NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Medical Technologies Evaluation Programme

Specification for sponsor submission of evidence

July 2011, Final version

(March 2010 template)

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Section A – Decision problem

1 Description of technology under assessment

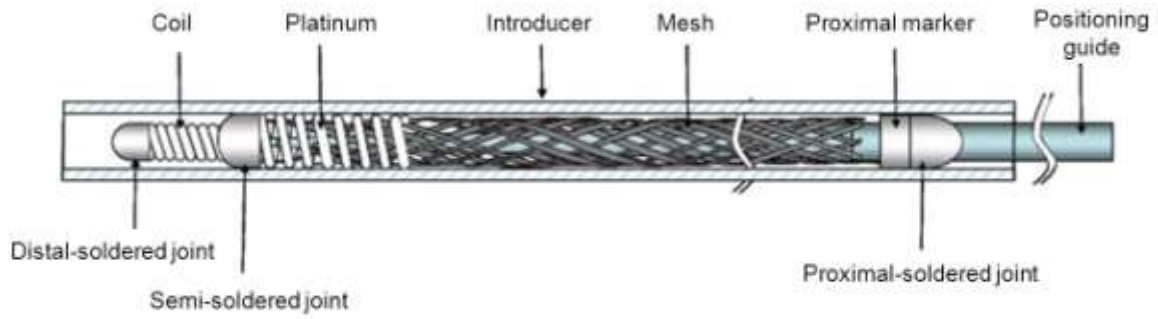
1.1 Give the brand name, approved name and details of any different versions of the same device.

The device's trade name is Pipeline™ Embolisation Device (PED). Its generic name is neurovascular embolisation device.

1.2 What is the principal mechanism of action of the technology?

PED is a braided, cobalt chromium and platinum cylindrical stent-like construct and is packaged within an introducer sheath collapsed upon a delivery wire (see Figure A1.1). During an endovascular procedure, PED is loaded into and delivered via a microcatheter that has been positioned across the neck of the intracranial aneurysm (IA) (1). PED is manufactured in lengths of 10, 12, 14, 16, 18, 20, 25, 30 and 35 mm and fully expanded diameters of 2.5 to 5 mm (in 0.25 mm increments). Multiple devices can be deployed within each other and/or in telescoped fashion to increase overall length of the construct or to increase the amount of metal surface coverage over a particular segment.

Figure A1.1 Diagram of the PED



PED, Pipeline™ embolisation device

PED works by three mechanisms (1):

- **Flow disruption:** placing the PED over the neck of the aneurysm disrupts the flow of blood into and out of the aneurysm by redirecting the blood flow through the reconstructed parent vessel.
- **Aneurysm thrombosis**: flow disruption causes stasis of blood in the aneurysm fundus, increasing blood viscosity and promoting thrombosis (clotting) in the aneurysm. Angiographic imaging has shown a progression towards complete occlusion following PED implantation, usually completed over a period of days to months. In some cases this may take longer.

- **Re-endothelialisation and thrombus resorption:** the PED forms a scaffold upon which endothelial cells can grow. After the flow of blood into the aneurysm is eliminated and the aneurysm is completely thrombosed, the construct is incorporated into the wall of the parent artery through a process of neointimal overgrowth and formation of endothelial tissue. This forms a permanent biological seal excluding the aneurysm from the circulation. As the aneurysmal thrombus mass begins to be reabsorbed, the size of the IA reduces and mass effect may decrease.

1.3 Does the technology have CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

PED received a CE mark on 8th June 2008 for endovascular embolisation of cerebral aneurysms.

Although the approved indication for PED is very broad, the analysis presented herein focuses on patients with complex intracranial/cerebral aneurysms, specifically those that are large or giant (≥10 mm in diameter) and have wide necks (≥4 mm) and/or are fusiform (with no discernible necks). This population is a sub-group of the CE mark indication.

PED may also be used as an alternative to coiling, most commonly stent-assisted coiling particularly in patients for whom standard coiling and/or stent-assisted coiling is unsuitable, not possible or for whom previous coiling/clipping procedures have failed.

PED is not recommended as a sole therapy for patients with acutely ruptured aneurysms as it requires pre-treatment with dual-antiplatelet therapy (similar to intracranial stents) and may not, by itself, lead to rapid aneurysm occlusion.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the (draft) assessment report (for example, CE marking)). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the licence).

The regulatory organisation reviewing PED had no issues regarding the device. There are no restrictions on conditions of use.

It should be noted that although the Medicine and Healthcare products Regulatory Agency (MHRA) issued an alert for a flow-diverting stent, the device described is different from PED. This alert refers to SILK (manufactured by Balt Extrusion and currently distributed in the UK by Sela Medical) and describes the potential for patient death if the SILK device is used to treat IAs without concomitant placement of embolisation coils. The manufacturers of SILK have subsequently altered the instructions for use to include mandatory use of embolisation

coils. This submission document clarifies the differences between Pipeline™ and SILK (see section 2.6), and reports safety data from PUFS (Pipeline™ for Uncoilable or Failed Aneurysms) that evaluated the use of Pipeline without embolisation coils (see section 5).

1.5 What is the (anticipated) CE marking, including the indication for use.

PED was CE marked in 8th June 2008. The indication statement reads: The PED is intended for endovascular embolisation of cerebral aneurysms.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

The PUFS study is ongoing. The following data are likely to be available in the next 12 months:

- Two-year follow-up data. Data collection began in November 2010, and is expected to be available by November 2011. This follow-up involves a phone call to study participants to assess their medical status and occurrence of adverse events (AEs).
- Long-term (3 year) follow-up data. Three year follow-up begins November 2011, and data are expected to be available by November 2012. This follow-up involves a focused medical history assessment, detailed neurological examination, and modified Rankin Score assessment. Patients will also be assessed for the occurrence of AEs.

