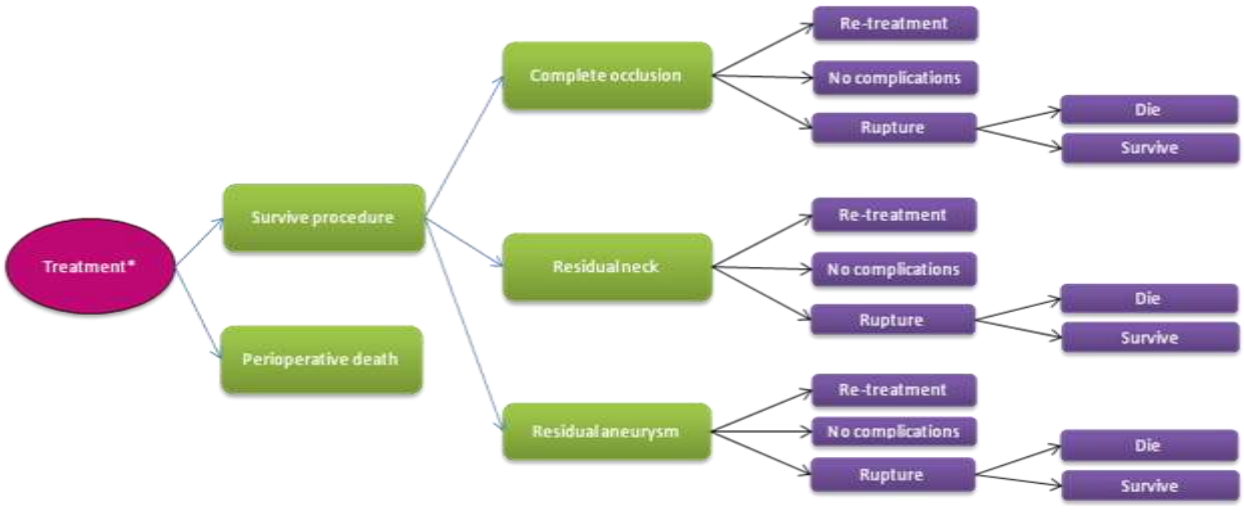
The population used in the model is patients with unruptured large or giant intracranial aneurysms (IAs). Different analyses are included in the model (as requested by the NICE scope), depending upon the patients' eligibility to receive certain interventions.

Model structure

6.2.3 Please provide a diagrammatical representation of the model you have chosen.

The economic model combined a 'decision tree' approach with Markov techniques to generate the costs and health outcomes associated with each intervention. Short-term data (i.e. the peri-procedural period) are captured in a decision tree, whilst long-term outcomes (based on the short-term markers) are calculated using Markov chain modelling.

Figure B6.1 Schematic of model structure



***Treatment options:** PED; Stent-assisted coiling; Neurosurgical clipping; Endovascular parent vessel occlusion; neurosurgical parent vessel occlusion; conservative management.

The green cells represent the short-term decision tree model, whilst the purple cells reflect the long-term Markov period. Probabilities within the long-term Markov model(s) are dependent upon the outcome within the short-term. For example, patients with complete occlusion following treatment are less likely to experience a rupture than patients who have a residual aneurysm.

6.2.4 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.4.

A decision tree structure is used to separate patients who have survived the procedure, based on a procedural mortality rate, into one of three occlusion categories: complete occlusion, residual neck and residual aneurysm. A Markov model structure is used for each of these categories to calculate the numbers of patients experiencing rupture and retreatment, which are modeled as the two major potential consequences of IAs. The health states used in the long-term Markov model are as follows:

- No complications;
- New non-fatal rupture;
- Post-rupture;
- Fatal rupture;
- Dead (all cause).

The transition probabilities for these health states are based on the rates of rupture and mortality following rupture. Further costs are included by modeling retreatment rate. Rupture and retreatment rates are based on occlusion category, which is used as a proxy. Treatment options are differentiated based on their proportion of patients in each occlusion category.

6.2.5 Please define what the health states in the model are meant to capture.

The health states in the model capture three key aspects:

- Cost (i.e. patients who experience a complication such as rupture or retreatment are likely to incur additional healthcare costs);
- Quality of life (that is, patients experiencing complications will be likely to suffer from reduced quality of life);
- Increased risk of mortality (patients experiencing rupture face an increased risk of death).

6.2.6 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

As described in Section 2.1, rupture is a major consequence of IAs, and large and giant aneurysms are more likely to rupture than smaller IAs. In order to compare treatments, occlusion rate is used to generate the short-term effectiveness of treatment. In turn, the level of occlusion drives the long-term rupture rate. Therefore, long-term outcomes differ by treatment based on the proportion of patients in each occlusion category following treatment.
IAs may require retreatment, with large and giant IAs being particularly susceptible to recurrence. Similarly to rupture, this is captured in the model by using short-term occlusion as a predictor of the likelihood for the need for retreatment in the future.

A half-cycle correction was used in the model. However, this was applied to the health outcomes (i.e. QALYs) only. Procedural costs are incurred at the start of the first cycle and, therefore, are not subjected to a half-cycle correction. Likewise, retreatment costs are one-off costs and are judged to occur as an *event* and, as such, are also not subjected to half-cycle correction.

6.2.7 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Table B6.2 Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	10 years	Outcomes of treatment for IAs continue long-term.	NICE guidance for manufacturers
Cycle length	6 months	This was considered suitable to capture the main consequences of the disease.	NICE guidance for manufacturers
Half-cycle correction	Included	To account for the fact that patients who die 'during' a cycle do not necessarily incur the full cost of that cycle.	NICE guidance for manufacturers
Discount of 3.5% for costs	3.5%	As set out in the NICE requirements.	NICE guidance for manufacturers
Perspective (NHS/PSS)	NHS/PSS	As set out in the NICE requirements.	NICE guidance for manufacturers
NHS, National Health Service; PSS, Personal Social Services.			

Technology

6.2.8 Are the intervention and comparator(s) implemented in the model as per their CE marking as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

The cost-effectiveness marking for PED is for endovascular embolisation of cerebral aneurysms. The current analysis focuses on a subgroup of the CE mark indication: patients with complex intracranial/cerebral aneurysms, specifically aneurysms that are large or giant (≥ 10mm in diameter), have wide necks (≥ 4mm) and/or are fusiform (with no discernable neck).

6.2.9 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

PED is a one-off procedural intervention and, as such, continuation rules are not applicable in this model. The same is also true for PED's comparators within the model.

6.3 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 5). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

6.3.1 Please demonstrate how the clinical data were implemented into the model.

The PUFS study (described in Section 5) provides the main source of clinical evidence for PED.

The procedural mortality rate (see Table B6.3) for patients treated with PED in the initial, decision tree section of the model was drawn from the PUFS study. For the surviving patients, the angiographic results giving the percentage of aneurysms in each occlusion category following treatment (complete occlusion, residual neck, residual aneurysm) were applied to the model cohort.

Table B6.3 Procedural mortality rate by treatment

	Procedural mortality rate	Source
PED	2.8%	PUFS
Stent-assisted coiling	19.0%	Darsaut *et al.* (2011)
Neurosurgical clipping	13.1%	Darsaut *et al.* (2011)
Endovascular PVO	21.0%	Darsaut *et al.* (2011)
Neurosurgical PVO	17.0%	Darsaut *et al.* (2011)
Conservative management	0.0%	Assumption, based on the definition of 'procedure-related' mortality.

Table B6.4 Initial occlusion rate by treatment

	Initial outcome (if survive)			
	Complete occlusion	Residual neck	Residual aneurysm	Source
PED	85.2%	8.4%	6.4%	PUFS study
Coiling	37.6%	51.7%	7.8%	Murayama *et al.* (2003)
Neurosurgical clipping	85.0%	10.0%	5.0%	Darsaut *et al.* (2011)
Endovascular PVO	41.0%	29.5%	29.5%	Darsaut *et al.* (2011)
Neurosurgical PVO	59.0%	20.5%	20.5%	Darsaut *et al.* (2011)
Conservative management	0.0%	0.0%	100.0%	Assumption

Occlusion rates (see Table B6.4) for PED were taken from the PUFS study. Four percent of patients from the PUFS trial were not categorised and had an unknown occlusion level. It was assumed that had these patients' occlusion categories been known they would have been split between the three occlusion categories in the same distribution as was observed for the other 96% of patients. Occlusion rates for stent-assisted coiling were taken from Murayama *et al.* (2003). These figures were calculated by summing patients from two groups: Group A (treated between December 1990 and December 1995) and Group B (treated between January 1996 and September 2002) and calculating a weighted average of large and giant aneurysms. Occlusion rates for neurosurgical clipping, endovascular PVO and neurosurgical PVO were drawn from Darsaut *et al.* (2011). This paper focused on large and giant aneurysms and was therefore appropriate for the current patient group. However, rates by treatment were only reported for complete occlusion. The remaining patients were split between the residual neck and residual aneurysm categories. For neurosurgical clipping this was done according to the ratio of residual neck to residual aneurysm occlusion rates from Molyneaux *et al.* (2005): 2:1. This paper was not specific to large and giant aneurysms and therefore was not an appropriate source from which to draw the complete occlusion rate. However, calculating the residual neck and residual aneurysm rates in this way is a conservative estimate as it is likely that for large and giant aneurysms the proportion of residual aneurysms, relative to residual necks, may be higher than in smaller aneurysms. This may have made the numbers of residual aneurysms for the comparators in the current analysis appear lower. The ratio of residual aneurysms to residual necks is certainly higher for PED than it is for neurosurgical clipping. Similar data were not available for neurosurgical PVO or endovascular PVO and so those patients whose aneurysms were not completely occluded were assumed to be split evenly between the residual neck and residual aneurysm categories. Conservative management patients were assumed to have 0% complete occlusion and residual neck occlusion and 100% residual aneurysm.

In order to quantify the consequences of a patient being in each occlusion category, additional evidence was used to identify the number of patients who would go on to experience aneurysm rupture and the number of patients who would go on to require retreatment due to recurrence of the aneurysm. Data on the rate of rupture in each occlusion category was drawn from Johnston *et al.* (2008). Data on the rate of retreatment in each occlusion category was drawn from Campi *et al.* (2008).

Mortality following rupture was taken from Johnston *et al.* (2008) and applied to those patients who had experienced a rupture, to give the post-procedural mortality rate.

6.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

For each occlusion category (complete occlusion, residual neck and residual aneurysm), participants were tracked through the health states, in 6-month cycles,

starting at six months, following on from the initial procedural period. The health states were as follows:

- No complications;
- New non-fatal rupture;
- Post-rupture;
- Fatal rupture;
- Dead (all cause).

For each occlusion category, at six months, all patients are in the 'No complications' category. In each subsequent cycle a proportion of these patients experience a rupture. These ruptures are differentiated based on whether or not they are fatal. Those patients experiencing a fatal rupture move into the 'Fatal rupture' state, according to the fatal rupture rate input for that occlusion category. This rate is based on the mortality rate following rupture, applied to the rupture rate, both from Johnston *et al.* (2008). The remaining patients having experienced a rupture move into the 'New non-fatal rupture' state. On the next cycle patients from the 'New non-fatal rupture' state move to the 'Post-rupture' state. It is assumed that once a patient is in the 'Post-rupture' state they will not move into the 'New non-fatal rupture' or 'Fatal rupture' states. Those patients in the 'Fatal rupture' state will move into the 'Dead (all cause)' state on the next cycle. Patients can also move into the 'Dead (all cause)' state from each of the other three health states due to age-related mortality. Age-specific annual mortality rates were derived from the UK Treasury's life tables and were converted into six-monthly rates. Mortality rates were not dichotomised into male and female rates, since the economic model did not use gender-specific inputs. The patient's age at diagnosis is generated at the start of the model, and increases thereafter, to ensure that non-disease related mortality is reflective of the ageing patient. The monthly all cause mortality rates are presented in full in Appendix 2.

6.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

Due to a lack of data suggesting otherwise it has been assumed that the transition probabilities will be constant over time.

6.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

Initial occlusion of the aneurysm (complete occlusion, residual neck, residual aneurysm) was linked to later outcomes of rupture and retreatment. Johnston *et al.* (2008) and Campi *et al.* (2008) show that better initial occlusion leads to lower rates of rupture and retreatment, respectively. Rupture and retreatment rates for each occlusion category were drawn from these two sources.

6.3.5 If clinical experts assessed the applicability of values available, or estimated or adjusted any values, please provide the following details[3]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method(s) used to collect and collate the opinions.

Clinical experts were not used to provide evidence of effectiveness within the model.

Summary of selected values

6.3.6 Please provide a list of all variables included in the cost impact analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

Table B6.5 Summary of variables applied in the economic model

Variable	Variable	CI (distribution)	Reference to section in submission
Age	57 years	Varied in sensitivity analysis.	Patient characteristics section 5.3.4, Table B5.8
Procedural mortality rate	Varies by treatment. Trial and published source (PUFS and	Varied in sensitivity analysis.	Table B6.3

[3] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

	Darsaut *et al.* (2011))		
Variable	**Variable**	**CI (distribution)**	**Reference to section in submission**
Initial outcome – occlusion rate (complete occlusion, residual neck, residual aneurysm)	Varies by treatment. Trial and published data. (Murayama *et al.* (2003), Darsaut *et al.* (2011), PUFS, Molyneaux *et al.* (2005)).	Varied in sensitivity analysis.	Table B6.4
Re-treament rate	Varies by occlusion category. Campi *et al.* (2007)	Varied in sensitivity analysis.	Tables B6.9 & B6.10
Rupture rate	Varies by occlusion category. Johnston *et al.* (2008)	Varied in sensitivity analysis.	Tables B6.9 & B6.10
Death rate following rupture	58% (Johnston *et al.* (2008))	Varied in sensitivity analysis.	Section 6.3.1
Age-related mortality	England & Wales Life Tables. Government's Actuary Department.	Not applicable	Section 6.3.2
Quality of life	Varies by health state. Bor *et al.* (2010).	Varied in sensitivity analysis.	See table B6.6
Procedure and equipment costs	Taken from national databases and published data.	Varied in sensitivity analysis.	Section 6.4
Adverse event rates	Varies by event	Only included in a scenario analysis.	Table B6.7
Adverse event disutilities	Varies by event	Only included in a scenario analysis.	Table B6.8
Adverse event costs	£8,046	Only included in a scenario analysis.	Table B6.15
Drug costs	British National Formulary 61	Not applicable	Section 6.4
Retreatment costs	Varies by treatment. Assumes full cost of appropriate second line treatment.	Varied in sensitivity analysis.	Section 6.4
Cost of rupture	Varies by outcome of rupture and by immediate and long-term costs.	Varied in sensitivity analysis.	Section 6.4
Resource use	Varies by	Varied in sensitivity	Section 6.4

	treatment. PUFS and published data.	analysis.	
CI, confidence interval			

One of the key benefits of using PED is that it reduces the long-term risk of complications such as rupture and, hence, further comorbidities such as SAH and/or stroke. Such complications are likely to significantly impair the patient's quality of life. As such, quality of life was included as an outcome in the model, by including health state utilities (and, subsequently, to generate quality-adjusted life years (QALYs)). The utility scores used within the model reflect the occurrence (or non-occurance) of subarachnoid haemorrhage.

