National Institute for Health and Clinical Excellence

Medical Technologies Evaluation Programme

MT82 Pipeline embolisation device for the treatment of complex intracranial aneurysms

Consultation Comments table

MTAC date: 19 January 2012

There are 50 consultation comments from 7 consultees (5 NHS professionals (including 1 on behalf of a Specialist Society, 1 on behalf of a Specialist Group and 1 on behalf of the UK Flow Diverter Registry), 1 manufacturer (the topic sponsor) and the Department of Health. The comments are reproduced in full in the table below. An additional analysis, carried out by the External Assessment Centre in response to selected consultation comments, is reproduced in full as an appendix to this table.

Com. no.	Consultee number and organisation	Sec. no.	Comments	Response
1	Consultee 3 **UK Flow Diverter Registry,** **Expert Adviser**	**1.3**	1.3 details of patients submitted to Registry should include information on complications and clinical outcomes	Thank you for your comment. Submission of data to the UK Neurointerventional Radiology Group audit database is recommended in Section 1.3 of the guidance to increase the evidence base and guide future use of this technology. The Committee considered this comment but, as the audit criteria already include specified clinical outcomes and complications, decided not to change the guidance.

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2	Consultee 5 **British Society of Neuroradiologists**	**1.1**	1.1 In some complex aneurysms,stenting and coiling is unlikely to be successful even when smaller number of coils are used. Pipeline type devices(FD) have shown promise in this cases and it would be useful to facilitate use of this device in controlled way in such aneurysms.	Thank you for your comment. The use of the Pipeline embolisation device in aneurysms that have failed treatment by stent assisted coiling is outside the scope of the evaluation. The Committee's considerations of the use of the Pipeline embolisation device in aneurysms that are unsuitable for stent assisted coiling are in sections 3.16 and 6.2 of the guidance, although no recommendations are made in this patient population because the population is outside the scope of the evaluation. Section 6.2 was expanded to clarify the Committee's considerations.
3	Consultee 6 **Sponsor, Covidien**	**1.1**	*Currently reads*: The case for adopting the Pipeline embolisation device in the NHS is supported by the current evidence when it is used in patients with giant or complex intracranial aneurysms which are unsuitable for surgery, which are being considered for stenting and where large numbers of coils are needed during stent-assisted coiling. *Suggested change:* The case for adopting the Pipeline embolisation device in the NHS is supported by the current evidence when it is used in patients with large, giant or complex intracranial aneurysms who are unsuitable for surgery, or in those who are being considered for stent-assisted coiling where large numbers of coils are needed. *Explanations*: see general comments 1 and 4.	Thank you for your comment. The Committee decided to change section 1.1 (and related text in sections 1.2 and 6) of the guidance to incorporate parts of the consultee's suggested text relating to aneurysm size but not the suggestions relating to "…aneurysms which were unsuitable for surgery…" on the basis that the changes did not provide additional clarity about the patient group to which the recommendations apply. *The 'general comments' referred to by the consultee are consultation comments 47 and 50.*
4	Consultee 6 **Sponsor, Covidien**	**1.2**	*Currently reads:* The Pipeline embolisation device is estimated to be cost saving when compared with stent-assisted coiling, in patients with giant or complex intracranial aneurysms when the number of Pipeline embolisation devices inserted does not	Thank you for your comment. The Committee decided to change sections 1.2 (and related text in sections 1.1 and 6) of the guidance to incorporate

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			exceed two and when treatment would otherwise require the use of 29 or more coils combined with one stent for stent-assisted coiling. If two Pipeline embolisation devices are used the total procedure cost is estimated as £30,354 compared with £30,775 for the use of 29 coils for stent assisted coiling (a saving of £421 using the Pipeline embolisation device). *Suggested change*: The Pipeline embolisation device is estimated to be cost saving when compared with stent-assisted coiling, in patients with large, giant or complex intracranial aneurysms when a) the number of Pipeline embolisation devices inserted equals one and treatment would otherwise require the use of *[insert number of coils from modelling]* or more coils combined with one stent for stent-assisted coiling, and b) the number of Pipeline embolisation devices inserted equals two and treatment would otherwise require the use of 29 or more coils combined with one stent for stent-assisted coiling. If two Pipeline embolisation devices … *Explanation:* see general comments 3 and 4. It would be useful for payers and physicians to know at the beginning of the document the circumstances where the Pipeline embolisation device is cost saving when either one or two devices are used (i.e. whole numbers of the device). The previous wording suggested that when the number of Pipeline embolisation devices is lower than 2, 29 or more coils would still be required to enable cost savings, which is not the case.	the consultee's suggested text about aneurysm size. However, it was advised that patients for whom only one Pipeline embolisation device is needed are likely to have smaller aneurysms and are therefore outside the scope of the guidance. Therefore, although the External Assessment Centre carried out additional analysis on the use of one Pipeline embolisation device, the Committee decided not to include this in the guidance because the aneurysms for which only one Pipeline embolisation device may be used are outside the scope of the main recommendations. The Committee's considerations of this point have been added to section 5.19 of the guidance. *The 'general comments' referred to by the consultee appear in this table as consultation comments 49 and 50.*
5	Consultee 5 **British Society of Neuroradiologists**	**1.2**	1.2 Restricting use purely on financial basis is not useful.It is however informative.	Thank you for your comment. Medical technologies guidance aims to promote the adoption of treatments which are clinically non-inferior and resource-releasing. In making its recommendations the Committee considers both the clinical and economic evidence.

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6	Consultee 5 **British Society of Neuroradiologists**	**1.3**	1.3 This is very important and use outside registry should not be allowed.	Thank you for your comment. The Committee decided not to change the guidance as submission of details to the UK Neurointerventional Radiology Group audit database is already one of its main recommendations.
7	Consultee 3 **UK Flow Diverter Registry,** **Expert Adviser**	**2.4**	2.4 The UK price is considerably higher than in most (?all Western) other healthcare economies and the reasons for this are not addressed. This cost does not include the necessary cost of a special microcatheter to deliver the PED. At almost 1000 pounds this is 2.5 times the cost of standard microcatheter used for coil assist stents. The extra microcathter cost should be clearly factored in, Im unclear if it has been or not	Thank you for your comment. The price of the Pipeline embolisation device quoted in section 2.4 of the guidance is that used by the sponsor in its cost analysis. The sponsor included the cost of one Marksman catheter with the Pipeline embolisation device and two microcatheters or Marksman catheters at equivalent costs for stent-assisted coiling. The Committee was advised that, in UK clinical practice, less costly microcatheters are routinely used during stent-assisted coiling, and Marksman catheters are not commonly used. The Committee considered the model inputs, and the costs applied in the de novo model were revised by the External Assessment Centre. Sections 1.2, 5.13, 5.21, 5.22, 5.27 and 6.1 of the guidance have been changed to reflect this difference. The supplementary report by the External Assessment Centre which includes this analysis is appended to this comments table.