Table B6.6 Quality of life weights for health states

	Utility	Source
No subarachnoid haemorrhage	0.73	Bor *et al.* (2010)
Post subarachnoid haemorrhage	0.64	Bor *et al.* (2010)

Adverse events were also modelled. However, due to a lack of reliable and consistent data between treatment groups, the inclusion of adverse events was restricted to a scenario analysis. Adverse event rates were taken from the PUFS study for PED and from Darsaut *et al.* (2011) for the comparators. By definition, patients in the conservative management arm experienced no treatment-related adverse events.

Thrombo-embolic stroke from Darsaut *et al.* (2011) was assumed to be equivalent to 'thrombotic stroke' and 'ischaemic stroke' from PUFS. Remote ICH stroke from Darsaut *et al.* (2011) was assumed to be equivalent to 'cerebral haematoma' and 'haemorrhage intracranial' from PUFS. There was one incident of SAH following PED in the PUFS study. This event was reported as 'hemorrhage intracranial'. Therefore, one incident of 'haemorrhage intracranial' was subtracted from the Remote ICH stroke category for PED and was classed as SAH in the model.

Table B6.7 Adverse event rates by treatment

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%

*In conservative management, the likelihood of aneurysm rupture resulting in a severe neurologic disorder was modelled elsewhere in the model.

Table B6.8 Disutility following adverse events

	Utility	Source
SAH	-0.09	Bor *et al.* (2010): Utility of patient with no complications minus the utility of a patient following SAH
Thrombo-embolic stroke	-0.16	Bor *et al.* (2010); Rosen (2010): Utility of a patient with no complications minus the utility of a patient following stroke
Remote ICH stroke	-0.16	Bor *et al.* (2010); Rosen (2010): Utility of a patient with no complications minus the utility of a patient following stroke

6.3.7 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? What assumptions and/or techniques were used for the extrapolation of longer term differences in clinical outcomes between the intervention and its comparator?

Rupture and retreatment rates were based on initial occlusion rate. The difference in clinical outcomes between the different treatment options resulted from the difference in the proportion of patients in each occlusion category (complete occlusion, residual neck, residual aneurysm). The rupture and retreatment rates were each extrapolated to the ten-year time horizon. This was done assuming that the risks for each were constant over the ten years. For each of rupture and retreatment the original risk (over a mean follow-up of 3.6 years for rupture and 6.1 years for retreatment) was converted to a risk for each six month cycle of the model. The following formula was used for the above-mentioned conversion.

Monthly rate = 1 – exp [ln (rate observed / time period)]

Table B6.9 Long-term rates of retreatment and rupture by level of occlusion

	Retreatment	Rupture
Complete occlusion	5.8%	1.1%
Residual neck	20.6%	3.58%
Residual aneurysm	18.8%	17.6%
Time period (years)	6.1	3.6

Fifty-eight percent of patients experiencing rupture will die (Johnston *et al.*, 2008). Therefore the probability of rupture was split into fatal and non-fatal ruptures before being converted to six-monthly rates. The subsequent outcomes are shown below.

Table B6.10 Long-term rates of retreatment and rupture by level of occlusion (converted to six-monthly rates)

	Retreatment	Fatal rupture	Non-fatal rupture
Complete occlusion	0.5%	0.2%	0.1%
Residual neck	1.9%	0.5%	0.2%
Residual aneurysm	1.7%	2.7%	1.1%

6.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Occlusion rates for neurosurgical clipping: rates of complete occlusion following neurosurgical clipping were taken from Darsaut *et al.* (2011). However, this source did not provide the proportion of incompletely occluded patients who had a residual aneurysm neck or a residual aneurysm. To provide these figures, the ratio of residual neck to residual aneurysm outcomes following neurosurgical clipping in Molyneaux *et al.* (2005), where 90% of aneurysms were smaller than 10mm, was applied to the incompletely occluded patients from Darsaut *et al.* (2005), a study specifically looking at large and giant aneurysms. It was assumed that the proportion of residual neck to residual aneurysm outcomes would be similar for large/giant and smaller aneurysms.

PVO occlusion rates: Similarly to occlusion rates for neurosurgical clipping, rates for complete occlusion following neurosurgical and endovascular PVO were drawn from Darsaut *et al.* (2011). However, no data were available for the rates of residual aneurysm neck and residual aneurysm. Unlike with neurosurgical clipping, there were no alternative sources giving these rates for smaller aneurysms and so those patients whose aneurysms were not completely occluded were split equally between the residual neck and residual aneurysm categories.

Rupture & retreatment rates: these were drawn from Johnston et al. (2008) and Campi et al. (2008) respectively, by occlusion category. Neither of these studies specifically refer to large/giant aneurysms. However, it is assumed that the effect of size on rupture and retreatment rates is due to the fact that larger aneurysms are harder to occlude in treatment. Occlusion rates for the current analysis were drawn from sources specifically concerned with large/giant aneurysms, which were used to infer the rupture and retreatment rates for each treatment. It was therefore assumed that the rupture and retreatment rates drawn from these sources would be appropriate for the current patient population.

SAH was assumed to occur in 100% of all ruptured aneurysms in order to allow the model to measure the impact (in terms of costs and quality of life) of ruptures. SAH is, therefore, used as the main indicator of outcomes and costs following rupture.

Anaesthetist time was assumed to be equal to the surgery time plus 1 hour, equivalent to 30 minutes spent both before and after the procedure.

6.4 Resource identification, measurement and valuation

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

6.4.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

Large and giant neck aneurysms are currently treated with a variety of different interventions, dependent upon the patient's suitability and eligibility for each type of technique. Long-term costs are likely to be incurred through the subsequent rupturing of aneurysms and the potential need for retreatment. These costs will differ, based on the initial effectiveness of the original treatment.

6.4.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

NHS Reference Costs 2009-2010 were used to cost the interventions and comparators. Tariffs are not appropriate, since the actual surgery time and recovery time may differ substantially between treatments.

Resource identification, measurement and valuation studies

6.4.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 7.9, appendix 9. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis
- technology costs.

The most significant cost impacting on the outcome of this analysis is the direct procedural cost of the intervention. All other costs, such as the cost of adverse events and the cost of long-term complications, are relatively modest compared to the treatment cost. Therefore, the key searches were focused on identifying studies estimating the cost of PED. The search strategy used to identify relevant studies is described in Section 6.1.1, and provided in detail in Appendix 1.

6.4.4 If clinical experts assessed the applicability of values available, or estimated or adjusted any values, please provide the following details[4]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method(s) used to collect and collate the opinions.

The uncertainty around these values should be addressed in the sensitivity analysis.

Due to a lack of data surrounding the length of time spent in the recovery ward, post intervention, a key opinion leader questionnaire was developed.

Covidien contacted six clinicians in total, based on their relationship, known experience with PED and its comparators. All six clinicians provided a response. A mean average duration of stay was calculated from their responses. Where a range was stated the mid-point was used.

[4] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

All of the model inputs are investigated through deterministic one-way sensitivity analysis. The results of which are explicitly reported in Section 6.6.

Intervention and comparators' costs

6.4.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, technology costs should be cross-referenced to sections 1.9. Provide a rationale for the choice of values used in the cost model discussed in section 6.2.3. Uncertainty around prices in sensitivity analysis.

The cost of interventions within the model is based on unit costs and level of resource utilisation. Unit costs are multiplied by the level of resource use in order to calculate the overall cost of the intervention and its associated costs. Table B6.11 shows the level of resource use associated with each intervention in the model, whilst Table B6.12 shows the unit cost associated with each resource.

Table B6.11 Procedural resource use

	PED	Stent-assisted coiling	Neurosurgical clipping	Endovascular PVO	Neurosurgical PVO	Conservative Management	Reference
Procedure time (hours)							
Length of procedure	2.07[a]	2.29[b]	3.56[b]	2.00[d]	3.56[d]	0	[a]PUFS; [b]Wolstenholme 2008; [c]Assumption (assumed one hour for balloon test and one hour for procedure); [d] Assumption (assumed equal to neurosurgical clipping)
Additional time for anaesthetist	1.00	1.00	1.00	1.00	1.00	0	Assumption: one additional hour for anaesthetist.
Staff (per hour)							
Surgeon	2.07	2.29	3.56	2.00	2.00	0	Based on procedure time (above)
Radiologist	2.07	2.29	3.56	2.00	2.00	0	Based on procedure time (above)
Nurse	2.07	2.29	3.56	2.00	2.00	0	Based on procedure time (above)
Anaesthetist	3.07	3.29	4.56	3.00	3.00	0	Based on procedure time (above) plus one hour
Hospital cost							
Neurology operating room (per hour)	2.07	2.29	0.00	2.00	0.00	0.00	Based on procedure time (above)
Neurosurgery operating room (per hour)	0.00	0.00	3.56	0.00	2.00	0.00	Based on procedure time (above)
Recovery ward	1.30	1.25	3.50	1.30	1.30	0.00	KOL survey
Imaging							
Angiogram	2	2	2	2	2	0	Assumption (assumes one at treatment and one follow-up)
Fluroscopy	1	1	0	1	1	0	Assumption (assumed for all treatments except neurosurgical clipping)
Magnetic resonance imaging	0	0	0	0	0	1	Assumed as follow-up monitoring for conservative

							management
Equipment/consumables							
PED	1.46	0	0	0	0	0	Data on file (Covidien).
Marksman catheter	1	2	0	1	0	0	One per procedure (other than neurosurgical clipping and neurosurgical PVO), although stent-assisted coiling also requires additional microcatheter.
Guidewire	1	1	0	1	1	0	One per procedure (other than neurosurgical clipping).
Distal access catheter	1	0	0	0	0	0	Assumed one use for PED.
Guide catheter	1	1	0	1	1	0	One per procedure (other than neurosurgical clipping)
Coil	0	40[a]	0	6[b]	0	0	[a]Hopkins *et al*. (2006). [b]Personal communication (Covidien).
Stent	0	1.00	0	0	0	0	Assumes one stent for stent-assisted coiling.
Clip	0	0	5	0	2	0	Assumed five clips for neurosurgical clipping and two for neurosurgical PVO.
Balloon	0	0.5	0	0	0	0	Assumes that 50% of patients receiving stent-assisted coiling require a balloon.
Balloon test	0	0	0	1	1	0	Assumed all patients undergoing endovascular and neurosurgical PVO require one balloon test.
Endovascular equip (per hour)	0.00	2.29	0.00	0.00	0.00	0.00	Based on procedure time (above)
Neurosurgical equip (per hour)	0.00	0.00	3.56	0.00	0.00	0.00	Based on procedure time (above)
Drugs (g)							
Aspirin	18	25	0	18	18	0	Nelson *et al*. (2011).
Clopidogrel	6.75	13.5	0	6.75	6.75	0	Nelson *et al*. (2011).

Long-term monitoring (MRI) per annum	0	0	0	0	0	1	Assumes one MRI per year for conservatively managed patients.

Table B6.12 Unit costs

Staff (per hour)		**Reference**
Surgeon	£403.00	Curtis, L. (2010). Table 15.6, unit cost per hour operating, including qualifications.
Radiologist	£403.00	Curtis, L. (2010). Assumed equal to surgeon cost. Table 15.6, unit cost per hour operating, including qualifications.
Nurse	£47.00	Curtis, L. (2010). Table 14.3, unit cost per hour of patient contact, including qualifications.
Anaesthetist	£403.00	Curtis, L. (2010). Assumed equal to surgeon cost. Table 15.6, unit cost per hour operating, including qualifications.
Hospital cost		
Neurology operating room (per hour)	£18.59	Taken from supplementary material for Riverio-Arias *et al.* (2009). Inflated to 2010 prices using the Hospital & Community Health Services Pay & Prices Index. Cost per day converted to cost per hour.
Neurosurgery operating room (per hour)	£19.11	Taken from supplementary material for Riverio-Arias *et al.* (2009). Inflated to 2010 prices using the Hospital & Community Health Services Pay & Prices Index. Cost per day converted to cost per hour.
Recovery ward	£327.01	NHS Reference Costs 2010. AA23Z: Haemorrhagic Cerebrovascular Disorders. Elective excess bed day.
Imaging		
Angiogram	£715.57	Wolstenholme *et al.* (2008). Inflated to 2010 prices using the Hospital & Community Health Services Pay & Prices Index.
Fluroscopy	£189.91	NHS Reference Costs 2010. Diagnostic Imaging: Outpatients RA18Z: Contrast fluroscopy procedures more than 40 minutes
Magnetic resonance imaging	£189.13	NHS Reference Costs 2010. Diagnostic Imaging: Outpatients RA02Z: Magnetic Resonance Imaging Scan, one area, post-contrast only

Equipment/consumables		Reference
PED	£10,171.00	List price; data on file
Marksman catheter	£1,030.00	List price; data on file
Guidewire	£160.00	List price; data on file
Distal access catheter	£500.00	List price; data on file
Guide catheter	£290.00	List price; data on file
Coil	£526.04	Taken from supplementary material for Riverio-Arias *et al.* (2009). Inflated to 2010 prices using the Hospital & Community Health Services Pay & Prices Index. Cost per day converted to cost per hour.
Stent	£2,750	List price of Enterprise stent; data on file
Clip	£210.19	Taken from supplementary material for Riverio-Arias *et al.* (2009). Inflated to 2010 prices using the Hospital & Community Health Services Pay & Prices Index. Cost per day converted to cost per hour.
Balloon	£717.00	List price of Hyperglide balloon (£717); data on file
Balloon test	£2,197.00	List price of Hyperglide balloon (£717) plus Marksman catheter (£1,030) plus Guidewire (£160) plus Guide catheter (£290); data on file
Endovascular equipment (per hour)	£89.40	Wolstenholme *et al.* (2008). Cost per minute of Siemens axiom artis FA/BA. Converted to cost per hour. Inflated to 2010 prices using the Hospital & Community Health Services Pay & Prices Index.
Neurosurgical equipment (per hour)	£10.20	Wolstenholme *et al.* (2008). Cost per minute of: Ziess microscope; Diathermy (Eschmann or vailab); Bipolar (Radiofrequency coagulator)(Eschmann); High speed drill (Codman); High speed drill (Midax-rex); Operating table (Eschmann); Yasargil retractor or Budd-Hal retractor. Converted to cost per hour. Inflated to 2010 prices using the Hospital & Community Health Services Pay & Prices Index.
Drug costs (per mg unless otherwise indicated)		
Aspirin	£0.00003	British National Formulary 61. Price per mg. Based on 32-tab pack of 300mg

		tablets = £0.31
Clopidogrel	£0.002	British National Formulary 61. Price per mg. Based on 30-tab pack of 75mg tablets.