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8	Consultee 6 **Sponsor, Covidien**	**2.3**	*Currently reads*: The Pipeline embolisation device is indicated for use in patients with unruptured, complex intracranial aneurysms, specifically large and giant, wide-necked and fusiform aneurysms. This is the group of patients covered by this guidance. It may also be used in patients whose aneurysms are unsuitable for standard coiling and/or stenting and for neurosurgical treatment; and in patients for whom previous coiling/clipping procedures have failed. *Suggested change*: The Pipeline embolisation device is indicated for use in patients with unruptured, complex intracranial aneurysms, specifically large and giant, wide-necked and fusiform aneurysms. ~~This is the group of patients covered by this guidance.~~ It may also be used in patients whose aneurysms are unsuitable for standard coiling and/or stenting and for neurosurgical treatment; and in patients for whom previous coiling/clipping procedures have failed. *Explanation: see general comment 1.*	Thank you for your comment. The Committee considered this comment and decided not to change the guidance because it considered the clarification of patients covered by the guidance to be useful to the reader. *The 'general comment' referred to by the consultee is consultation comment number 47.*
9	Consultee 5 **British Society of Neuroradiologists**	**2.5**	2.5 Benefits are overstated. We strongly believe that this device offers benefits in some patients. However, a vast number aneurysms including some complex aneurysms are succesfully treated using current devices. In a recently completed multicentre randomised study, good outcomes were seen in 96% of patients.	Thank you for your comment. The benefits in section 2.5 are those claimed by the sponsor and which form the basis of the evaluation of the single technology. The evaluation carried out by NICE tested the benefits claimed by the sponsor.

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10	Consultee 5 **British Society of Neuroradiologists**	**3**	Puffs study included vast majority of cases in the cavernous carotid location. These aneurysms frequently do not need treatment and have lower clinical risk. In the Uk very few centres would treat asymptomatic aneurysm in this location and practice in USA is different. We need to be careful when you use this data for UK practice. There is limited evidence in favour of Pipeline device.	Thank you for your comment. Differences in clinical practice between the UK and US were discussed extensively by the Committee when making its recommendations at both draft and final guidance stages. These discussions were informed by UK expert advisers working in the NHS. Section 3.20 includes the Committee's consideration on the difference in clinical practice between the UK and US.
11	Consultee 3 **UK Flow Diverter Registry,** **Expert Adviser**	**3**	The occurrence of previously unseen (with conventional coiling or stent assisted coiling) adverse events is not as clearly stated as it could be. These are: a) delayed rupture of previously unruptured aneurysm following flow diverter b) delayed ipsilateral parenchymal haemorrhage distal to FD c) very delayed FD occlusion with resultant parent vessel occlusion It is the appearance of such unexpected/unpredictable AEs that has led to several Registries bein gset up around the world	Thank you for your comment. Section 3 of the guidance provides a summary of the key clinical outcomes identified in the decision problem. Full details on adverse events are presented in Table 2 (p32) of the External Assessment Centre report. The expert advisers' opinions on the technology and possible adverse events are summarised in Appendix B of the Assessment Report Overview. To increase the evidence base and guide future use of this technology the Committee recommends submission of data to the UK Neurointerventional Radiology Group audit database.
12	Consultee 6 **Sponsor,** **Covidien**	**3.13**	*Currently reads:* The FDA report (2011) described Rankin scoring (a general measure of neurological function) for 101 patients. The scores improved from baseline in 20% (21/101) of patients, remained unchanged in 65% (70/101) and deteriorated in 9% (10/101) at 180 days follow-up. *Correct to*: The FDA report (2011) described Rankin scoring (a	Thank you for your comment. The wording of section 3.13 of the guidance has been amended as suggested by the consultee.

<table>
<tr><th>Com. no.</th><th>Consultee number and organisation</th><th>Sec. no.</th><th>Comments</th><th>Response</th></tr>
<tr><td></td><td></td><td></td><td>general measure of neurological function) for 104 patients. The scores improved from baseline in 20% (21/104) of patients, remained unchanged in 67% (70/104) and deteriorated in 9.6% (10/104) at 180 days follow-up.
Explanation: Of 107 patients in the safety analysis set in PUFS, 101 patients were assessed using the modified Rankin score (3 died and were assigned a mRs of 6; 3 withdrew from study). Of the patients that were assessed or died (n=104), 21 patients showed improvement (20%), 70 patients remained unchanged (67%), and 10 patients deteriorated (9.6%)

Table 31. Change in modified Rankin scale at 180 days compared to baseline in PUFS.
Shaded cells show subjects who worsened. Bolded values show subjects who were the same at baseline and follow-up. (Safety population)
<table><tr><th>Frequency</th><th></th><th colspan="8">Score at 180 days</th></tr><tr><th></th><th></th><th>ND</th><th>0</th><th>1</th><th>2</th><th>3</th><th>4</th><th>6</th><th>Total</th></tr><tr><td rowspan="8">Score at baseline</td><td>ND</td><td>0</td><td>1</td><td>0</td><td>0</td><td>0</td><td>0</td><td>1</td><td>2</td></tr><tr><td>0</td><td>3*</td><td>48</td><td>5</td><td>1</td><td>0</td><td>0</td><td>1</td><td>58</td></tr><tr><td>1</td><td>1</td><td>12</td><td>20</td><td>1</td><td>0</td><td>0</td><td>1</td><td>35</td></tr><tr><td>2</td><td>1**</td><td>2</td><td>5</td><td>1</td><td>0</td><td>0</td><td>0</td><td>9</td></tr><tr><td>3</td><td>0</td><td>0</td><td>1</td><td>1</td><td>0</td><td>0</td><td>0</td><td>2</td></tr><tr><td>4</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>1</td><td>0</td><td>1</td></tr><tr><td>Total</td><td>5</td><td>63</td><td>31</td><td>4</td><td>0</td><td>1</td><td>3</td><td>107</td></tr></table>*: Subjects withdrew from study
**: Subject stopped participating prior to day 30 but still in contact with study site.
Source: PMA Table 12-25 updated by Amendment 3 Table 35

[Table copied from FDA executive summary P100018.]</td><td></td></tr>
<tr><td>13</td><td>Consultee 6
Sponsor, Covidien</td><td>3.13</td><td>*Currently reads:* There was an improvement in visual field sensitivity (not otherwise described) from baseline in 19% (19/101) of patients, no change in 65% (65/101) of patients and deterioration in eye function in 5% (5/101) of patients at follow-up of 180 days (FDA 2011).
Change to: There was an improvement in visual field sensitivity (not otherwise described) from baseline in 21% (19/89) of patients, no change in 73% (65/89) of patients and deterioration in eye function in 5.6% (5/89) of patients at follow-up of 180 days (FDA 2011).
Explanation: At 180 days in the PUFS study, 101 patients had an eye examination; of these, only 89 patients were assessed for visual field sensitivity.</td><td>Thank you for your comment. The wording of section 3.13 of the guidance has been amended as suggested by the consultee.</td></tr>
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14	Consultee 6 **Sponsor, Covidien**	**3.5**	*Currently reads*: A report to the FDA by the sponsor (FDA 2011) described the clinical evidence at 1 year from the PUFS study: an ongoing prospective, multicentre, single-arm study of 107 patients with 110 intracranial aneurysms that were wide necked (> 4 mm or no discernable neck and a size > 10 mm), large or giant (2.5–5 mm). *Change to*: A report to the FDA by the sponsor (FDA 2011) described the clinical evidence for up to 1 year from the PUFS study: an ongoing prospective, multicentre, single-arm study of108 patients with a single large or giant target aneurysm that had a neck >4 mm or no discernible neck, and a size (maximum fundus diameter) >10 mm. *Explanation*: correction of PUFS inclusion criteria (the 2.5–5 mm measurement refers to the parent vessel diameter).	Thank you for your comment. The total number of patients in the PUFS study and the definition of the patient population have been amended at section 3.5 and more information about the trial added.
15	Consultee 3 **UK Flow Diverter Registry, Expert Adviser**	**4**	If PED is used for recurrent aneurysm as well as giant or otherwise untreatable aneurysms then considerbaly more than 60 patients per year will be treated with PED	Thank you for your comment. The cost analysis in the scope specified de novo or repeat treatment. The PUFS study included patients who had received previous treatment; 6 by coil embolisation, 1 by surgery and 1 by other methods. The PITA study included 13 patients who had been treated previously by coil embolisation and 6 by stenting. Clinical outcomes for these patients were not presented separately by the sponsor but the numbers of patients for whom previous treatment had failed in both studies has been added to the guidance in sections 3.4 and 3.5.

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16	Consultee 5 **British Society of Neuroradiologists**	**4.3**	4.3 Agree. This is important use of pipeline device.	Thank you for your comment.
17	Consultee 3 **UK Flow Diverter Registry,** **Expert Adviser**	**5.13**	5.13 It is unclear how this calculation was reached. If 1 PED costs 10,170 then(as currently charged by manufacturer) 2 will cost 20340. Going from 22 to 29 coils should be 7 x approx 500 £3500, much less than the 10,170 cost of an extra PED. Can this be clarified please?	Thank you for your comment. Please also see response to consultation comment number 7. In responding to this comment, a number of parameters in the cost model were clarified and discussed by the Committee. The expert advisers raised issues in four areas: the use of high cost Marksman / equivalent Microcatheters (also referred to in comment 7); the use of a balloon for stent-assisted coiling; drug costs; and additional endovascular equipment. The sponsor consistently used data from clinical trials to justify the model inputs, but these data often do not account for differences in clinical practice in the UK compared with other countries, in particular the US. The Committee considered the impact of these changes and relevant sections of the guidance were changed to describe the impact of varying these parameters on the overall cost savings associated with the Pipeline embolisation device. A supplementary report by the External Assessment Centre which includes the further analyses is appended to this comments table. See also section

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				5.12 of the guidance.
18	Consultee 5 **British Society of Neuroradiologists**	**5**	Cost consideration are only relevant when the aneurysm can treated by two devices and both are likely to produce similar outcomes. In those aneurysms where Pipline is the only possible treatment, it should be allowed without cost consideration. In large aneurysms, we would use Pipeline with coils. The serious risk of haemmorrhage in these aneurysms is an important consideration.	Thank you for your comment. The scope of medical technologies guidance is based on the claimed benefits made by the sponsor for the specific intervention, compared with standard care. The use of the Pipeline embolisation device with coils is outside the scope of the guidance.
19	Consultee 6 **Sponsor, Covidien**	**5.13**	*Currently reads*: When 1.658 Pipeline embolisation devices were used, the Pipeline embolisation device was more costly compared to stent-assisted coiling if 22 coils were used (an estimated cost increase of £19), but cost saving when 23 coils were used. The cost saving when using 1.658 Pipeline embolisation devices compared with 23 coils was estimated to be £588 (£26,546 and £27,134 respectively). When two Pipeline embolisation devices were used, the Pipeline embolisation device was more costly by an estimated £185 when 28 coils were used but less costly when 29 coils were used. The cost saving when using two Pipeline embolisation devices compared with 29 coils was estimated to be £421 (£30,354 and £30,775 respectively). *Suggested change*: Would it be possible to include a comparison with 1 PED for practical reasons? – see general comment 3.	Thank you for your comment. The Committee was advised that patients for whom only one Pipeline embolisation device is needed are likely to have smaller aneurysms and therefore be outside the scope of the guidance. A Committee consideration to reflect its discussions on the use of one Pipeline embolisation device has been added to section 5.19 of the guidance. Because the aneurysms for which only one Pipeline embolisation device may be used are outside the scope of the main recommendations, the Committee decided not to include this scenario in the guidance. *The 'general comment' referred to by the consultee is consultation comment number 49.*

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20	Consultee 6 **Sponsor, Covidien**	**5.15**	*Currently reads*: The Committee noted that, in UK clinical practice, patients who might currently be considered for the Pipeline embolisation device would be those for whom surgery would not be possible and for whom stent-assisted coiling would be the only other potential intervention. It therefore considered that comparison of costs with those for stent-assisted coiling was of particular relevance. The Committee noted that for this cost comparison, the main drivers of cost were the numbers of Pipeline embolisation devices used and the numbers of coils used. It received differing advice about the number of Pipeline embolisation devices and coils normally needed to treat each patient, but expert advice and data from the sponsor both suggested that the use of two Pipeline embolisation devices was a reasonable estimate for practice in the UK. *Suggested change*: … It received differing advice about the number of Pipeline embolisation devices and coils normally needed to treat each patient, but expert advice and data from the sponsor both suggested that the use of two Pipeline embolisation devices was a reasonable estimate for practice in the UK. Actual clinical usage from the UK indicates that in almost 60% of cases, only one PED is required (data up to September 2011). *Explanation*: see general comment 3.	Thank you for your comment. The Committee considered this comment and decided to add a consideration to section 5.19 of the guidance but not, for the reasons set out in the response to comment 19, to include the cost scenario in the guidance. *The 'general comment' referred to by the consultee is consultation comment number 49 in this table.*

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21	Consultee 6 **Sponsor, Covidien**	**5.15-5.16**	*Suggested new statement (immediately after 5.15):* The Pipeline embolisation device is cost effective as a life-saving treatment at a Willingness to pay threshold of £30,000. It is dominant vs. stent-assisted coiling, and cost-effective vs. its comparators (where neurosurgical clipping is not feasible). The key drivers of the short-term costs are the number of coils per aneurysm and the number of Pipeline embolisation devices – the numbers of which vary for each clinical case. However, the Pipeline embolisation device has the most favourable outcome in terms of QALYs vs. its comparators (due to the mid- and long-term benefits offered by the device). *Explanations: see general comment 2.*	Thank you for your comment. The sponsor submitted a cost effectiveness analysis and this was available to the Committee when it made its decision on the technology. However, in line with the MTEP Methods Guide, the assessment of the economic evidence for the Pipeline embolisation by the External Assessment Centre was carried out using a cost consequences approach. Within the Programme's methodology, it is not possible to use multiple economic approaches concurrently. The Committee discussed the cost consequences analysis in detail, and this was the basis for its recommendations. The Committee decided not to change the guidance. *The 'general comment' referred to by the consultee is consultation comment number 48.*
22	Consultee 7 **Consultant Neuroradiologist**	**5.7**	In calculating the cost of the procedure one has to consider the cost of retreatment and the cost of dealing with procedural complications. Based on the available evidence from case series of both techniques, the complication rate and recurrence rate associated with PED is lower than Stent assisted coiling of complex intracranial aneurysms.	Thank you for your comment. The cost of retreatment and some adverse events are included in the cost analysis. No comparative data were presented by the sponsor for the Pipeline embolisation device compared with stent assisted coiling. Full details of the costs associated with retreatment and adverse events are included in the Assessment Report Summary and External Assessment centre report.

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23	Consultee 5 **British Society of Neuroradiologists**	**6**	as above	Thank you for your comment. Please see response to comment number 18.
24	Consultee 6 **Sponsor, Covidien**	**6.1**	*Currently reads:* The Committee concluded that current evidence supports the case for adoption of the Pipeline embolisation device when it is used in highly selected patients with giant or complex intracranial aneurysms which would require 29 or more coils during stent-assisted coiling and which are unsuitable for neurosurgical treatment. For these patients use of the Pipeline embolisation device appears efficacious and is less costly than stent-assisted coiling. *Suggested change:* The Committee concluded that current evidence supports the case for adoption of the Pipeline embolisation device when it is used in highly selected patients with large, giant or complex intracranial aneurysms which would require 29 or more coils during stent-assisted coiling and which are unsuitable for neurosurgical treatment. For these patients use of the Pipeline embolisation device appears efficacious and is less costly than stent-assisted coiling. *Explanation:* see general comment 4.	Thank you for your comment. Section 6.1 (and related text in sections 1.1 and 1.2) of the guidance have been changed to include 'complex giant or large aneurysms'.