Health-state costs

6.4.6 Please summarise, if appropriate, the costs included in each health state (Explanation of definition of health-state). Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost model. The health states should refer to the states in section 6.2.5.

Table B6.13 List of health states and associated costs in the economic model

Variable Name	Items	Value	Reference in submission
New non-fatal rupture	Non-fatal rupture initial cost	£8,046	The National Collaborating Centre (2006)
Post-rupture	Non-fatal rupture subsequent cost	£1,080	The National Collaborating Centre (2006)
Fatal rupture	Fatal rupture initial cost	£781	Curtis, L. (2010); NHS Reference Costs 2010
Dead (all cause)		£0	Assumption

Due to a lack of evidence for the cost of rupture (excluding the cost of retreatment, which is already included in the model), the model uses the cost of stroke, which is assumed to be representative of the cost of a rupture. The cost is divided into two time periods: (i) the initial cost of the rupture, which is likely to include high-intensity treatment and follow-up, and (ii) the long-term costs, which include rehabilitation therapy and other, more modest, medical costs. The latter was a monthly cost, which was multiplied to represent a six-monthly cycle.

The average cost of a fatal rupture is not known. As such, it was assumed that a patient dying from a rupture would incur the cost of one ambulance visit and one non-elective inpatient short-stay. This is likely to be a conservative estimate. However, no details are available to suggest the level of healthcare resources used following a fatal rupture.

Retreatment costs are also incorporated into the model. The type of retreatment modelled depends on the initial treatment. Costs applied to each retreatment type are assumed to be the same as the full cost for that treatment when used as the first treatment (see above for full calculations).

Table B6.14 Cost of retreatment

Initial Treatment	Cost of retreatment	Assumption
PED	£25,429	Assumes further use of PED
Stent-assisted coiling	£20,073	Assumes further use of stent-assisted coiling
Neurosurgical clipping	£20,073	Assumes full cost of stent-assisted coiling
Endovascular PVO	£9,098	Assumes full cost of neurosurgical clipping
Neurosurgical PVO	£9,098	Assumes full cost of neurosurgical clipping
Conservative management	£20,073	Assumes full cost of stent-assisted coiling

Adverse-event costs

6.4.7 Please summarise the costs for each adverse event listed in section 5.7 (Adverse events). These should include the costs of therapies identified in section 2.7. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost impact model discussed in section 6.2.3. Adverse event and complications episodes. Include all adverse events and complications costs, both during and longer term post-treatment cost.

Table B6.15 List of adverse events and summary of costs included in the economic model

Adverse events	Items	Value	Reference in submission
SAH	Assumes cost of stroke	£8046	The National Collaborating Centre (2006)
Thrombo-embolic stroke	Assumes cost of stroke	£8046	The National Collaborating Centre (2006)
Remote ICH stoke	Assumes cost of stroke	£8046	The National Collaborating Centre (2006)

Miscellaneous costs

6.4.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

No other costs have been included in the model.

6.4.9 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Because PED has been demonstrated to lead to improved health outcomes, it is likely that many cost savings may become apparent in the long-term. For example, improved rates of occlusion may result in substantial savings in terms of follow-up and monitoring costs. However, no reliable evidence is, so far, available, and so these potential savings have not been included within this analysis.

6.5 Sensitivity analysis

This section should be read in conjunction with NICE's 'Evaluation Pathway Programme methods guide',

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses.

All inputs used in the analysis will be estimated with a degree of imprecision.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

6.5.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

The economic model uses short-term outcomes (i.e. level of occlusion) to predict long-term outcomes. To do this, three different levels of occlusion were chosen, since those three (i.e. complete occlusion, residual neck, and residual aneurysm) were the outcomes for which data were available to link short- and long-term outcomes. Whilst it would be preferable to undertake structural uncertainty analysis on the number of outcome states (for example, to assess the impact of using four, five or six 'states'), unfortunately no data exist to support such an analysis.

One scenario analysis was been undertaken, where only the short-term impact of treatment (i.e. procedural mortality rate) was included in the model.

6.5.2 Was deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How variables were varied and what was the rationale for this? Where relevant, the distributions and their sources should be clearly stated. If any parameters or variables listed in section 6.2.7 were omitted from sensitivity analysis, please provide the rationale.

Extensive univariate sensitivity analyses were undertaken, assessing the impact of varying a range of different model parameters. These include:

- Starting age;
- Discounting rate – costs;
- Discounting rate – benefits;
- Time horizon;
- Procedural mortality rate (PED);
- Procedural mortality rate (comparator);
- Complete occlusion rate (PED);
- Complete occlusion rate (comparator);
- Retreatment rate (complete occlusion);
- Retreatment rate (residual neck);
- Retreatment (residual aneurysm);
- Rupture rate (complete occlusion);
- Rupture rate (residual neck);
- Rupture rate (residual aneurysm);
- Death rate following rupture;
- QoL (no complications);
- QoL (after SAH);
- Cost of PED;
- Cost of stent;
- Cost of coil;
- Cost of retreatment;
- Cost of retreatment;
- Cost of rupture (initial non-fatal);
- Cost of rupture (subsequent);
- Cost of rupture (initial fatal);
- Number of coils;
- Number of clips;
- Number of stents;
- Number of PEDs;
- Days in recovery (PED);
- Days in recovery (comparator);

- Length of procedure (PED);
- Length of procedure (comparator);
- Anaesthetist time.

The sensitivity analyses are reported in two different ways. Firstly, individual charts are presented for each parameter's sensitivity analysis, assessing a range of alternative values. Secondly, the 'maximum' and 'minimum' values for each parameter are shown within a tordano diagram, to help the decision maker to identify which parameters are the key drivers of the model.

6.6 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Costs.
- Disaggregated results such as costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A tabulation of the mean cost results.
- Results of the sensitivity analysis

Clinical outcomes from the model

6.6.1 For the outcomes highlighted in the decision problem (see section 4), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical studies. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

The economic model provides results for PED against five different comparators:

- Stent-assisted coiling;
- Neurosurgical clipping;
- Endovascular PVO;
- Neurosurgical PVO;
- Conservative management (i.e. no treatment).

As such, the model generates clinical outputs for each of the stated interventions. Unfortunately, there remains very little evidence on the *long-term* outcomes associated with each treatment. Therefore, the model uses short-term outcomes of surgery to predict long-term outcomes (i.e. rate of retreatment and rate of rupture).

Table B6.16 Summary of model results compared with clinical data

Outcome	Clinical study result	Model result
Short-term surgery outputs	Varies by treatment	Model uses exactly the same data as the trial
Mean life expectancy	Long-term data are not available by treatment	Varies by treatment – see below
Long-term rate of retreatment	Long-term data are not available by treatment	Varies by treatment – see below
Long-term rate of rupture	Long-term data are not available by treatment	Varies by treatment – see below
Adverse events	Varies by treatment	Model uses exactly the same data as the trial

Even in some cases where data are available for specific treatments, outcomes are not reported by size of aneurysm and, as such, it is not possible to validate the model using comparative trial data. Furthermore, data reported in published literature for outcomes such as rate of retreatment are usually reported *per surviving patient*. In the economic model presented here, the model generates *average* outputs for the entire cohort, which includes some patients who die during the peri-procedural period. As such, it is not necessarily appropriate to compare the model's outputs with those numbers reported in the literature.

6.6.2 Please provide details of the disaggregated costs by health state, and costs by category of cost. Suggested formats are presented below.

The economic model produces outputs based on the *type* of cost, rather than by health state. Costs broken down by type of cost are shown in the following five tables; one for each of the comparison treatments.

Table B6.17 Summary of expected costs by category of cost: PED vs stent-assisted coiling

	PED	Stent-assisted coiling	Incremental	Absolute increment	% absolute increment
Staff costs	£2,999	£3,282	-£283	£283	2%
Hospital costs	£464	£451	£12	£12	0%
Imaging costs	£1,621	£1,621	£0	£0	0%
Equipment costs	£16,830	£26,660	-£9,830	£9,830	75%
Drug costs	£11	£21	-£10	£10	0%
Retreatment costs	£2,076	£4,956	-£2,880	£2,880	22%
Cost of rupture (inc. stroke)	£341	£460	-£119	£119	1%
Total cost	**£24,341**	**£37,451**	**-£13,110**	**£13,134**	**100%**

Table B6.18 Summary of expected costs by category of cost: PED vs neurosurgiocal clipping

	PED	Neurosurgical clipping	Incremental	Absolute increment	% absolute increment
Staff costs	£2,999	£4,877	-£1,878	£1,878	10%
Hospital costs	£464	£1,213	-£749	£749	4%
Imaging costs	£1,621	£1,431	£190	£190	1%
Equipment costs	£16,830	£1,087	£15,742	£15,742	81%
Drug costs	£11	£0	£11	£11	0%
Retreatment costs	£2,076	£2,765	-£689	£689	4%
Cost of rupture (inc. stroke)	£341	£284	£57	£57	0%
Total cost	**£24,341**	**£11,658**	**£12,684**	**£19,316**	**100%**

Table B6.19 Summary of expected costs by category of cost: PED vs endovascular PVO

	PED	Endovascular PVO	Incremental	Absolute increment	% absolute increment
Staff costs	£2,999	£2,915	£84	£84	1%
Hospital costs	£464	£462	£1	£1	0%
Imaging costs	£1,621	£1,621	£0	£0	0%
Equipment costs	£16,830	£6,833	£9,996	£9,996	79%
Drug costs	£11	£11	£0	£0	0%
Retreatment costs	£2,076	£4,309	-£2,233	£2,233	18%
Cost of rupture (inc. stroke)	£341	£741	-£400	£400	3%
Total cost	**£24,341**	**£16,893**	**£7,448**	**£12,715**	**100%**

Table B6.20 Summary of expected costs by category of cost: PED vs neurosurgical PVO

	PED	Neurosurgical PVO	Incremental	Absolute increment	% absolute increment
Staff costs	£2,999	£4,877	-£1,878	£1,878	11%
Hospital costs	£464	£493	-£30	£30	0%
Imaging costs	£1,621	£1,621	£0	£0	0%
Equipment costs	£16,830	£3,067	£13,762	£13,762	81%
Drug costs	£11	£11	£0	£0	0%
Retreatment costs	£2,076	£998	£1,078	£1,078	6%
Cost of rupture (inc. stroke)	£341	£587	-£246	£246	1%
Total cost	**£24,341**	**£11,654**	**£12,687**	**£16,994**	**100%**

Table B6.21 Summary of expected costs by category of cost: PED vs conservative management

	PED	Conservative management	Incremental	Absolute increment	% absolute increment
Staff costs	£2,999	£0	£2,999	£2,999	10%
Hospital costs	£464	£0	£464	£464	2%
Imaging costs	£1,621	£189	£1,432	£1,432	5%
Equipment costs	£16,830	£0	£16,830	£16,830	57%
Drug costs	£11	£0	£11	£11	0%
Retreatment costs	£2,076	£6,566	-£4,489	£4,489	15%
Cost of rupture (inc. stroke)	£341	£2,365	-£2,024	£2,024	7%
Long-term monitoring (conservative management)	£0	£1,232	-£1,232	£1,232	4%
Total cost	**£24,341**	**£10,352**	**£13,989**	**£29,480**	**100%**

In addition to the cost outputs described previously, the model also generates health outcomes data for each intervention. This is primarily driven by survival (peri-procedural and long-term), although quality of life is also affected by the occurance of long-term events. The charts below show the long-term survival curves generated by the economic model.

Please note that, because outputs from the model are recorded at six-monthly intervals, the level of granularity shown in charts B6.1 to B6.6 may not show the exact timing of events. For example, procedural mortality is shown to have occurred *by* month six, whereas in reality this would occur almost immediately.

Chart B6.1 Survival over time (PED vs stent-assisted coiling)

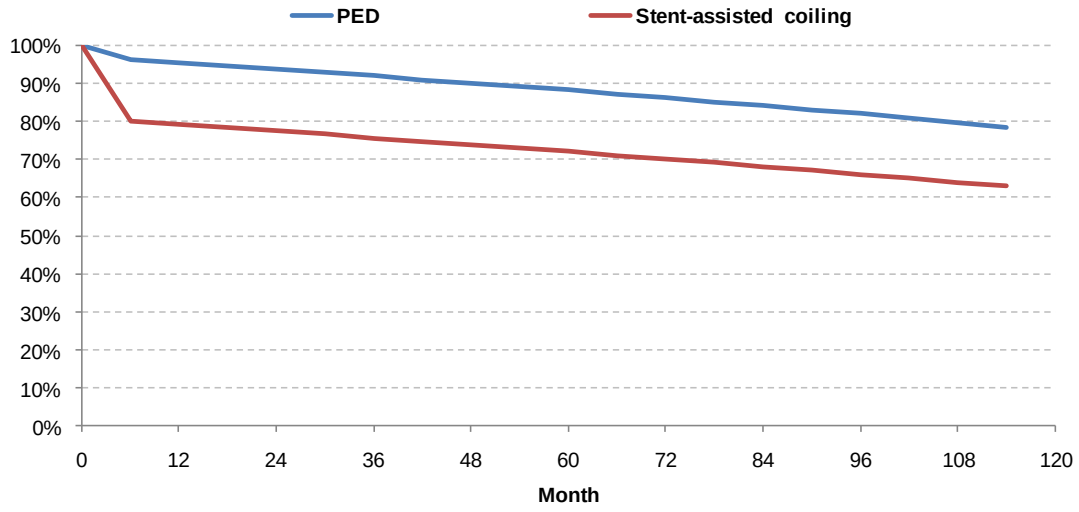


Chart B6.2 Survival over time (PED vs neurosurgical clipping)