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25	Consultee 6 **Sponsor, Covidien**	**6.2**	*Currently reads*: The Committee noted that the Pipeline embolisation device may be the only feasible intervention for some patients whose giant or complex intracranial aneurysms are unsuitable in size or shape for stent-assisted coiling or surgery, and for whom parent vessel occlusion would result in stroke or death. This group of patients are outside the scope of the recommendations. *Suggested change*: The Committee noted that the Pipeline embolisation device may be the only feasible intervention for some patients whose large, giant or complex intracranial aneurysms are unsuitable in size or shape for stent-assisted coiling or neurosurgical clipping, and for whom parent vessel occlusion would result in stroke or death. *Explanation:* see general comments 1 and 4.	Thank you for your comment. Section 6.2 (and related text in sections 1.1 and 1.2 of the guidance) will be changed to include 'complex giant or large aneurysms'. The Committee decided not to change the guidance in light of the consultee's request for 'neurosurgical clipping' based on expert advice that neurosurgery is a more appropriate term and the current guidance best describes this group of patients.
26	Consultee 1 **Consultant Interventional Neuroradiologist**	**6.2**	The Committee noted that the Pipeline embolisation device may be the only feasible intervention for some patients whose giant or complex intracranial aneurysms are unsuitable in size or shape for stent-assisted coiling or surgery, and for whom parent vessel occlusion would result in stroke or death. This group of patients are outside the scope of the recommendations. This section is important as many of the aneurysms treated are in this group. Large Aneurysms causing symptoms due to mass effect do not do have a good outcome from stent and coil.I do not see why this group is outside the scope of the recommendations and should be included.	Thank you for your comment. The management of the patients covered by this guidance will be determined by a multidisciplinary team and local decisions made on treatment with the Pipeline embolisation device. The evaluation did not find that the Pipeline embolisation device was cost-saving in patients for whom conservative management was the only option and Section 6.2 of the guidance has been expanded to further clarify the Committee's considerations.
27	Consultee 1 **Consultant Interventional Neuroradiologist**	**6.2**	Pipeline also is a feasible treatment for recurrent aneurysms post coiling not mentioned in the document.	Thank you for your comment. Please see response to comment number 15.

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28	Consultee 1 **Consultant Interventional Neuroradiologist**	**6.2**	The important point is as made , patients with these complex aneurysms need to be discussed by experienced Neurointerventionalists and vascular neurosurgeons at an MDT and all treatment methods evaluated before being considered for pipeline .If that criteria is met pipeline should be available and recommended for use by NICE in the UK Not to would be a retrograde step.	Thank you for your comment. The Committee considered this comment and decided not to change the guidance. The management of the patients covered by this guidance will be determined by a multidisciplinary team and local decisions made on their treatment with the Pipeline embolisation device. Section 3.19 of the guidance includes a Committee consideration on patient selection and Section 6.2 of the guidance has been expanded to further clarify the Committee's considerations.
29	Consultee 2 **NICE Sponsor Team, Department of Health**	**General**	Thank you for the opportunity to comment on the evaluation of the above medical technology. I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation	Thank you for your comment.
30 Cost	Consultee 3 **UK Flow Diverter Registry, Expert Adviser**	**General**	I run UK FD Registry on behalf of UK Neurointerventional Group & Br Soc Neuroradiology, which is part funded by manufactuerer of PED	Thank you for your comment.
31	Consultee 4 **UK NeuroInterventional Group (UKNG)**	**General**	I apologise for the late response. The request to reply to this consultation on behalf of the UK Neurointerventional Group (UKNG) has only come to my attention today. Consequently I have not had the opportunity to study the documents in as much detail as I would wish. Nonetheless, I am well acquainted with the device and the current debate surrounding its role in the treatment of complex cerebral aneurysms. I am happy to communicate further on any points raised	Thank you for your comment.

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32	Consultee 4 **UK NeuroInterventional Group (UKNG)**	**General**	We must recognise the severe limitations of discussing optimum treatment for 'complex' cerebral aneurysms particularly when reduced to a discussion about a single technique (flow diversion), let alone a single device. The condition is too heterogeneous and successful treatment so highly dependent on individual/Centre skill and experience that generalisation is difficult.	Thank you for your comment. MTEP evaluates a single medical technology based on the claimed patient and healthcare system benefits and not comparing it with similar technologies in a broader class. The single technology approach is fundamental to achieving the Programme's aims of promoting faster uptake of innovative technologies in the NHS. It enables the specific claimed benefits of innovative products to be rapidly evaluated and guidance published to the NHS. NICE anticipates that the guidance will be applied in the context of clinical judgement and in centres with appropriate expertise.
33	Consultee 4 **UK NeuroInterventional Group (UKNG)**	**General**	We cannot be sure that figures quoted for aneurysm rupture following flow diversion treatment are accurate	Thank you for your comment. The External Assessment Centre, which is independent of NICE, critically appraises the clinical and economic evidence presented by the sponsor in the sponsor's submission of evidence and presents their review in the Assessment report. All figures included in the guidance are referenced in the supporting documents.

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34	Consultee 4 **UK NeuroInterventional Group (UKNG)**	**General**	We lack reliable, long term safety and efficacy data for flow diversion treatment.	Thank you for your comment. The sponsor presented outcome data up to 2-years. The Committee considerations on the limitations of the clinical data are included in sections 3.21, 3.23 and 4.2 of the guidance. Section 1.3 of the guidance recommends further data collection: "Clinicians should submit details of all patients being treated with the Pipeline embolisation device to the UK Neurointerventional Radiology Group audit database, to increase the evidence base and guide future use of this technology."
35	Consultee 4 **UK NeuroInterventional Group (UKNG)**	**General**	Such data that exists comprises a heterogeneous group of aneurysms that may have very different natural histories and may respond very differently to flow diversion treatment	Thank you for your comment. The Committee recognised the complexity of the disease and included its considerations on this point in section 3.19 of the guidance.
36	Consultee 4 **UK NeuroInterventional Group (UKNG)**	**General**	There is insufficient evidence to promote the superiority of flow diversion treatment over other forms of treatment for complex large and giant cerebral aneurysm	Thank you for your comment. The focus of the MTEP is to identify and evaluate promising innovative single technologies that offer advantages to patients and the NHS. The specific draft recommendations on the Pipeline embolisation device are not intended to limit the use of other relevant technologies which may offer similar advantages.
37	Consultee 4 **UK NeuroInterventional Group (UKNG)**	**General**	There is however compelling anecdotal evidence that flow diversion treatment with PED offers a chance for successful treatment of some aneurysms that could not be safely achieved with any other form of treatment.	Thank you for your comment. The Committee considered this issue very carefully, and received expert advice. Sections 3.16, 4.3 and 6.2 reflect its Committee's considerations.

Com. no.	Consultee number and organisation	Sec. no.	Comments	Response
38	Consultee 4 **UK NeuroInterventional Group (UKNG)**	**General**	The possible role of PED in the treatment of large and giant complex saccular and fusiform aneurysms must occur in the context of a multidisciplinary discussion that considers endovascular alternatives (parent artery occlusion, stent and coil etc), surgical treatment and conservative management	Thank you for your comment. The Committee's considerations on patient selection and the importance of a multidisciplinary team are included in section 3.19 of the guidance.
39	Consultee 4 **UK NeuroInterventional Group (UKNG)**	**General**	It may be the case that the financial premium for 'flow diverter' devices compared to conventional stents has influenced, and possibly overshadowed, scientific objectivity in relation to the safety and desirability of treating aneurysms in a radically different way i.e. purely endoluminal rather than endosaccular.	Thank you for your comment. The Committee considered both clinical and economic evidence, as well as expert advice and ongoing research when developing its recommendations. Topics selected for development of MT guidance are those which claim to offer either additional benefit to patients at the same or lower cost to the NHS, or to provide equivalent benefit to patients at lower cost to the NHS.
40	Consultee 4 **UK NeuroInterventional Group (UKNG)**	**General**	There is a danger that the debate surrounding the possible role for PED is reduced to a purely financial one e.g. cost effective in aneurysms requiring > 28 coils; no more that 2 PED devices placed etc. This could adversely affect the appropriate use of the device	Thank you for your comment. In developing MT guidance, where technologies are claimed to be resource-releasing with the same or more patient benefit, it is essential to assess the resource consequences using appropriate health economic methods. This enables the Committee's decision-making to be balanced by both clinical and economic considerations and to provide guidance which is of value to the NHS.

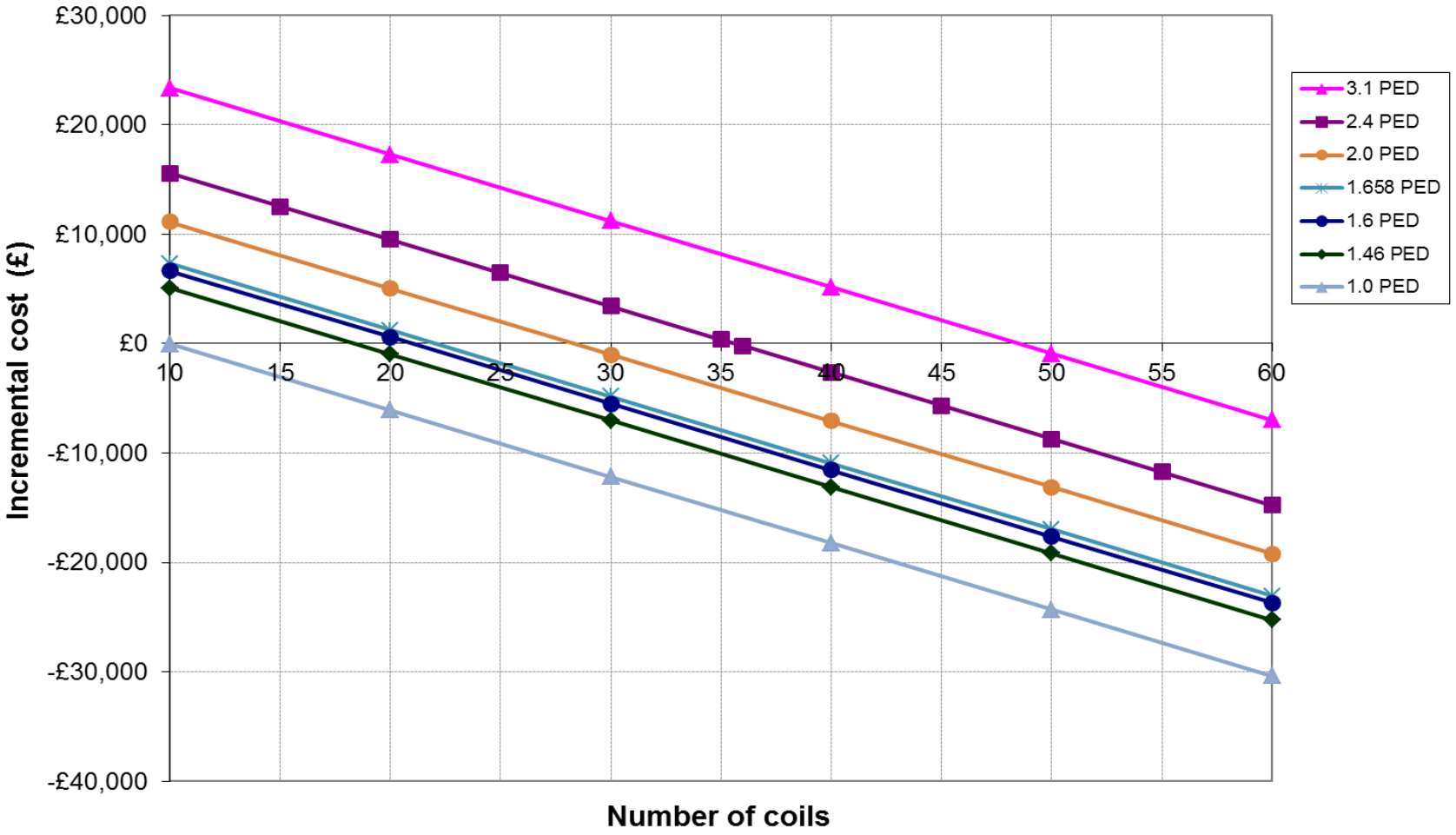
Com. no.	Consultee number and organisation	Sec. no.	Comments	Response
41	Consultee 4 **UK NeuroInterventional Group (UKNG)**	**General**	There is, in any case, a body of opinion that suggests that large (e.g. >15mm) and giant aneurysms should be coiled in conjunction with flow diverting stents such as PED because of the unpredictable risk of post implantation aneurysm rupture.	Thank you for your comment. Committee opinion on the safety of the Pipeline embolisation device is included in section 3.17 of the guidance. The use of the Pipeline embolisation device with coils is outside the scope of the guidance. No data were presented during the evaluation to demonstrate an unpredictable risk of post implantation aneurysm rupture.
42	Consultee 4 **UK NeuroInterventional Group (UKNG)**	**General**	Furthermore, regarding cost, in some cases of fusiform aneurysms treated with this device, the PED may be used in conjunction with conventional stents to create a primary scaffold.	Thank you for your comment. The use of the Pipeline embolisation device in combination with stents is outside the scope of the guidance.
43	Consultee 4 **UK NeuroInterventional Group (UKNG)**	**General**	It is my view and one shared I believe by many in the UK, that flow diversion treatment i.e. the use of a high mesh density stent without coiling of an aneurysm, definitely has a place to play in the treatment of a selected group of complex, large and giant saccular or fusiform aneurysms. The device should be available to appropriately selected patients in the UK, on the NHS. Caution is urged that selection of patients and the use of the device is made on the basis of current clinical experience and not on purely on the basis of comparative cost analysis. There may be a requirement for the use of multiple devices and adjunctive coiling.	Thank you for your comment. The Committee considers the clinical and economic evidence alongside advice from experts when making its decisions. The Committee acknowledges the complexities of patient selection in the guidance.

Com. no.	Consultee number and organisation	Sec. no.	Comments	Response
44	Consultee 4 **UK NeuroInterventional Group (UKNG)**	**General**	There is probably a good case to be made that experience with the device should be concentrated in a small number of expert Centres and continued entry of data on the implantation of these devices into a national registry should remain compulsory until such time as clear evidence of benefit emerges.	Thank you for your comment. Specifying which units should use the Pipeline embolisation device is outside the remit of MT guidance. Section 1.3 of the guidance makes a recommendation for clinicians to submit details of all patients being treated with the Pipeline embolisation device to the UKNG audit database. Section 1.3 of the guidance recommends further data collection: "Clinicians should submit details of all patients being treated with the Pipeline embolisation device to the UK Neurointerventional Radiology Group audit database, to increase the evidence base and guide future use of this technology."
45	Consultee 5 **British Society of Neuroradiologists**	**General**	I have used embolisation devices for over 20 years. I have used devices supplied by EV3 which provides Pipeline device. I act as a consultant to several device manufacturing companies mostly related to educational activities.	Thank you for your comment.
46	Consultee 6 **Sponsor, Covidien**	**General**	There are four general comments, plus some changes to factual inaccuracies, which we would like to be considered in the Consultation Document. As these comments affect multiple statements, I have listed these key considerations below.	Thank you for your comment.