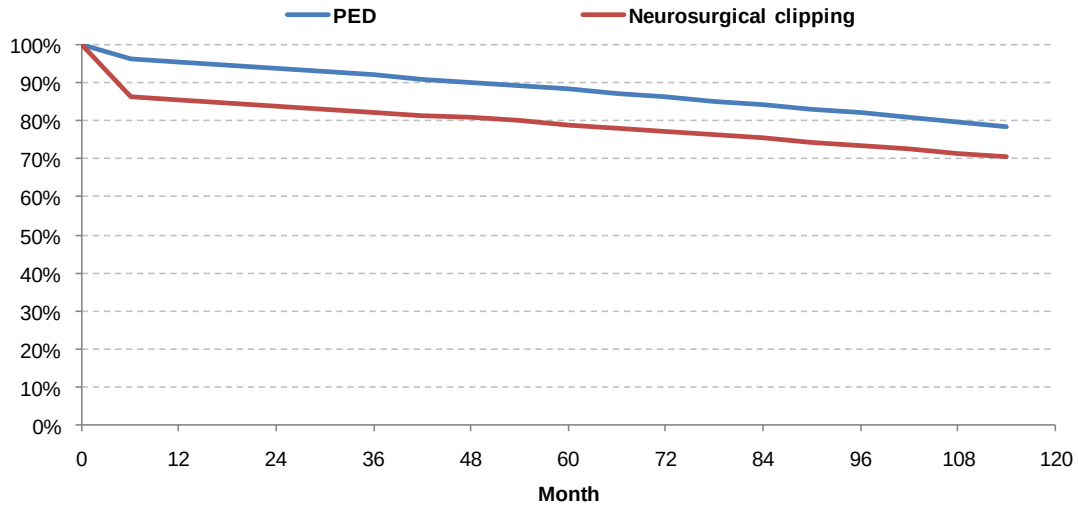


Chart B6.3 Survival over time (PED vs endovascular PVO)

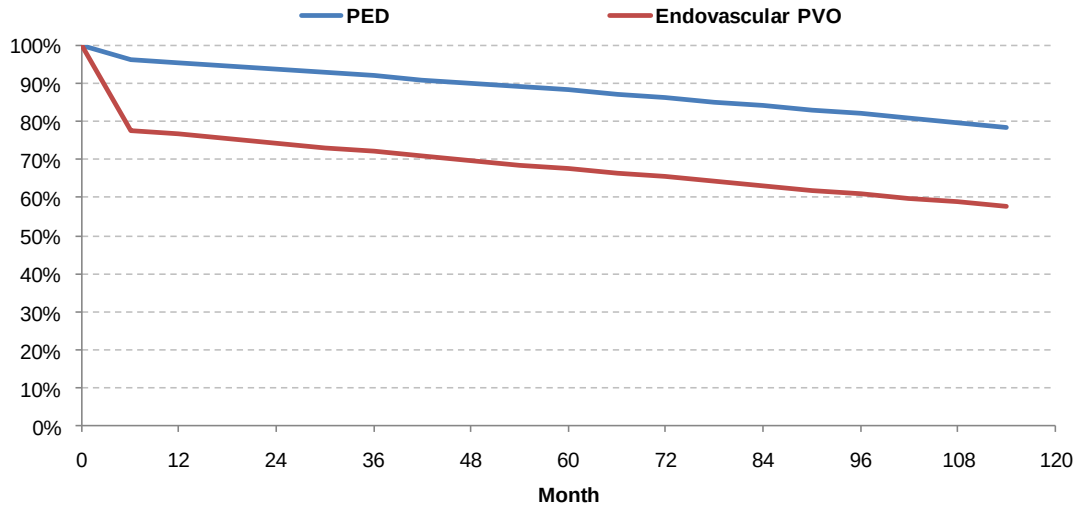


Chart B6.4 Survival over time (PED vs neurosurgical PVO)

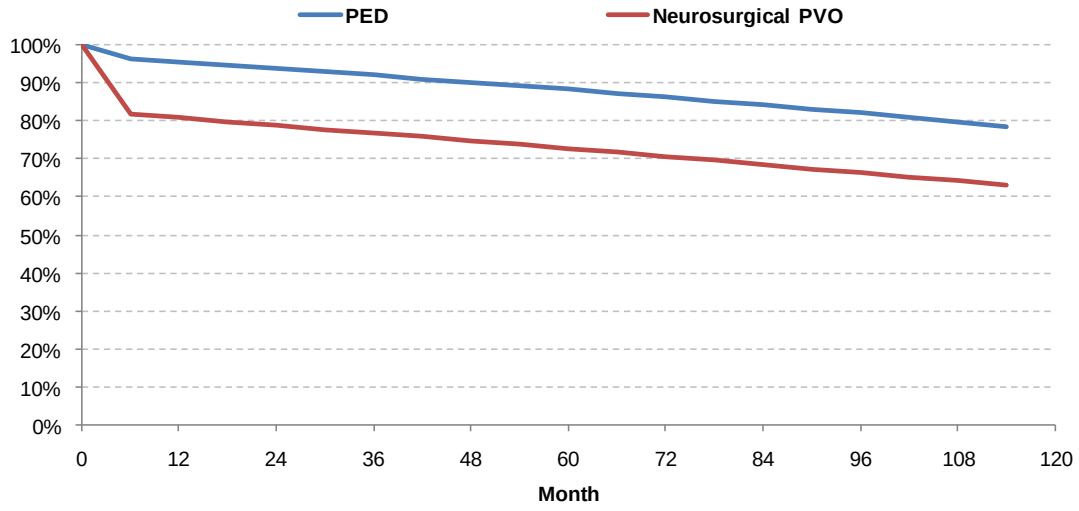
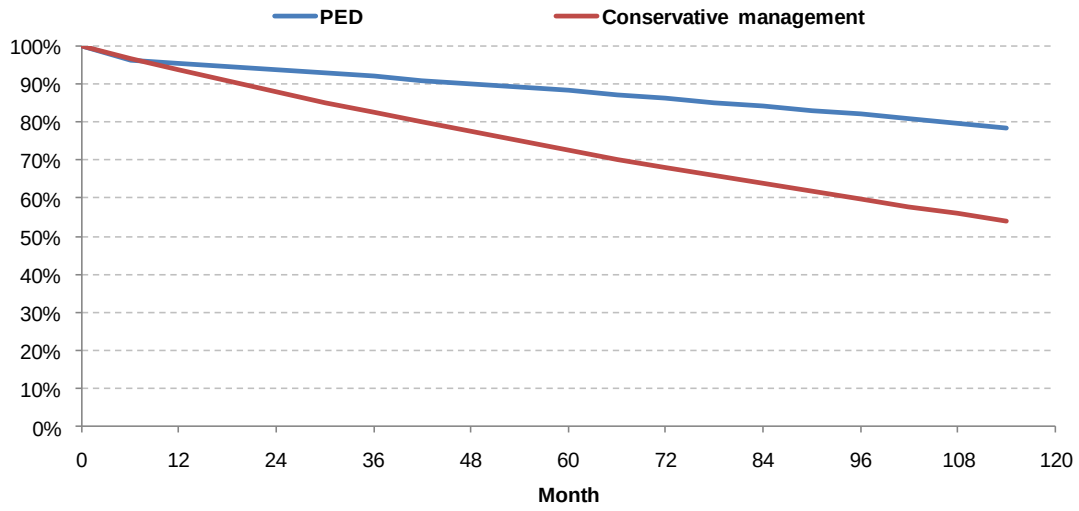


Chart B6.5 Survival over time (PED vs conservative management)



Base-case analysis

6.6.3 Please present your results in the following table. List interventions and comparator(s) from least to most expensive.

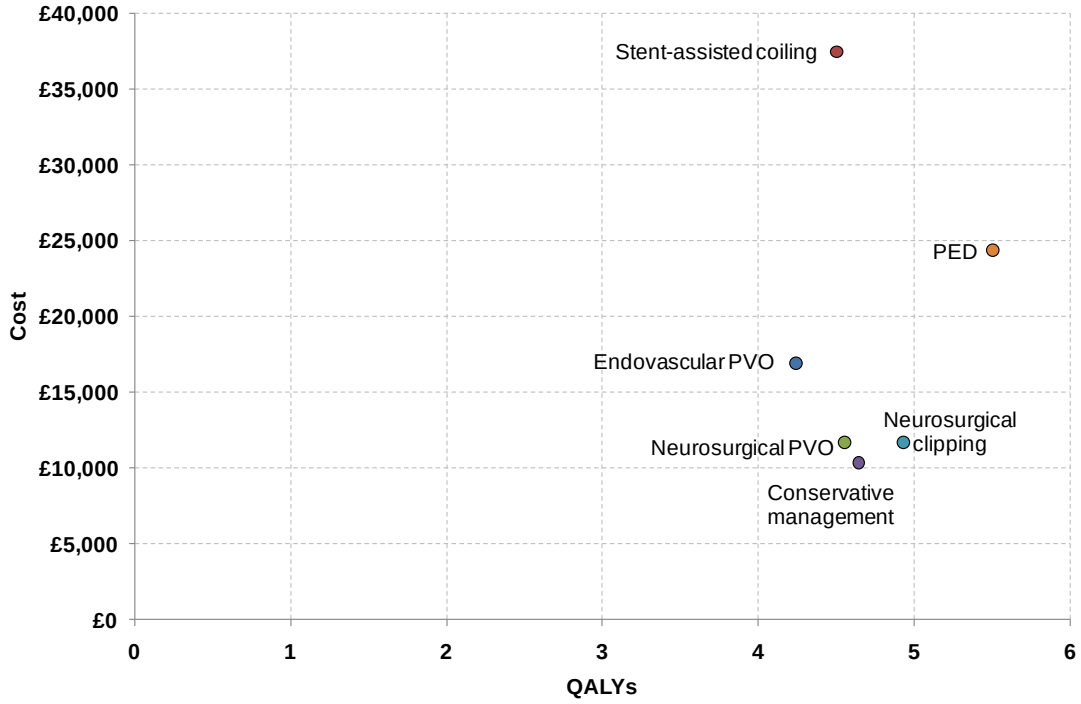
Table B6.22 Base-case results

Technology	Total expected costs (£)	Life years	QALYs	Ruptures (per 1,000 patients)	Years free from rupture or retreatment
PED	£24,341	8.84	5.506	70.9	8.2
Stent-assisted coiling	£37,451	7.23	4.503	95.7	6.7
Neurosurgical clipping	£11,658	7.92	4.932	59.3	7.4
Endovascular PVO	£16,893	6.82	4.241	152.5	6.2
Neurosurgical PVO	£11,654	7.31	4.552	120.9	6.7
Conservative management	£10,352	7.50	4.643	482.5	6.3

The results above suggest that PED delivers far greater health benefit than any of the other interventions. This is largely due to the substantial difference in the rate of peri-procedural mortality (as observed in charts B6.1 to B6.5). The health benefits observed with PED come at an increased cost, compared with some of the other interventions. As such, it is appropriate to consider incremental cost-effectiveness analysis to determine the most efficient use of NHS resources. This is demonstrated in Chart B6.6, showing a cost-effectiveness plane.

It may be noted that conservative management is not the least effective of the treatments. This is because many of the interventions are highly risky procedures, associated with a high peri-procedural mortality rate. For some patients, therefore, conservative management may, currently, be the most appropriate option. This does not necessarily imply that conservative management is more suitable than, say, endovascular PVO for *all* patients. Instead, treatments are usually selected on a case by case basis, depending on the unique characteristics of each patient.

Chart B6.6 Cost-effectiveness plane



As can be seen, some treatments are 'dominated' by others. That is, they cost more and are less effective than those alternatives. For example, stent-assisted coiling is shown to cost more, and be less effective, than PED. Therefore, based on this analysis, PED would be preferred to stent-assisted coiling in all scenarios.

Table B6.23 shows an incremental analysis of all treatments, ordered by effectiveness (as measured by quality-adjusted life years).

Table B6.23 Incremental analysis

Technology	Total costs (£)	QALYs	ICER
Endovascular PVO	£16,893	4.241	
Stent-assisted coiling	£37,451	4.503	£78,534
Neurosurgical PVO	£11,654	4.552	Dominant
Conservative management	£10,352	4.643	Dominant
Neurosurgical clipping	£11,658	4.932	£4,518
PED	£24,341	5.506	£22,079

The analysis in table B6.23 demonstrates that, at a willingness-to-pay (WTP) threshold of £30,000 per QALY, PED is the most cost-effective option. For a WTP value of £20,000, however, neurosurgical clipping is the most cost-effective intervention.

In line with the NICE scope, an alternative analysis was undertaken for patients who are not suitable for neurosurgical clipping. The incremental analysis for such patients is shown in Table B6.24.

Table B6.24 Incremental analysis (patients not suitable for neurosurgical clipping)

Technology	Total costs (£)	QALYs	ICER
Endovascular PVO	£16,893	4.241	
Stent-assisted coiling	£37,451	4.503	£78,534
Neurosurgical PVO	£11,654	4.552	Dominant
Conservative management	£10,352	4.643	Dominant
PED	£24,341	5.506	£16,202

For patients not suitable for neurosurgical clipping, PED is demonstrated to be the most cost-effective option, with WTP values of £30,000 or £20,000.

The NICE scope also requested an analysis of patients who are not suitable for stent-assisted coiling, and for patients not suitable for PVO. However, in both cases, the results would remain unchanged, since those interventions were demonstrated to be less preferable to conservative management.

For completeness, the incremental results of PED against each of the comparators is shown in Table B6.25.

Table B6.25 Incremental analysis (PED against all alternatives)

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

Sensitivity analyses

6.6.4 Please present results of deterministic sensitivity analysis.

Consider the use of tornado diagrams.

Extensive one-way sensitivity analyses were undertaken on all key parameters in the model. There are 34 separate parameters varied within the model, over a range of potential values. However, because five alternative comparators are included in the anlaysis, this would mean a total of 170 charts. For brevity, these charts are not presented in this report, but are available in the accompanying electronic model. Instead, summary 'tornado' diagrams and tables are provided, for each comparison. The charts show the change in incremental cost-effectiveness ratio (ICER). However, in the case of PED versus stent-assisted coiling, the results are 'dominant' and, therefore, the tornado table and diagram show net cost impact only.

Table B6.26 Sensitivity analysis table (PED vs stent-assisted coiling)

Basecase net cost impact	-£13,110	Low Value		High Value	
Parameter	**Basecase Value**	**Value**	**Net cost impact**	**Value**	**Net cost impact**
Starting age	57	47.00	-£13,227	67.00	-£12,824
Discounting rate - costs	3.5%	0%	-£13,634	6%	-£12,807
Discounting rate - benefits	3.5%	0%	-£13,110	6%	-£13,110
Time horizon (years)	10	5	-£11,743	10	-£13,110
Procedural mortality rate (PED)	2.77%	1.39%	-£13,076	4.16%	-£13,145
Procedural mortality rate (Stent-assisted coiling)	19.00%	8.50%	-£13,812	25.50%	-£12,676
Complete occlusion rate (PED)	85.21%	70.00%	-£12,392	100.00%	-£13,808
Complete occlusion rate (Stent-assisted coiling)	37.64%	20.00%	-£14,066	50.00%	-£10,003
Re-treatment rate (complete occlusion)	5.80%	2.90%	-£13,416	8.70%	-£12,795
Re-treatment rate (residual neck)	20.60%	10.30%	-£11,359	30.90%	-£15,083
Re-treatment (residual aneurysm)	18.80%	9.40%	-£13,027	28.20%	-£13,202
Rupture rate (complete occlusion)	1.10%	0.55%	-£13,153	1.65%	-£13,068
Rupture rate (residual neck)	3.58%	1.79%	-£13,088	5.37%	-£13,130
Rupture rate (residual aneurysm)	17.60%	8.80%	-£13,124	26.40%	-£13,097
Death rate following rupture	58.00%	25.00%	-£13,195	75.00%	-£13,066
QoL (no complications)	0.73	0.365	-£13,110	0.9	-£13,110
QoL (after SAH)	0.64	0.32	-£13,110	0.9	-£13,110
Cost of PED	£10,171.00	£5,086	-£21,237	£15,257	-£4,981
Cost of stent	£2,750.00	£1,250	-£11,380	£3,750	-£14,264
Cost of coil	£526.04	£263	-£971	£789	-£25,245
Cost of retreatment (PED)	£21,923.76	£11,240	-£14,122	£33,720	-£11,993
Cost of retreatment (Stent-assisted coiling)	£32,240.19	£5,000	-£8,923	£40,000	-£14,303

Cost of rupture (initial non-fatal)	£8,046.00	£4,023	-£13,085	£12,069	-£13,135
Cost of rupture (subsequent)	£1,080.00	£540	-£13,082	£1,620	-£13,139
Cost of rupture (initial fatal)	£781.00	£300	-£13,103	£1,500	-£13,121
Number of coils	40.00	5	£8,131	100	-£49,524
Number of clips	5	1	-£13,110	10	-£13,110
Number of stents	1.00	1	-£13,110	5	-£25,801
Number of PEDs	1.46	1	-£18,232	3	£4,037
Days in recovery (PED)	1.3	1	-£13,208	10	-£10,265
Days in recovery (Stent-assisted coiling)	1.25	1	-£13,028	10	-£15,971
Length of procedure (PED)	2.07	1	-£14,450	5	-£9,426
Length of procedure (Stent-assisted coiling)	2.29	1	-£11,488	5	-£16,512
Anaesthetist time	1.00	0.25	-£13,092	2	-£13,134

Chart B6.7 Tornado diagram (PED vs stent-assisted coiling)

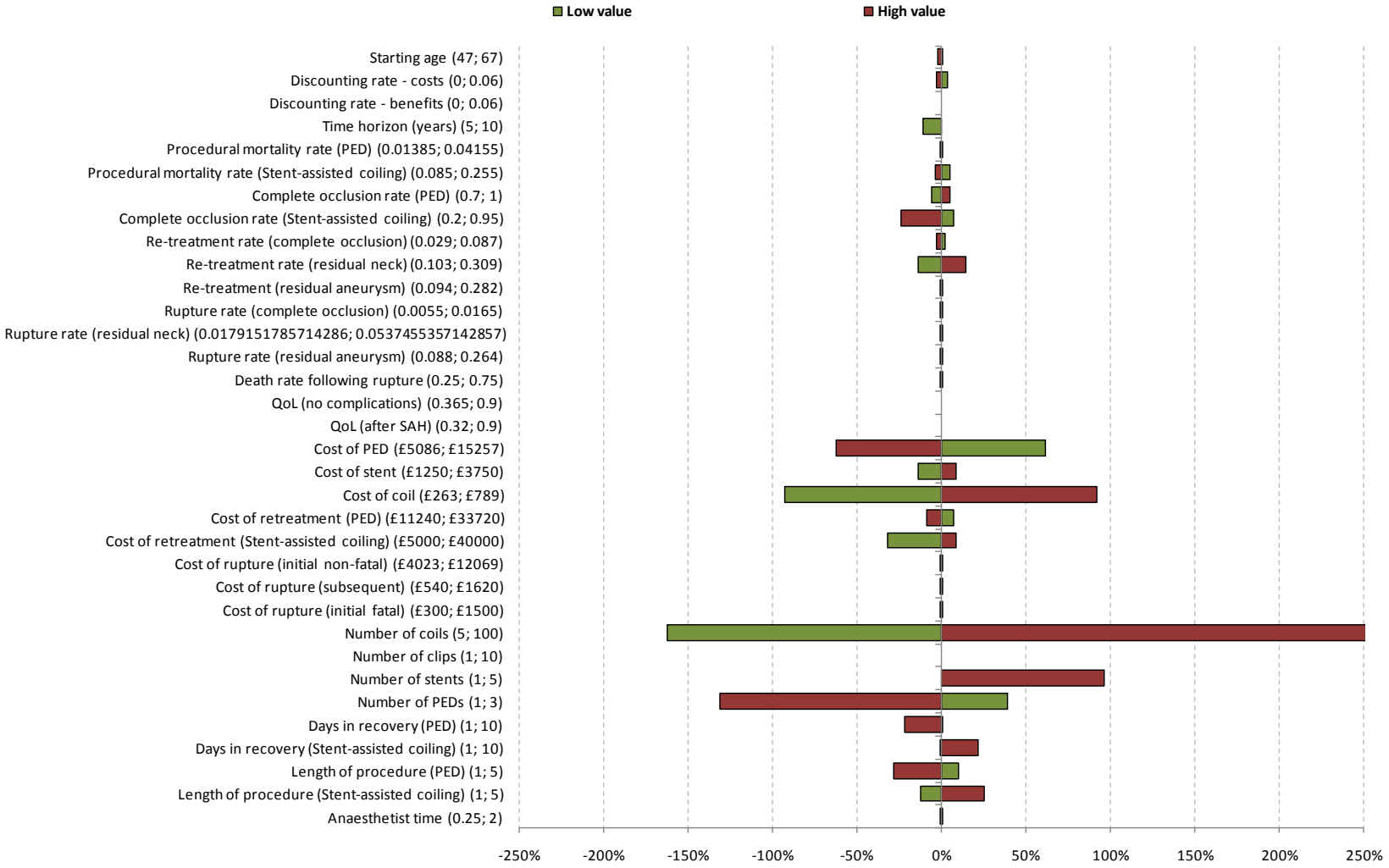


Table B6.27 Sensitivity analysis table (PED vs neurosurgical clipping)

Basecase ICER	**£22,079**	**Low Value**		**High Value**	
Parameter	**Basecase Value**	**Value**	**ICER**	**Value**	**ICER**
Starting age	57	47.00	£21,211	67.00	£24,507
Discounting rate - costs	3.5%	0%	£21,888	6%	£22,189
Discounting rate - benefits	3.5%	0%	£18,985	6%	£24,379
Time horizon (years)	10	5	£39,238	10	£22,079
Procedural mortality rate (PED)	2.77%	1.39%	£19,479	4.16%	£25,500
Procedural mortality rate (Neurosurgical clipping)	13.10%	8.50%	£39,954	25.50%	£10,264
Complete occlusion rate (PED)	85.21%	70.00%	£27,423	100.00%	£18,218
Complete occlusion rate (Neurosurgical clipping)	85.00%	20.00%	£10,495	95.00%	£24,934
Re-treatment rate (complete occlusion)	5.80%	2.90%	£22,440	8.70%	£21,707
Re-treatment rate (residual neck)	20.60%	10.30%	£22,326	30.90%	£21,800
Re-treatment (residual aneurysm)	18.80%	9.40%	£22,087	28.20%	£22,069
Rupture rate (complete occlusion)	1.10%	0.55%	£21,917	1.65%	£22,241
Rupture rate (residual neck)	3.58%	1.79%	£22,095	5.37%	£22,063
Rupture rate (residual aneurysm)	17.60%	8.80%	£21,659	26.40%	£22,458
Death rate following rupture	58.00%	25.00%	£22,135	75.00%	£22,049
QoL (no complications)	0.73	0.365	£43,398	0.9	£17,968
QoL (after SAH)	0.64	0.32	£22,274	0.9	£21,923
Cost of PED	£10,171.00	£5,086	£7,932	£15,257	£36,229
Cost of stent	£2,750.00	£1,250	£22,303	£3,750	£21,930
Cost of coil	£526.04	£263	£23,650	£789	£20,508
Cost of retreatment (PED)	£21,923.76	£11,240	£20,318	£33,720	£24,023

Cost of retreatment (Neurosurgical clipping)	£32,240.19	£5,000	£26,146	£40,000	£20,920
Cost of rupture (initial non-fatal)	£8,046.00	£4,023	£22,059	£12,069	£22,099
Cost of rupture (subsequent)	£1,080.00	£540	£22,055	£1,620	£22,103
Cost of rupture (initial fatal)	£781.00	£300	£22,073	£1,500	£22,088
Number of coils	40.00	5	£24,828	100	£17,367
Number of clips	5	1	£20,249	10	£23,542
Number of stents	1.00	1	£22,079	5	£20,437
Number of PEDs	1.46	1	£13,163	3	£51,927
Days in recovery (PED)	1.3	1	£21,908	10	£27,031
Days in recovery (Neurosurgical clipping)	3.5	1	£23,502	10	£18,379
Length of procedure (PED)	2.07	1	£19,747	5	£28,492
Length of procedure (Neurosurgical clipping)	3.56	1	£27,680	5	£18,935
Anaesthetist time	1.00	0.25	£22,074	2	£22,085

Chart B6.8 Tornado diagram (PED vs neurosurgical clipping)

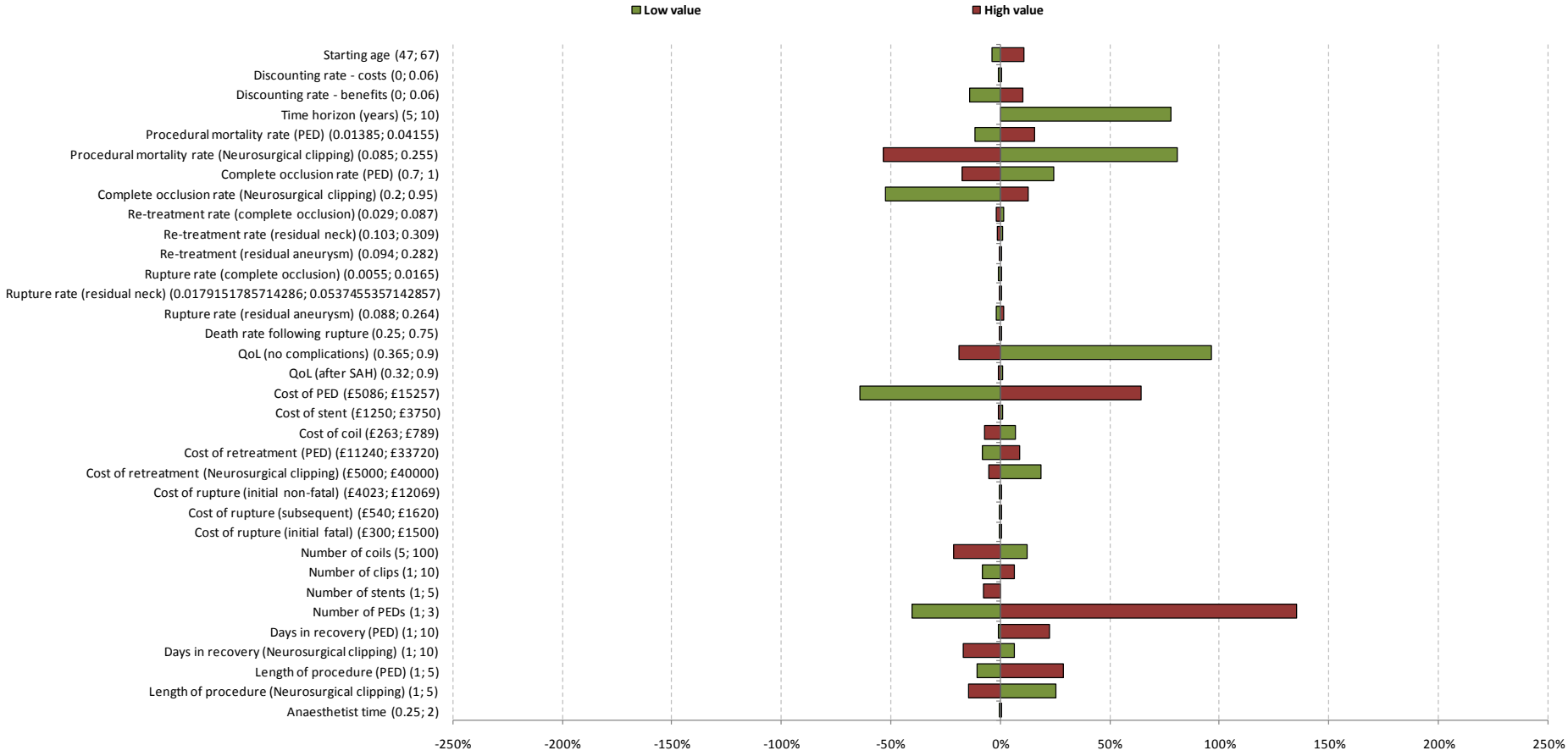


Table B6.28 Sensitivity analysis table (PED vs endovascular PVO)

Basecase ICER	£5,887	Low Value		High Value	
Parameter	**Basecase Value**	**Value**	**ICER**	**Value**	**ICER**
Starting age	57	47.00	£5,572	67.00	£6,776
Discounting rate - costs	3.5%	0%	£5,528	6%	£6,095
Discounting rate - benefits	3.5%	0%	£5,004	6%	£6,552
Time horizon (years)	10	5	£12,980	10	£5,887
Procedural mortality rate (PED)	2.77%	1.39%	£5,569	4.16%	£6,247
Procedural mortality rate (Endovascular PVO)	21.00%	8.50%	£11,190	25.50%	£5,134
Complete occlusion rate (PED)	85.21%	70.00%	£6,924	100.00%	£5,005
Complete occlusion rate (Endovascular PVO)	41.00%	20.00%	£4,633	95.00%	£10,355
Re-treatment rate (complete occlusion)	5.80%	2.90%	£5,663	8.70%	£6,117
Re-treatment rate (residual neck)	20.60%	10.30%	£6,527	30.90%	£5,166
Re-treatment (residual aneurysm)	18.80%	9.40%	£6,406	28.20%	£5,309
Rupture rate (complete occlusion)	1.10%	0.55%	£5,759	1.65%	£6,018
Rupture rate (residual neck)	3.58%	1.79%	£5,986	5.37%	£5,794
Rupture rate (residual aneurysm)	17.60%	8.80%	£6,395	26.40%	£5,512
Death rate following rupture	58.00%	25.00%	£5,685	75.00%	£5,995
QoL (no complications)	0.73	0.365	£12,478	0.9	£4,725
QoL (after SAH)	0.64	0.32	£5,725	0.9	£6,025
Cost of PED	£10,171.00	£5,086	Dominant	£15,257	£12,312
Cost of stent	£2,750.00	£1,250	£6,045	£3,750	£5,781
Cost of coil	£526.04	£263	£8,246	£789	£3,529
Cost of retreatment (PED)	£21,923.76	£11,240	£5,087	£33,720	£6,770
Cost of retreatment (Endovascular PVO)	£32,240.19	£5,000	£8,764	£40,000	£5,067