Com. no.	Consultee number and organisation	Sec. no.	Comments	Response
47	Consultee 6 **Sponsor, Covidien**	**General**	**1. Patient population** There is some lack of clarity with regard to the group of patients who are “unsuitable for standard coiling and/or stenting and for neurosurgical treatment; and those for whom previous coiling/clipping procedures have failed”. Covidien assume these patients are also being recommended for funding, due to the following sections within the public consultation document: • Section 2.3 states that the Pipeline embolisation device may be used in these patients • Section 3.16 states that the committee recognised that the Pipeline embolisation device offers the only possible intervention for these patients • Section 4.3 states that the potential benefits offered by the Pipeline embolisation device are important in this patient population. However, Sections 2.3 and 6.2 state that these patients are not covered by the recommendations/are outside the scope of the recommendations. Suggested amends to these statements are provided in the table below	Thank you for your comment. Please see response to comment numbers 3, 8 and 25 in this table.
48	Consultee 6 **Sponsor, Covidien**	**General**	**2. Pipeline embolisation device is a life-saving treatment** The Pipeline embolisation device is cost effective as a life-saving treatment at a ‘Willingness to pay’ threshold of £30,000. It is dominant vs. stent-assisted coiling and is cost effective vs. its comparators (where neurosurgical clipping is not a feasible option; as shown by the modelling conducted by NICE see p46 and Table 6 [p37] of the overview assessment report). It may also be the only feasible intervention for some patients (see Section 6.2). Covidien does not feel that the life-saving benefits of Pipeline embolisation device are given enough prominence in the provisional recommendations. The assessment report clearly states that the Pipeline embolisation device is the most favourable outcome in terms of QALYs (p34). See below for suggested amends.	Thank you for your comment. Please see response to comment number 21 in this table.

Com. no.	Consultee number and organisation	Sec. no.	Comments	Response
49	Consultee 6 **Sponsor, Covidien**	**General**	**3. Practical advice around numbers of Pipeline embolisation devices used per procedure** The number of Pipeline embolisation devices used in clinical practice will equal 1, 2 or 3 etc. Although Covidien acknowledges that 2 Pipeline embolisation devices is considered by the committee to be a reasonable estimate for practice in the UK, the current average is 1.658 (September 2011; based on actual usage collected in the UK), demonstrating that in many cases only 1 Pipeline embolisation device will be used (58% of cases). Further this average is skewed due to a minority of patients who had more than 2 Pipeline embolisation devices inserted (13% of cases). Therefore, it would be useful for payers and physicians to understand the number of coils at which Pipeline embolisation device becomes cost saving with only one Pipeline embolisation device. Suggested amends in table below.	Thank you for your comment. Please see response to comment numbers 4, 19 and 20.
50	Consultee 6 **Sponsor, Covidien**	**General**	**4. Pipeline embolisation device is indicated for large and giant intracranial aneurysms** Occasionally, it seems like the word ‘large’ has been omitted from some statements. Covidien believes this to be a mistake as the scope considers intracranial aneurysms, specifically those that are large and giant. Further, the clinical evidence from PUFS supports using the Pipeline embolisation device to treat large and giant aneurysms. We have highlighted these statements in the table below.	Thank you for your comment. Please see response to comment numbers 3, 4, 24, and 25.

Further analysis carried out by the External Assessment Centre in response to consultation comment numbers 4, 6 and 49: Incremental cost of the Pipeline embolisation device over stent-assisted coiling, varying number of Pipeline embolisation devices and coils per procedure



External Assessment Centre response to consultation comment number 17

“As well as the costs for the PED and coils themselves, other costs within the model also need to be considered. For example treatment with PED includes the cost of the PED itself (£10,171) as well as additional consumables including: 1 Marksman catheter (£1030); 1 Guide wire (£160); 1 Distal Access Catheter (£500); 1 Guide catheter (£290). Treatment with stent-assisted coiling includes coils at £526.04 each (£15,342.16 for 29 coils) 2 Marksman catheters (£2060); 1 Guide wire (£160); 1 Guide catheter (£290); 1 stent (£2750) and endovascular equipment.
Other aspects which must be included in the calculation include hospital costs (operating room, recovery room), staff costs (surgeons, radiologists, nurses and anaesthetists) the costs of imaging (angiogram, fluoroscopy) and drug costs. The surgery procedure time and recovery period for PED is different than the procedure time for coiling which has an effect on these.
A full breakdown of these costs for the two procedures is provided below.”

Procedural resource use	PED	Stent-assisted coiling
Procedure time (hours)		
Length of procedure	2.07	2.29
Additional time for anaesthetist	1.00	1.00
Staff (per hour)		
Surgeon	2.07	2.29
Radiologist	2.07	2.29
Nurse	2.07	2.29
Anaesthetist	3.07	3.29
Hospital cost		
Neurology operating room (per hour)	2.07	2.29
Recovery ward	1.30	1.25
Imaging		
Angiogram	2	2
Fluoroscopy	1	1
Equipment/consumables		
PED	2.00	0
Marksman / microcatheter	1	2
Guidewire	1	1
Distal access catheter	1	0
Guide catheter	1	1
Coil	0	29
Stent	0	1.00
Balloon	0	0.5
Endovascular equip (per hour)	0.00	2.29
Drug costs (per mg unless otherwise indicated)		
Aspirin	18,000	25,000
Clopidogrel	6,750	13,500
Total procedural cost	£27,416.10	£26,453.75

Peri-operative unit costs	
Staff (per hour)	
Surgeon	£403.00
Radiologist	£403.00
Nurse	£47.00
Anaesthetist	£403.00
Hospital cost	
Neurology operating room (per hour)	£18.59
Recovery ward	£327.01
Imaging	
Angiogram	£715.57
Fluroscopy	£189.91
Equipment/consumables	
PED	£10,171.00
Marksman / microcatheter	£1,030.00
Guidewire	£160.00
Distal access catheter	£500.00
Guide catheter	£290.00
Coil	£526.04
Stent	£2,750.00
Clip	£210.19
Balloon	£717.00
Endovascular equip (per hour)	£89.40
Drug costs (per mg unless otherwise indicated)	
Aspirin	£0.00003
Clopidogrel	£0.002

Pipeline Embolization Device for the treatment of complex intracranial aneurysms

Supplementary Report

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Background

Following the MTAC decision, the EAC was asked to review the following elements of the cost model to ensure that it reflected normal UK practice:

- Microcatheters used for stent assisted coiling (SAC)
- Balloon use relevant to UK practice in stent assisted coiling
- Drug costs in PED (Pipeline Embolization Device) use and stent assisted coiling
- Endovascular equipment in stent assisted coiling

Discussion

There may be differences in clinical trial protocols and standard practice. The economic modeller must decide whether to use resource data derived from clinical trials which may differ from standard clinical practice. Using resource data from clinical trials may under or over-estimate resource use in NHS practice, but will match effectiveness data from trials. The manufacturer has consistently used data from clinical trials in the model and this is a valid approach (Miners 2008). The EAC has modified some model inputs where there is evidence to support such a change. The EAC has also run the model with modifications to reflect changes where UK practice differs significantly from that used in the model and there is a substantial impact on the model outcome.