Cost of rupture (initial non-fatal)	£8,046.00	£4,023	£5,951	£12,069	£5,823
Cost of rupture (subsequent)	£1,080.00	£540	£5,965	£1,620	£5,808
Cost of rupture (initial fatal)	£781.00	£300	£5,906	£1,500	£5,858
Number of coils	40.00	5	£7,832	100	£2,553
Number of clips	5	1	£5,887	10	£5,887
Number of stents	1.00	1	£5,887	5	£4,725
Number of PEDs	1.46	1	£1,839	3	£19,439
Days in recovery (PED)	1.3	1	£5,809	10	£8,135
Days in recovery (Endovascular PVO)	1.3	1	£5,964	10	£3,638
Length of procedure (PED)	2.07	1	£4,828	5	£8,799
Length of procedure (Endovascular PVO)	2.00	1	£6,880	5	£2,909
Anaesthetist time	1.00	0.25	£5,896	2	£5,874

Chart B6.9 Tornado diagram (PED vs endovascular PVO)

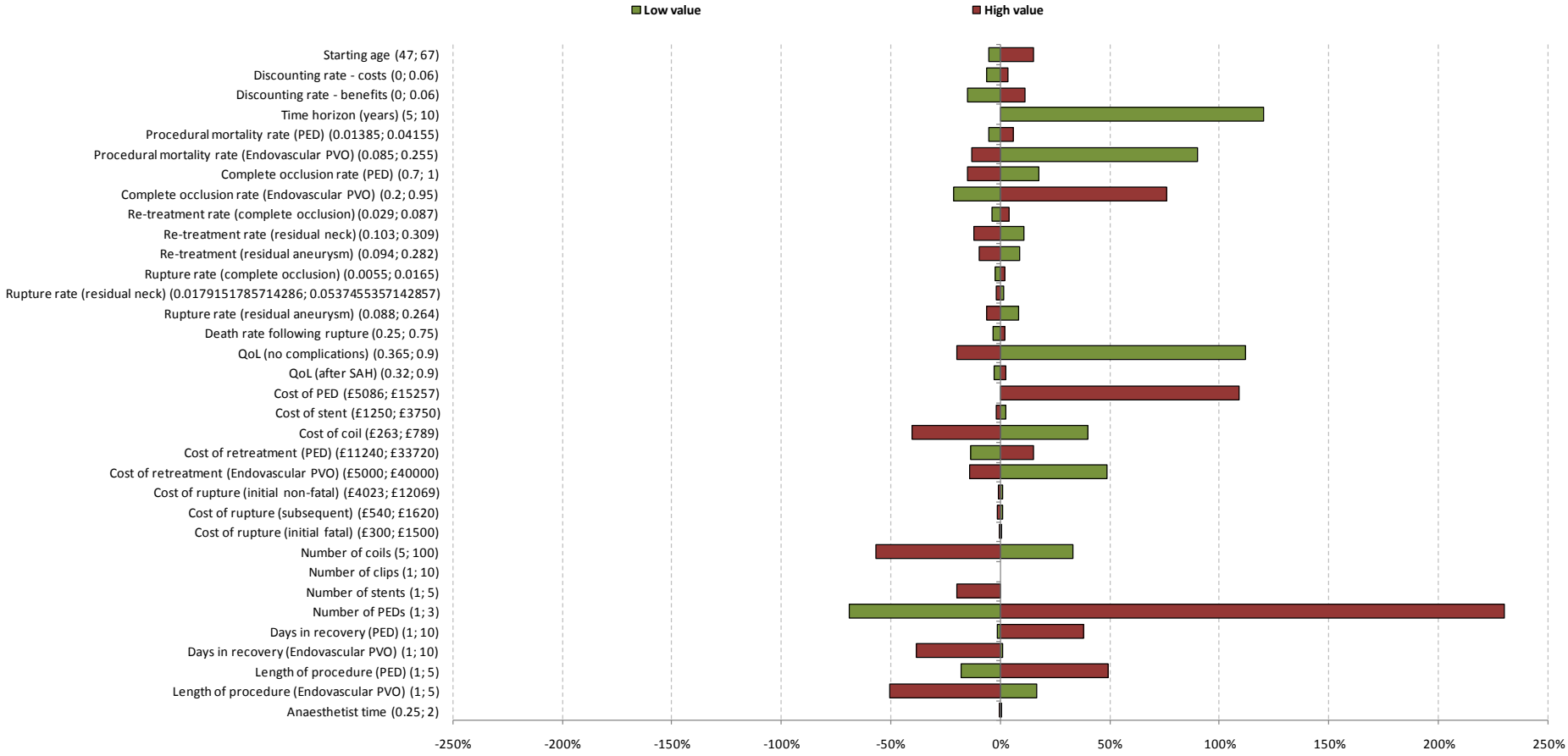


Table B6.29 Sensitivity analysis table (PED vs neurosurgical PVO)

Basecase ICER	£13,297	Low Value		High Value	
Parameter	**Basecase Value**	**Value**	**ICER**	**Value**	**ICER**
Starting age	57	47.00	£12,797	67.00	£14,707
Discounting rate - costs	3.5%	0%	£13,446	6%	£13,211
Discounting rate - benefits	3.5%	0%	£11,321	6%	£14,784
Time horizon (years)	10	5	£24,265	10	£13,297
Procedural mortality rate (PED)	2.77%	1.39%	£12,320	4.16%	£14,449
Procedural mortality rate (Neurosvascular PVO)	17.00%	8.50%	£25,668	25.50%	£9,047
Complete occlusion rate (PED)	85.21%	70.00%	£15,437	100.00%	£11,555
Complete occlusion rate (Neurosvascular PVO)	59.00%	20.00%	£10,159	95.00%	£17,722
Re-treatment rate (complete occlusion)	5.80%	2.90%	£12,760	8.70%	£13,850
Re-treatment rate (residual neck)	20.60%	10.30%	£13,248	30.90%	£13,353
Re-treatment (residual aneurysm)	18.80%	9.40%	£13,309	28.20%	£13,283
Rupture rate (complete occlusion)	1.10%	0.55%	£13,080	1.65%	£13,519
Rupture rate (residual neck)	3.58%	1.79%	£13,489	5.37%	£13,115
Rupture rate (residual aneurysm)	17.60%	8.80%	£14,319	26.40%	£12,510
Death rate following rupture	58.00%	25.00%	£13,165	75.00%	£13,369
QoL (no complications)	0.73	0.365	£27,876	0.9	£10,693
QoL (after SAH)	0.64	0.32	£12,998	0.9	£13,550
Cost of PED	£10,171.00	£5,086	£4,779	£15,257	£21,817
Cost of stent	£2,750.00	£1,250	£13,297	£3,750	£13,297
Cost of coil	£526.04	£263	£13,297	£789	£13,297
Cost of retreatment (PED)	£21,923.76	£11,240	£12,237	£33,720	£14,468
Cost of retreatment (Neurosvascular PVO)	£8,607.94	£5,000	£13,736	£40,000	£9,483

Cost of rupture (initial non-fatal)	£8,046.00	£4,023	£13,349	£12,069	£13,245
Cost of rupture (subsequent)	£1,080.00	£540	£13,361	£1,620	£13,233
Cost of rupture (initial fatal)	£781.00	£300	£13,313	£1,500	£13,274
Number of coils	40.00	5	£13,297	100	£13,297
Number of clips	5	1	£13,169	10	£13,399
Number of stents	1.00	1	£13,297	5	£13,297
Number of PEDs	1.46	1	£7,929	3	£31,268
Days in recovery (PED)	1.3	1	£13,194	10	£16,279
Days in recovery (Neurosvascular PVO)	1.3	1	£13,400	10	£10,315
Length of procedure (PED)	2.07	1	£11,893	5	£17,159
Length of procedure (Neurosvascular PVO)	3.56	1	£16,670	5	£11,404
Anaesthetist time	1.00	0.25	£13,304	2	£13,288

Chart B6.10 Tornado diagram (PED vs neurosurgical PVO)

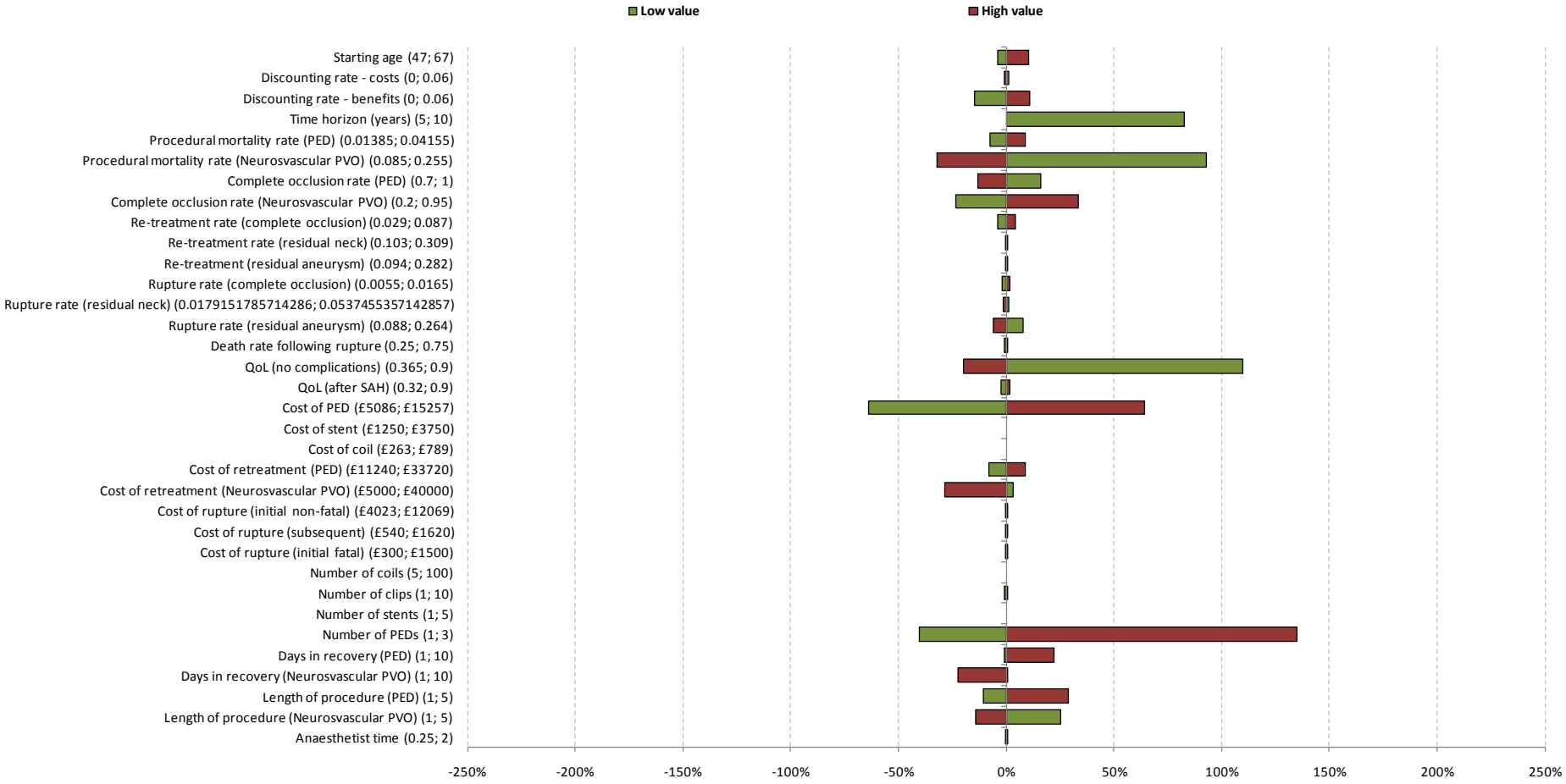
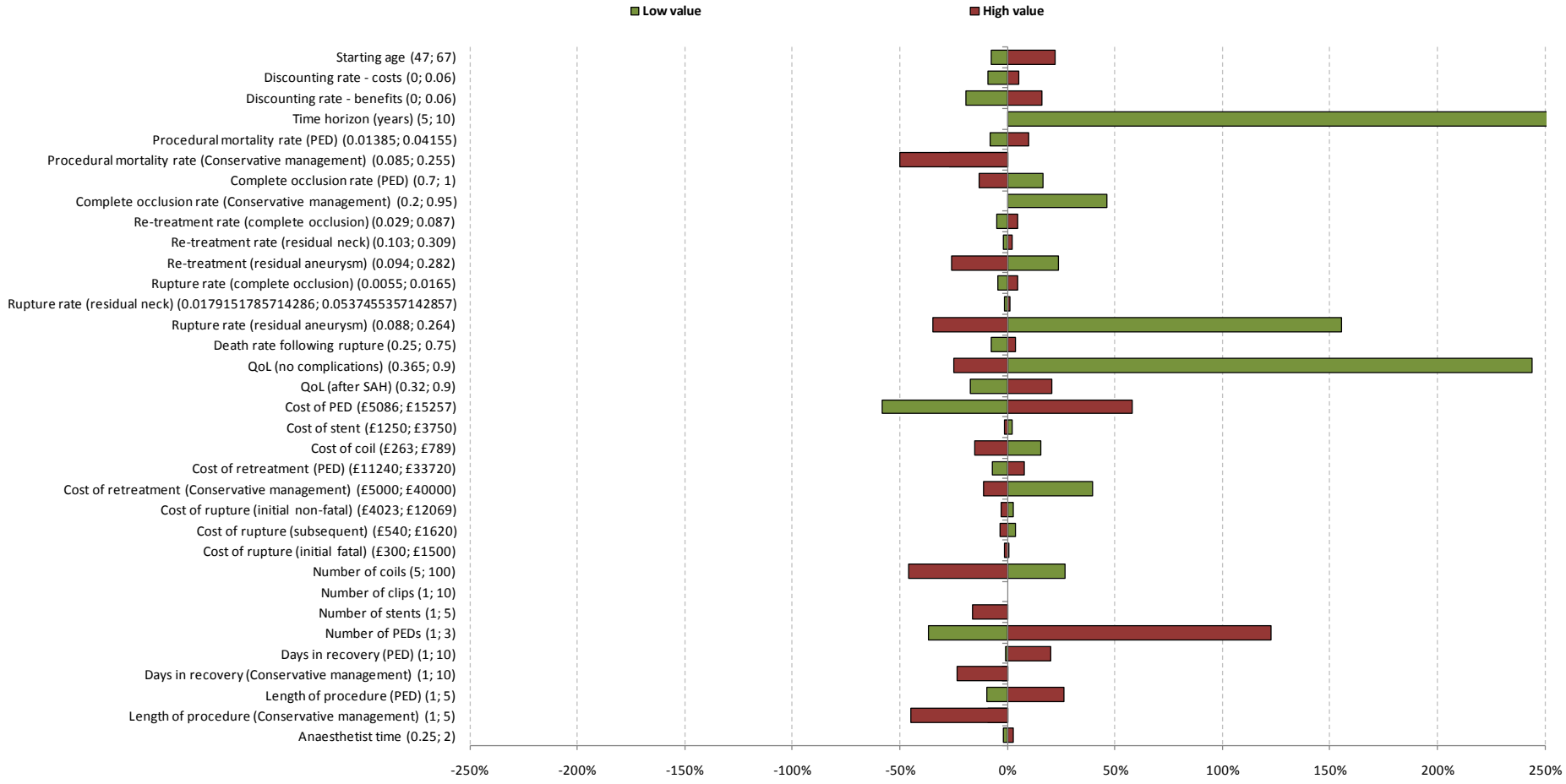


Table B6.30 Sensitivity analysis table (PED vs conservative management)

Basecase ICER	£16,202	Low Value		High Value	
Parameter	**Basecase Value**	**Value**	**ICER**	**Value**	**ICER**
Starting age	57	47.00	£15,004	67.00	£19,772
Discounting rate - costs	3.5%	0%	£14,702	6%	£17,073
Discounting rate - benefits	3.5%	0%	£13,041	6%	£18,769
Time horizon (years)	10	5	£71,323	10	£16,202
Procedural mortality rate (PED)	2.77%	1.39%	£14,889	4.16%	£17,777
Procedural mortality rate (Conservative management)	0.00%	8.50%	£11,800	25.50%	£8,087
Complete occlusion rate (PED)	85.21%	70.00%	£18,912	100.00%	£14,037
Complete occlusion rate (Conservative management)	0.00%	20.00%	£23,698	95.00%	Less effective
Re-treatment rate (complete occlusion)	5.80%	2.90%	£15,429	8.70%	£16,997
Re-treatment rate (residual neck)	20.60%	10.30%	£15,907	30.90%	£16,534
Re-treatment (residual aneurysm)	18.80%	9.40%	£20,018	28.20%	£11,956
Rupture rate (complete occlusion)	1.10%	0.55%	£15,507	1.65%	£16,948
Rupture rate (residual neck)	3.58%	1.79%	£15,988	5.37%	£16,415
Rupture rate (residual aneurysm)	17.60%	8.80%	£41,343	26.40%	£10,570
Death rate following rupture	58.00%	25.00%	£14,965	75.00%	£16,847
QoL (no complications)	0.73	0.365	£55,762	0.9	£12,178
QoL (after SAH)	0.64	0.32	£13,396	0.9	£19,524
Cost of PED	£10,171.00	£5,086	£6,789	£15,257	£25,617
Cost of stent	£2,750.00	£1,250	£16,556	£3,750	£15,966
Cost of coil	£526.04	£263	£18,684	£789	£13,721
Cost of retreatment (PED)	£21,923.76	£11,240	£15,030	£33,720	£17,496
Cost of retreatment (Conservative management)	£32,240.19	£5,000	£22,627	£40,000	£14,372

Cost of rupture (initial non-fatal)	£8,046.00	£4,023	£16,675	£12,069	£15,728
Cost of rupture (subsequent)	£1,080.00	£540	£16,785	£1,620	£15,619
Cost of rupture (initial fatal)	£781.00	£300	£16,344	£1,500	£15,989
Number of coils	40.00	5	£20,544	100	£8,757
Number of clips	5	1	£16,202	10	£16,202
Number of stents	1.00	1	£16,202	5	£13,607
Number of PEDs	1.46	1	£10,270	3	£36,061
Days in recovery (PED)	1.3	1	£16,088	10	£19,497
Days in recovery (Conservative management)	0	1	£15,823	10	£12,414
Length of procedure (PED)	2.07	1	£14,650	5	£20,469
Length of procedure (Conservative management)	0.00	1	£14,747	5	£8,928
Anaesthetist time	1.00	0.25	£15,890	2	£16,618

Chart B6.11 Tornado diagram (PED vs conservative management)



6.6.5 Please present the results of PSA.

Probabilistic analysis was not undertaken, due to a lack of suitable data surrounding the variation on key parameters.

6.6.6 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

In the base case analysis, the costs and health outcomes associated with adverse events were not included. An alternative analysis was undertaken, including the consequences of adverse events. The results of that analysis are shown below.

Table B6.31 Scenario analysis: including adverse events

Technology	Total costs (£)	QALYs	ICER
Endovascular PVO	£18,356	4.217919	
Stent-assisted coiling	£38,345	4.490378	£73,367
Neurosurgical PVO	£12,190	4.543144	Dominates
Conservative management	£10,352	4.642711	Dominates
Neurosurgical clipping	£12,328	4.920794	£7,105
PED	£25,018	5.493676	£22,151

The results of the economic model are presented over a total period of ten years. However, the vast majority of healthcare costs and health gains appear to be gained or lost during the peri-procedural period. As such, an alternative scenario analysis was undertaken, limited to the first six months after therapy. In this analysis, the model is somewhat simplified, and reports only two factors: (i) the proportion of patients surviving, and (ii) the total procedural cost of the intervention. The results are shown below, in Table B6.32. It should be noted that these results contain no extrapolation, and are based purely on the trial period. It should further be noted that the results are conservative from the perspective of PED, since PED's mortality rate is reported at 180 days, whilst the mortality of the other interventions is reported at 31 days. Finally, conservative management has been excluded from this scenario analysis, since it does not have a 'peri-procedural' mortality rate.

Table B6.32 Scenario analysis: short-term outcomes only

	Proportion surviving	Procedural cost	Cost per additional survivor
Endovascular PVO	79.0%	£11,842	
Stent-assisted coiling	81.0%	£32,240	£1,019,891
Neurosurgical PVO	83.0%	£10,069	Dominant
Neurosurgical clipping	86.9%	£8,608	Dominant
PED	97.2%	£21,924	£128,904

This demonstrates that PED is the most cost-effective option, if the value of a saved *life* is deemed to worth £128,904 or greater.

6.6.7 What were the main findings of each of the sensitivity analyses?

The sensitivity analysis presented above demonstrates that the results of the economic model are relatively robust to changes in the vast majority of parameters.

6.6.8 What are the key drivers of the cost results?

As would be expected, the cost of the intervention (PED) impacts on the cost results. Likewise the number of PEDs required per intervention is also a key driver of the cost-effectiveness results. For the comparators, the cost of consumable equipment drives the cost outcomes; this is particularly true for the stent-assisted coiling intervention, where the cost (and number) of coils impacts significantly upon the cost-effectiveness and net cost findings.

6.7 Validation

6.7.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

A number of 'stress tests' were undertaken on the economic model, and these are presented, in Table B6.33.

Table B6.33 Model validation

	Test	Expected effect	Observed effect	Action required?
1	Set initial number of patients to 0	Costs and QALYs equal 0 across treatments	Model creates errors (due to dividing by zero)	No – model does not produce costs or outcomes
2	Set initial number of cases to 1	ICER unaltered	ICER unaltered	No
3	Set both treatment and comparator to same intervention	Costs and QALYs to be equal.	As expected	No
4	Set treatment to 'comparator' and comparator to 'treatment'	Costs and QALYs to be the same as base-case, but inverted.	As expected	No
5	Set mortality rate to 0% at all ages	No deaths in model	Some deaths occur due to rupture	No cases of 'all cause' mortality
6	Set mortality rate to 100% at all ages	All patients dead at cycle 1but still generate some expected costs and QALYs	As expected	No
7	Set mortality rate to 100% at age 70	All patients dead after x years (starting age 70 - x) but still generate expected costs and QALYs.	As expected	No
8	Increase mortality rate	Reduced costs.	As expected	No
9	Health state utilities same for all states	Same QALYs for surviving patients (life years and QALYs should have same ratio in both arms)	As expected	No
10	Health state utilities and adverse events all set to 0.	Total QALYs = 0 for treatment and comparator.	As expected	No
11	Health state utilities for states all set to 1 and adverse events all set to 0	Total QALYs same as life years	Different	No – differences due to QALYs being discounted, but LYs not discounted. When discount rates = 0%, QALYs = LYs.
12	Unit costs of treatments set to 0.	Total cost of treatment = 0	As expected	No
13	Doubled unit costs of treatment	Treatment costs doubled	As expected	No

14	Unit costs of administration visit cost and follow-up visit cost set to 0.	Total administration costs = 0.	As expected	No
15	Doubled unit costs of administration visits and follow-up visits	Total administration costs doubled	As expected	No
16	Alter time horizon	Total costs and QALYs to increase/decrease in accordance with longer/shorter durations.	As expected	No

6.8 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

6.8.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical effectiveness or cost impact due to known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 5.3.7.

Robust data were not available for different subgroups of patients. Analysis has already been undertaken, as described in Section 6.6, for patients not suitable for certain interventions.

One aspect of the patient's condition that may have a significant impact upon the cost impact will be the size of the aneurysm. This analysis has been based on patients with large *or* giant aneurysms. However, it is likely that the size of the

aneurysm will impact on the likely cost of equipment, particularly in the case of PED and stent-assisted coiling. The larger, the aneurysm, the greater the need for additional consumable equipment.

6.8.2 Please clearly define the characteristics of patients in the subgroup.

Insufficient data were available by size of aneurysm to allow for meaningful comparison between different treatments.

6.8.3 Please describe how the statistical analysis was undertaken.

As above, insufficient data were available by size of aneurysm to allow for meaningful comparison between different treatments.

6.8.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 6.6.3 (Base-case analysis).

To assess the impact of different uses of PED and stent-assisted coiling, a two-way sensitivity analysis was undertaken. This analysis shows the net cost impact (not the ICER) for PED versus stent-assisted coiling.

Table B6.34 Two-way sensitivity analysis of PED vs stent-assisted coiling

		Number of PEDs										
		1.0	1.2	1.4	1.6	1.8	2.0	2.2	2.4	2.6	2.8	3.0
Number of coils	10	-£25	£2,202	£4,429	£6,656	£8,883	£11,109	£13,336	£15,563	£17,790	£20,017	£22,244
	15	-£3,059	-£832	£1,394	£3,621	£5,848	£8,075	£10,302	£12,529	£14,755	£16,982	£19,209
	20	-£6,094	-£3,867	-£1,640	£587	£2,814	£5,040	£7,267	£9,494	£11,721	£13,948	£16,175
	25	-£9,128	-£6,901	-£4,675	-£2,448	-£221	£2,006	£4,233	£6,460	£8,686	£10,913	£13,140
	30	-£12,163	-£9,936	-£7,709	-£5,482	-£3,255	-£1,029	£1,198	£3,425	£5,652	£7,879	£10,106
	35	-£15,197	-£12,971	-£10,744	-£8,517	-£6,290	-£4,063	-£1,836	£391	£2,617	£4,844	£7,071
	40	-£18,232	-£16,005	-£13,778	-£11,551	-£9,325	-£7,098	-£4,871	-£2,644	-£417	£1,810	£4,037
	45	-£21,266	-£19,040	-£16,813	-£14,586	-£12,359	-£10,132	-£7,905	-£5,679	-£3,452	-£1,225	£1,002
	50	-£24,301	-£22,074	-£19,847	-£17,620	-£15,394	-£13,167	-£10,940	-£8,713	-£6,486	-£4,259	-£2,032
	55	-£27,335	-£25,109	-£22,882	-£20,655	-£18,428	-£16,201	-£13,974	-£11,748	-£9,521	-£7,294	-£5,067
	60	-£30,370	-£28,143	-£25,916	-£23,689	-£21,463	-£19,236	-£17,009	-£14,782	-£12,555	-£10,328	-£8,102
	65	-£33,404	-£31,178	-£28,951	-£26,724	-£24,497	-£22,270	-£20,043	-£17,817	-£15,590	-£13,363	-£11,136
	70	-£36,439	-£34,212	-£31,985	-£29,758	-£27,532	-£25,305	-£23,078	-£20,851	-£18,624	-£16,397	-£14,171
	75	-£39,474	-£37,247	-£35,020	-£32,793	-£30,566	-£28,339	-£26,112	-£23,886	-£21,659	-£19,432	-£17,205
	80	-£42,508	-£40,281	-£38,054	-£35,828	-£33,601	-£31,374	-£29,147	-£26,920	-£24,693	-£22,466	-£20,240
	85	-£45,543	-£43,316	-£41,089	-£38,862	-£36,635	-£34,408	-£32,182	-£29,955	-£27,728	-£25,501	-£23,274
	90	-£48,577	-£46,350	-£44,123	-£41,897	-£39,670	-£37,443	-£35,216	-£32,989	-£30,762	-£28,536	-£26,309
	95	-£51,612	-£49,385	-£47,158	-£44,931	-£42,704	-£40,477	-£38,251	-£36,024	-£33,797	-£31,570	-£29,343
	100	-£54,646	-£52,419	-£50,192	-£47,966	-£45,739	-£43,512	-£41,285	-£39,058	-£36,831	-£34,605	-£32,378

However, it should be noted that some of comparisons in this table are unlikely, when assessing the different sizes of aneurysm. For example, it would not be appropriate to compare a low number of coils against a higher number of PEDs, or *vice versa*. As such, the top-left and bottom-right of the two-way sensitivity analysis can be excluded, as shown in Table B6.35.