Microcatheter use

The manufacturer's model assumes that treatment with Pipeline will require the use of one Marksman / microcatheter, while stent assisted coiling will require two. It specifies that the cost of the microcatheters used in SAC will be comparable to the cost of a Marksman. Discussions with the expert advisors confirmed the use of two microcatheters for SAC but suggested that cheaper alternatives would be used as standard practice within the UK. Due to the large number of microcatheters available and a large price variation within these, the four expert advisors were asked to provide information on the details of the microcatheters most commonly used for stent assisted coiling within the UK. The names and product codes of several appropriate microcatheters were received by the EAC and prices subsequently obtained, these are detailed in Table 1 below. Manufacturer list prices have been used in line with standard practice.

Table 1. Microcatheters used in the UK for SAC

Manufacturer	Product Name	List Price
Covidien	Echelon 14	£453
Covidien	Echelon 10	£453
Codman (Johnson & Johnson)	Prowler 14	£490
Codman (Johnson & Johnson)	Prowler Plus	£490
Codman (Johnson & Johnson)	Prowler Select	£514
Codman (Johnson & Johnson)	Prowler Select Plus	£514
Boston Scientific	Excelsior SL-10	£395
Microvention	Headway 17	£375
		Mean = £460.50

As definitive data on the use of specific microcatheters used for SAC is not available, it was felt that the use of an mean list price for these products would be appropriate for inclusion in the economic model.

A weakness in the manufacturer's model puts Marksman / microcatheter in the same cell which means that changes cannot be made to the two prices individually. Due to this, the model was run twice to illustrate the impact of the changes detailed on the total procedural costs for the two comparative treatment options. Total procedural costs including these updates are illustrated in Table 2.

Balloon use

The manufacturer's economic model assumes that balloons are used in 50% of SAC procedures while none are used in procedures using Pipeline. While it is recognised that the use of balloons does occur in stent assisted coiling, discussions with the expert advisors determined that their use is less frequent than assumed in the model. Furthermore, balloons are also occasionally used during procedures using Pipeline, for example to assist with opening the device in some cases. While it was not possible to determine an absolute rate of use of balloons in either procedure, it was determined that their use is relatively uncommon for both procedures and for the purposes of the model the inclusion of balloons should be removed for stent assisted coiling and also remain at nil use for Pipeline.

Drug resource use

The drugs resource use used in the manufacturers model for Pipeline and stent assisted coiling were calculated using data taken from two non-comparative studies. The reason for selecting these studies as sources of drugs use data is not specified in the model.

Pipeline

The drug use for Pipeline patients was taken from the Pipeline for Intracranial Treatment of Aneurysms (PITA) study (Nelson 2011) which had available data for 31 patients. This is a multi-centre trial carried out in Germany (4 patients), Austria (12 patients), Budapest (9 patients) and Buenos Aires in Argentina (6 patients). It was a prospective single-arm feasibility study in patients with unruptured wide necked intracranial aneurysms (IAs) with unfavourable dome/neck ratios (<1.5) or who had failed previous therapy.

SAC

The drug use for SAC was calculated using data from a study of 1137 consecutive patients, 216 of whom were treated with stent assisted coiling (Piotin 2010). A single centre French study, with a mean aneurysms size of <10mm; 83.8% of the aneurysms treated with SAC were unruptured. In three cases Pipeline “stents” were used.

As these are non-comparative studies there will be justifiable differences between the two and directly comparable data is not currently available. The source of drug use data for Pipeline is based on a trial protocol and not clinical use for which little published data is currently available. A range of potential drug regimes are feasible in clinical practise reflecting use in different patient populations. While long term clinical use of Pipeline may reflect different drug usage to that shown in the model, due to the low cost of these drugs this will have an insignificant impact on the overall procedural costs. Equally the use of different drug regimes used in SAC will also have a negligible overall impact. As there has been no systematic literature search on the comparators the EAC is not able to confirm that this is the best available data source. However, currently the data provided in the cost model is not inappropriate and is therefore unchanged.

Calculation errors

Two calculation errors were present in the original model where the number of days of drug therapy was entered incorrectly. This made minor differences of <£10, slightly reducing the overall cost of both Pipeline and stent assisted coiling. These changes have been included in Table 2.

Endovascular equipment

Resource use data on length of procedure for Pipeline and SAC are taken from non-comparative studies. Wolstenholme (2008) prospectively collected data from seven UK centres and details results of patient pathways, resource utilisation and costs up to 24 month post randomisation for neurovascular and endovascular treatment of aneurismal subarachnoid haemorrhage. These data are based on a subsample of all patients randomised in the ISAT (International Subarachnoid Aneurysm Trial) which containing 1644 patients across 22 UK centres (Molyneux 2005). The model takes the figures from the paper as weighted averages and the figures in the formula for SAC length of procedure agree with data from the paper, equating to a mean procedure time of 3.56 hours.

The Pipeline for Uncoilable or Failed Aneurysms (PUFS) trial is and American unpublished, ongoing prospective single-arm open label interventional trial in 108 patients with wide neck, large and giant intracranial aneurysms. One year data are available for this study which is expected to end in July 2014. Data from this unpublished trial are available via the Food and Drug Administration (FDA 2011). Mean procedure time for this trial was 124 minutes (range 39 – 427 minutes), equating to 2.07 hours in the manufacturer model.

No systematic review of comparators was undertaken therefore the EAC is unable to determine whether the Wolstenholme (2008) study is the best available source for SAC length of procedure. As both references are appropriately and accurately used in the model no changes to the model are justified with regards to procedure time for SAC or Pipeline.

The additional endovascular equipment included in the manufacturers model is based on the length of procedure, however there is no explanation of why it is included for SAC but not for Pipeline or the other comparators. There is also no explanation of why it is only included in calculations of the retreatment cost but not the initial procedure cost. If the costs of additional endovascular equipment are removed from the model this will have a cost reduction impact in favour of SAC. This change has been included in Table 2

Analysis

Following the MTAC Committee decision, the EAC updated the Manufacturers base case model, incorporating the changes discussed above. The effects of these changes on the total overall costs for Pipeline and SAC have been tabulated incrementally below.