Table B6.35 Two-way sensitivity analysis of PED vs stent-assisted coiling (inappropriate comparisons removed)

		Number of PEDs										
		1.0	1.2	1.4	1.6	1.8	2.0	2.2	2.4	2.6	2.8	3.0
Number of coils	10	-£25	£2,202	£4,429	£6,656	£8,883	£11,109	£13,336	£15,563	£17,790	£20,017	£22,244
	15	-£3,059	-£832	£1,394	£3,621	£5,848	£8,075	£10,302	£12,529	£14,755	£16,982	£19,209
	20	-£6,094	-£3,867	-£1,640	£587	£2,814	£5,040	£7				£16,175
	25	-£9,128	-£6,901	-£4,675	-£2,448	-£221	£2,006	£4				£13,140
	30	-£12,163	-£9,936	-£7,709	-£5,482	-£3,255	-£1,029	£1,198	£3,425	£5,652	£7,879	£10,106
	35	-£15,197	-£12,971	-£10,744	-£8,517	-£6,290	-£4,063	-£1,836	£391	£2,617	£4,844	£7,071
	40	-£18,232	-£16,005	-£13,778	-£11,551	-£9,325	-£7,098	-£4,871	-£2,644	-£417	£1,810	£4,037
	45	-£21,266	-£19,040	-£16,813	-£14,586	-£12,359	-£10,132	-£7,905	-£5,679	-£3,452	-£1,225	£1,002
	50	-£24,301	-£22,074	-£19,847	-£17,620	-£15,394	-£13,167	-£10,940	-£8,713	-£6,486	-£4,259	-£2,032
	55	-£27,335	-£25,109	-£22,882	-£20,655	-£18,428	-£16,201	-£13,974	-£11,748	-£9,521	-£7,294	-£5,067
	60	-£30,370	-£28,143	-£25,916	-£23,689	-£21,463	-£19,236	-£17,009	-£14,782	-£12,555	-£10,328	-£8,102
	65	-£33,404	-£31,178	-£28,951	-£26,724	-£24,497	-£22,270	-£20,043	-£17,817	-£15,590	-£13,363	-£11,136
	70	-£36,439	-£34,212	-£31,985	-£29,758	-£27,532	-£25,305	-£23,078	-£20,851	-£18,624	-£16,397	-£14,171
	75	-£39,474	-£37,247	-£35,020	-£32,793	-£30,566	-£28,339	-£26,112	-£23,886	-£21,659	-£19,432	-£17,205
	80	-£42,508				,601	-£31,374	-£29,147	-£26,920	-£24,693	-£22,466	-£20,240
	85	-£45,543				,635	-£34,408	-£32,182	-£29,955	-£27,728	-£25,501	-£23,274
	90	-£48,577				,670	-£37,443	-£35,216	-£32,989	-£30,762	-£28,536	-£26,309
	95	-£51,612	-£49,385	-£47,158	-£44,931	-£42,704	-£40,477	-£38,251	-£36,024	-£33,797	-£31,570	-£29,343
	100	-£54,646	-£52,419	-£50,192	-£47,966	-£45,739	-£43,512	-£41,285	-£39,058	-£36,831	-£34,605	-£32,378

Should not compare high number of PEDs with low number of coils

Should not compare low number of PEDs with high number of coils

This analysis can, now, be used to assess the likely cost impact of using PED to treat a range of different sizes of aneurysm, as shown in Table B3.36.

Table B6.36 Two-way sensitivity analysis of PED vs stent-assisted coiling (demonstrating aneurysm size)

Number of coils	Number of PEDs: 1.0	1.2	1.4	1.6	1.8	2.0	2.2	2.4	2.6	2.8	3.0
10	-£25	£2,202	£4,429	£6,656	£8,883	£11,109	£13,336	£15,563	£17,790	£20,017	£22,244
15	-£3,059	-£832	£1,394	£3,621	£5,848	£8,075	£10,302	£12,529	£14,755	£16,982	£19,209
20	-£6,094	-£3,867	-£1,640	£587	£2,814				£11,721	£13,948	£16,175
25	-£9,128	-£6,901	-£4,675	-£2,448	-£221				£8,686	£10,913	£13,140
30	-£12,163	-£9,936	-£7,709	-£5,482	-£3,255				£5,652	£7,879	£10,106
35	-£15,197	-£12,971	-£10,744	-£8,517	-£6,290				£2,617	£4,844	£7,071
40	-£18,232	-£16,005	-£13,778	-£11,551	-£9,325	-£7,098		-£2,644			
45	-£21,266	-£19,040	-£16,813	-£14,586	-£12,359	-£10,13[illegible]		-£5,679			
50	-£24,301	-£22,074	-£19,847	-£17,620	-£15,394	-£13,167	-£10,940	-£8,713			
55	-£27,335		-£22,882	-£20,655	-£18,428	-£16,201	-£13,974	-£11,748			
60	-£30,370		-£25,916	-£23,689	-£21,463	-£19,236	-£17,009	-£14,782			
65				-£26,724	-£24,497	-£22,270	-£20,043	-£17,817	-£15,590		-£11,136
70				-£29,758	-£27,532	-£25,305	-£23,078	-£20,851	-£18,624		-£14,171
75				-£32,793	-£30,566	-£28,339	-£26,112	-£23,886	-£21,659	-£19,432	-£17,205
80				-£35,828	-£33,601	-£31,374	-£29,147	-£26,920	-£24,693	-£22,466	-£20,240
85	-£45,543	-£43,316	-£41,089	-£38,862	-£36,635	-£34,408	-£32,182	-£29,955	-£27,728	-£25,501	-£23,274
90	-£48,577	-£46,350	-£44,123	-£41,897	-£39,670	-£37,443	-£35,216	-£32,989	-£30,762	-£28,536	-£26,309
95	-£51,612	-£49,385	-£47,158	-£44,931	-£42,704	-£40,477	-£38,251	-£36,024	-£33,797	-£31,570	-£29,343
100	-£54,646	-£52,419	-£50,192	-£47,966	-£45,739	-£43,512	-£41,285	-£39,058	-£36,831	-£34,605	-£32,378

This analysis suggests that the likely cost savings associated with PED are likely to be greater for large and giant aneurysms that for smaller aneurysms. Further, it can be concluded that the greater the size of the aneurysm, the greater the likely cost saving from using PED.

6.8.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 4.

It may be that different outcomes could be observed for patients depending on the *location* of the aneurysms within the brain. However, there were insufficient data to allow for a meaningful comparison of outcomes associated with the different treatments.

6.9 Interpretation of economic evidence

6.9.1 Are the results from this cost impact analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

Only one cost analysis of PED has been undertaken previously. The results in this analysis differ fairly substantially from that analysis. Specifically, the present analysis appears to present a far more conservative case than the previous analysis. This is because the previous analysis assumed significant costs associated with retreatment for stent-assisted coiling (in fact, assuming that almost all patients require retreatment), whilst PED patients were assumed to require no further treatment.

6.9.2 Is the cost impact analysis relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 4?

As far as possible, the economic analysis presented in this submission has used data representative of the type of patients who could potentially benefit from the technology. In some cases (such as estimating the cost of rupture), it was necessary to take evidence from other disease areas. The model is explicit in stating the assumptions used in such cases, and sensitivity analysis has explored the potential implications of alternative inputs being used.

6.9.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

This is the first analysis to undertake a comprehensive approach towards measuring the costs and health outcomes associated with PED and its comparators. The model uses the best available evidence to combine short-term outcomes and long-term implications in order to estimate the true impact of each technology. In addition to the cost implications of treatment, this model demonstrates the significant health benefits that can be achieved by appropriately managing a patient with an aneurysm.

This is the first model to estimate the long-term life expectancy and quality-adjusted life year outcomes associated with treatment.

As with any economic model, there are limitations due to a lack of appropriate data to populate the analysis in some areas. In particular, there is a lack of head-to-head comparative data. This meant that the model has to use data from single arm trials, or non-comparative studies. Where uncertainties remained, extensive sensitivity analysis was undertaken around key model parameters.

6.9.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

As described above, it is recommended that attempts be made to generate head-to-head comparative data for PED and its comparators.

However, a randomized trial of PED versus any particular individual treatment would be infeasible since a reasonably large proportion of subjects assigned to a particular alternative treatment may not be eligible for that treatment. Such subjects would have to undergo some other treatment, rendering the information from such a trial inapplicable. A randomized trial of PED versus any treatment, i.e., a strategy in which any alternative treatment could be applied, would result in variations in treatment in the control group and would not give high-quality information on any individual treatment.

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Appendices

Appendix 1

SEARCH STRATEGY FOR COST-EFFECTIVENESS STUDIES (SECTION 6.1)

The specific databases searched and the service provider used

- MEDLINE and MEDLINE In-Process (OvidSP)
- EMBASE (OvidSP)
- EconLit (OvidSP)
- NHS Economic Evaluation Database (NHS EED) (Cochrane Library)

The date on which the search was conducted

All searches were conducted on 7th June 2011.

The date span of the search

- MEDLINE and MEDLINE In-Process (1948-2011/May week 4)
- EMBASE (1980-2011/week 22)
- EconLit (1969-2011/March)
- NHS Economic Evaluation Database (NHS EED) (2011 Issue 2)

The complete search strategies used, including all search terms

MEDLINE and MEDLINE In-Process

1 Intracranial Aneurysm/ (18855)
2 (cerebral adj3 aneurysm$).ti,ab. (4887)
3 (intracerebral adj3 aneurysm$).ti,ab. (235)
4 (cranial adj3 aneurysm$).ti,ab. (96)
5 (intracranial adj3 aneurysm$).ti,ab. (6157)
6 (brain adj3 aneurysm$).ti,ab. (402)
7 (giant adj3 aneurysm$).ti,ab. (2196)
8 (berry adj3 aneurysm$).ti,ab. (225)
9 (basilar adj3 aneurysm$).ti,ab. (906)
10 or/1-9 (21631)
11 economics/ (26016)
12 exp "costs and cost analysis"/ (156410)
13 economics, dental/ (1827)
14 exp "economics, hospital"/ (17170)
15 economics, medical/ (8397)
16 economics, nursing/ (3846)
17 economics, pharmaceutical/ (2230)
18 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).tw. (334412)
19 (expenditure$ not energy).tw. (14155)
20 (value adj1 money).tw. (20)
21 budget$.tw. (14379)
22 or/11-21 (446674)
23 ((energy or oxygen) adj cost).ti,ab. (2277)
24 (metabolic adj cost).ti,ab. (590)

25 ((energy or oxygen) adj expenditure).ti,ab. (13056)
26 or/23-25 (15310)
27 22 not 26 (443192)
28 10 and 27 (210)
29 animals/ not (humans/ and animals/) (3505641)
30 28 not 29 (207)

EMBASE

1 exp intracranial aneurysm/ (20709)
2 (cerebral adj3 aneurysm$).ti,ab. (6087)
3 (intracerebral adj3 aneurysm$).ti,ab. (279)
4 (cranial adj3 aneurysm$).ti,ab. (132)
5 (intracranial adj3 aneurysm$).ti,ab. (7434)
6 (brain adj3 aneurysm$).ti,ab. (509)
7 (giant adj3 aneurysm$).ti,ab. (2725)
8 (berry adj3 aneurysm$).ti,ab. (216)
9 (basilar adj3 aneurysm$).ti,ab. (1102)
10 or/1-9 (24779)
11 Health Economics/ (30157)
12 exp Economic Evaluation/ (167390)
13 exp Health Care Cost/ (161100)
14 exp PHARMACOECONOMICS/ (137113)
15 or/11-14 (385152)
16 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (431715)
17 (expenditure$ not energy).ti,ab. (17181)
18 (value adj2 money).ti,ab. (913)
19 budget$.ti,ab. (18188)
20 or/16-19 (450222)
21 15 or 20 (678872)
22 (metabolic adj cost).ti,ab. (650)
23 ((energy or oxygen) adj cost).ti,ab. (2536)
24 ((energy or oxygen) adj expenditure).ti,ab. (15138)
25 or/22-24 (17658)
26 21 not 25 (674863)
27 editorial.pt. (373519)
28 note.pt. (444555)
29 letter.pt. (731021)
30 or/27-29 (1549095)
31 26 not 30 (604306)
32 (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dogs or dog or cats or bovine or sheep).ti,ab,sh. (4028596)
33 exp animal/ (1659234)
34 Nonhuman/ (3647030)
35 or/32-34 (5761219)
36 exp human/ (12415315)
37 exp human experiment/ (289598)
38 36 or 37 (12416698)
39 35 not (35 and 38) (4536322)
40 31 not 39 (561832)

41 10 and 40 (316)

EconLit

1 (cerebral adj3 aneurysm$).ti,ab. (1)
2 (intracerebral adj3 aneurysm$).ti,ab. (0)
3 (cranial adj3 aneurysm$).ti,ab. (0)
4 (intracranial adj3 aneurysm$).ti,ab. (0)
5 (brain adj3 aneurysm$).ti,ab. (0)
6 (berry adj3 aneurysm$).ti,ab. (0)
7 (basilar adj3 aneurysm$).ti,ab. (0)
8 or/1-7 (1)

NHS EED

#1	MeSH descriptor **Intracranial Aneurysm** explode all trees	333
#2	(cerebral NEAR/3 aneurysm*):ti,ab,kw	145
#3	(intracerebral NEAR/3 aneurysm*):ti,ab,kw	4
#4	(cranial NEAR/3 aneurysm*):ti,ab,kw	3
#5	(intracranial NEAR/3 aneurysm*):ti,ab,kw	430
#6	(brain NEAR/3 aneurysm*):ti,ab,kw	35
#7	(giant NEAR/3 aneurysm*):ti,ab,kw	7
#8	(berry NEAR/3 aneurysm*):ti,ab,kw	2
#9	(basilar NEAR/3 aneurysm*):ti,ab,kw	2
#10	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)	507

Appendix 2

AGE-RELATED MORTALITY

Age-related mortality			
Age	Annual rate	Age	Annual rate
0	0.48%	51	0.31%
1	0.03%	52	0.34%
2	0.02%	53	0.38%
3	0.02%	54	0.42%
4	0.01%	55	0.47%
5	0.01%	56	0.50%
6	0.01%	57	0.54%
7	0.01%	58	0.59%
8	0.01%	59	0.65%
9	0.01%	60	0.70%
10	0.01%	61	0.77%
11	0.01%	62	0.84%
12	0.01%	63	0.95%
13	0.01%	64	1.04%
14	0.01%	65	1.13%
15	0.02%	66	1.24%
16	0.02%	67	1.36%
17	0.03%	68	1.52%
18	0.04%	69	1.67%
19	0.04%	70	1.82%
20	0.04%	71	2.00%
21	0.04%	72	2.22%
22	0.04%	73	2.49%
23	0.04%	74	2.75%
24	0.05%	75	3.06%
25	0.05%	76	3.46%
26	0.05%	77	3.83%
27	0.05%	78	4.26%
28	0.06%	79	4.85%
29	0.06%	80	5.44%
30	0.06%	81	6.09%
31	0.07%	82	6.76%
32	0.07%	83	7.56%
33	0.08%	84	8.49%
34	0.09%	85	9.42%
35	0.09%	86	10.45%
36	0.09%	87	11.55%
37	0.10%	88	12.26%
38	0.11%	89	13.44%
39	0.12%	90	14.59%
40	0.13%	91	16.66%
41	0.14%	92	18.73%
42	0.15%	93	20.37%
43	0.16%	94	22.06%
44	0.17%	95	24.47%
45	0.19%	96	26.26%
46	0.20%	97	28.01%
47	0.22%	98	30.02%
48	0.24%	99	31.89%
49	0.26%	100	33.62%
50	0.29%	> 100	33.62%