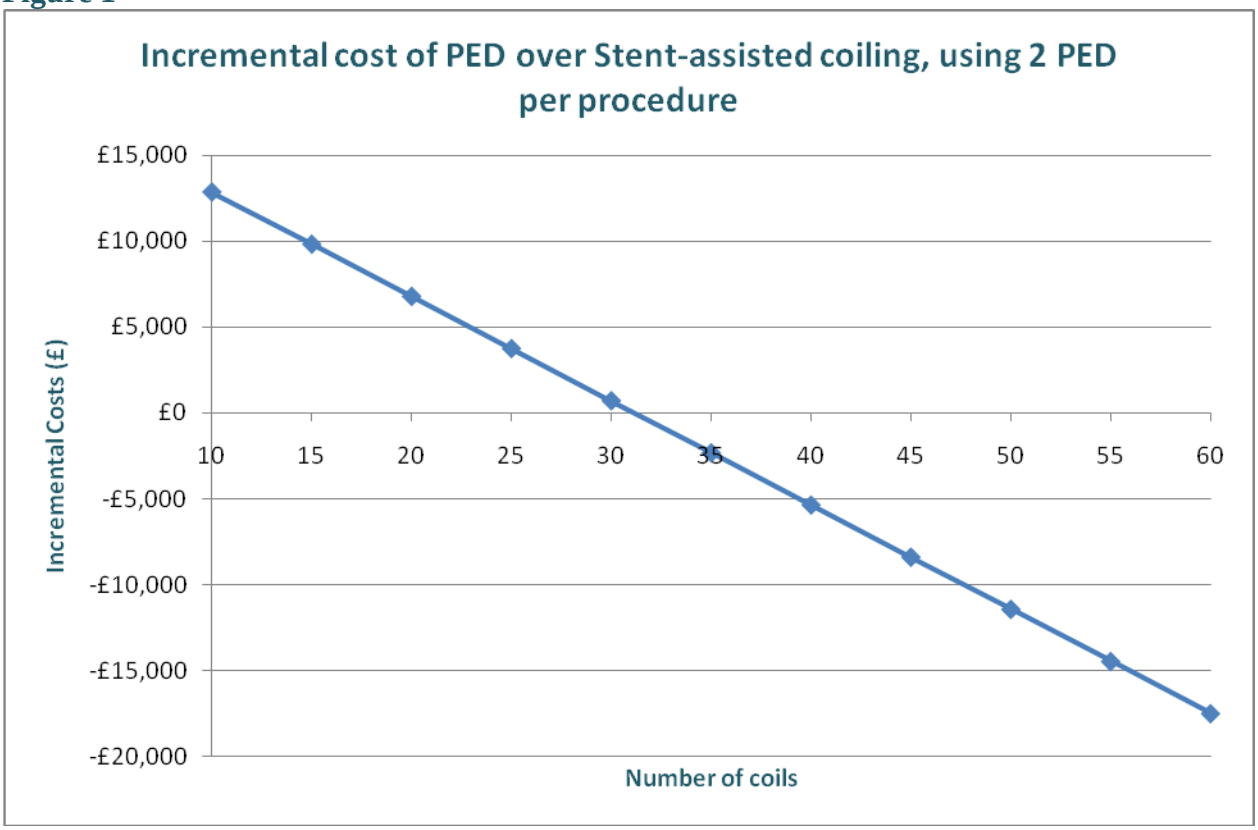
Table 2. Incremental Cost Changes

		Total Cost (£'s)	
		PED	SAC
1)	Manufacturers Base Case (1.46 PED, 40 coils)	24,341	37,451
2)	As 1) but with 2 PEDs	30,354	37,451
3)	As 2), but with PED using Marksman @ £1030, SAC using other microcatheter @£460.50	30,354	36,137
4)	As 3) with balloon use removed	30,354	35,725
5)	As 4) but with corrected drug regime	30,346	35,724
6)	As 5) but with corrected endovascular equipment	30,346	35,693
7)	As 6) but with 31 coils	30,346	30,231
8)	As 7) but with 32 coils	30,346	30,838

Results

The sum result of these changes is illustrated in Figure 1 below.

Figure 1



The incremental cost of the Pipeline embolisation device over stent assisted coiling with varying numbers of Pipeline embolisation devices and coils are shown in Figure 2 below.

Figure 2. Updated Incremental cost of PED over Stent-assisted coiling, varying number of PED devices and coils per procedure

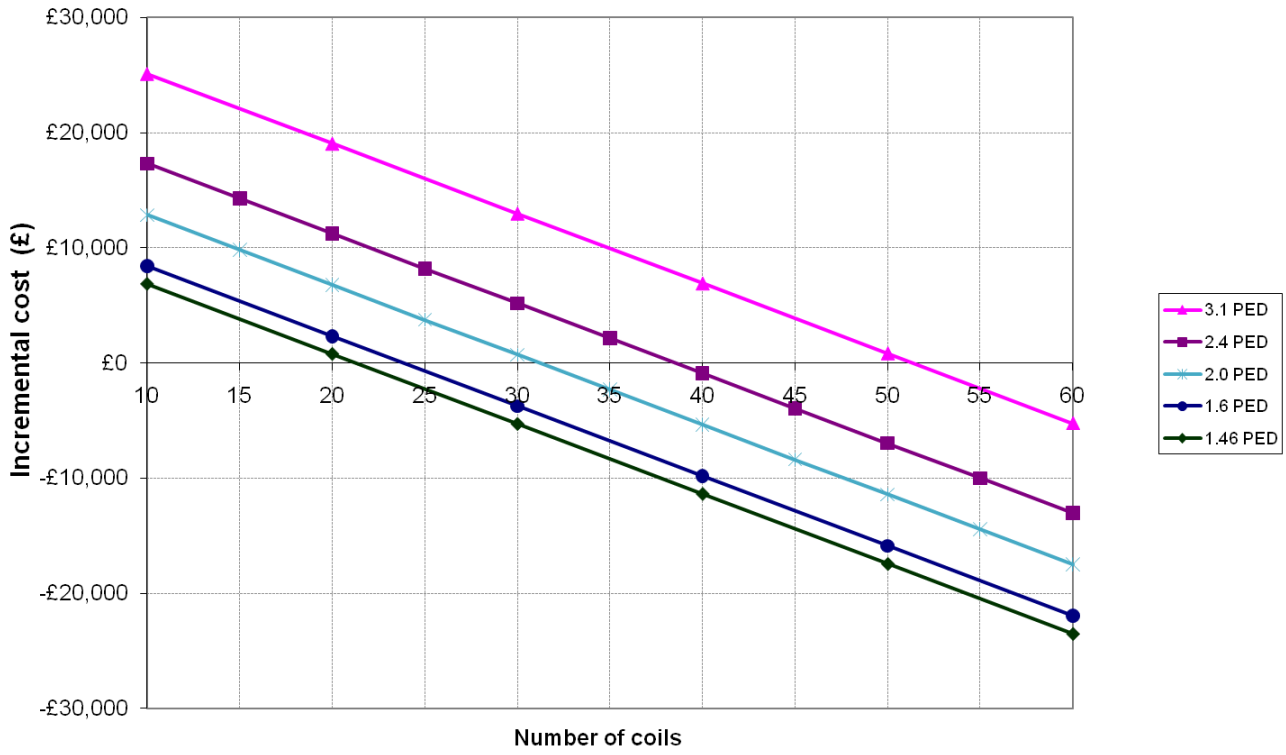


Table 3 also demonstrates the incremental cost of the PED over stent assisted coiling with varying numbers of Pipeline embolisation devices and coils.

Table 3. Updated incremental cost of the Pipeline embolisation device over stent assisted coiling, varying the number of Pipeline embolisation devices and coils

Number used		Total procedure cost		
Pipeline embolisation device	Coil**	Pipeline embolisation device	Stent-assisted coiling	Incremental cost*
1.46	40	£24,334	£35,693	-£11,359 (base case)
2.4	25	£34,800	£26,589	£8,211 (EAC judged most appropriate estimate in original report)
1.46	22	£24,334	£24,769	-£435
1.6	24	£25,892	£25,982	-£90
2.4	39	£34,800	£35,086	-£286
3.1	52	£42,594	£42,976	-£382

*Negative cost indicates cost saving for Pipeline embolisation device vs stent-assisted coiling

**1 stent used for each intervention

Conclusion

Overall, this is a complex economic model including numerous data inputs for both Pipeline, stent assisted coiling and several other comparator treatments. Due to lack of long term clinical data for Pipeline and the lack of a systematic literature review of the comparator treatments there are uncertainties surrounding many of the inputs throughout the model. Sensitivity analysis showed that the model is particularly sensitive to the number of PEDs and coils, and these continue to remain a source of uncertainty, however many other variables also exist. However, the changes made to the costs illustrated above more accurately reflects current UK use of Pipeline and SAC. Incorporating these changes into the cost model, the use of two Pipeline devices becomes cost saving when the number of coils is equal to or greater than 32.

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