In addition, there is a mandatory UK flow diversion audit that requires all cases with PED (or SILK) to be registered. This is an independent audit run by the UK Neuro-interventional Group.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

PED was formally launched in the UK in September 2009. The first case was performed on 21st July 2009, and 140 cases with PED have been performed in the UK to date.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

As of June 2011, PED is approved in 54 countries outside of the UK:

- Argentina
- Australia
- Austria
- Belgium
- Brazil
- Bulgaria
- Canada
- Chile
- Colombia

- Cyprus
- Czech Republic
- Denmark
- Estonia
- Finland
- France
- Germany
- Greece
- Hong Kong
- Hungary
- Iran
- Ireland
- Israel
- Italy
- Jordan
- Korea
- Latvia
- Lebanon
- Lithuania
- Luxembourg
- Malaysia
- Malta
- The Netherlands
- New Zealand
- Peru
- Philippines
- Poland
- Portugal
- Romania
- Russia
- Saudi Arabia
- Singapore
- Slovakia
- Slovenia
- Spain
- Sweden
- Switzerland
- Thailand
- Tunisia
- Turkey
- United Arabs Emirates
- United States of America
- Uruguay
- Venezuela
- Vietnam

1.9 Please complete the table below. If the list price of the technology(s) is not yet known, provide details of the anticipated list price, including the range of possible list prices.

Unit costs are provided in Table A1.1.

Table A1.1 Unit costs of technology being appraised

List price (excluding VAT)	£10,171 per PED (depends on size and/or number of aneurysms)
Average selling price	Proprietary
Range of selling prices	Proprietary
Consumables (if applicable) **Per consumable: name, list price, average/range selling price, frequency**	£1030 Marksman catheter (1) £160 Guidewire (1) £500 Distal Access Catheter (1) £290 Guide Catheter (1)
Service/maintenance cost and frequency (if applicable)	N/A
Anticipated life span of technology	Lifetime
Average length of use per treatment	N/A
Average frequency of use	N/A
Average cost per treatment	£12,151 per treatment (assuming 1 PED) Additional PEDs may be required.

1.10 Would this technology require changes to the way current services are organised or delivered?

The use of PED does not require changes to the way current services are organised or delivered. PED is an additional tool for use by physicians with expertise in aneurysm treatment (neuroradiologists, neurosurgeons). No special services or additional devices are required to deliver PED.

1.11 Would other facilities or technologies need to be acquired or used alongside the technology being considered, in order for the claimed benefits to be realised?

The use of PED does not require additional facilities or technologies to be acquired. PED may be delivered into the parent artery using commonly available microcatheter technology.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements or a need for monitoring of patients over and above usual clinical practice for this technology?

No additional tests or investigations are required for selection or administration of PED. There is no need for monitoring patients over and above usual clinical practice.

Due to the high rate of angiographic cure of complex aneurysms seen with PED use, overall monitoring of patients treated with PED may be less than with other technologies.

1.13 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

Consistent with use of all other neurovascular stents, PED requires the use of oral dual-antiplatelet therapy consisting of aspirin and clopidogrel (patients allergic to clopidogrel may take ticlopidine). Currently, patients are pre-treated with aspirin and clopidogrel for 2–7 days, and are maintained on these medications for at least 3–6 months after PED implantation (2). As with most neurointerventional procedures, intravenous (IV) heparin is used during PED placement.

1.14 Does the technology require additional infrastructure to be put in place?

No additional infrastructure is needed. As with any new technology, training on the use of the device is required and is provided by the device's manufacturer.

Physician training consists of:

- an approved in-service presentation from a qualified clinical specialist including clinical information, case management, device overview, and procedural steps
- a one-to-one discussion between the physician and clinical specialist
- an overview of the device on a flow model that mimics the neurovascular anatomy
- practice navigation and deployment of the device under fluoroscopy to provide real-life visualisation; the physician learns how the device will perform, and what landmarks to look for during imaging.

A certified physician proctor is provided for the first five cases, and is available for subsequent cases should the physician need it. The device's manufacturer handles the logistics.

2 Context

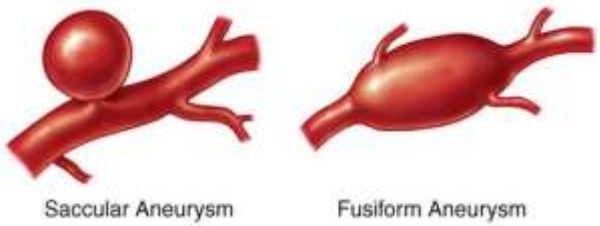
2.1 Please provide a brief overview of the disease or condition for which the technology is being considered in the scope.

Intracranial aneurysms (IAs)

An IA, also known as a cerebral or brain aneurysm, is an abnormal, localised dilation that balloons or bulges from an artery that supplies blood to the brain (3). They are commonly defined by their size, shape and location (see Figure A2.1 and Figure A2.2). A recent systematic review by Vlak et al, 2011, reported a mean overall prevalence rate of 2.8% (95% CI: 2.0–3.9) for unruptured IAs with a higher prevalence of unruptured IAs in women than men (prevalence ratio: 1.57; 95% CI: 1.04–2.37) (4).

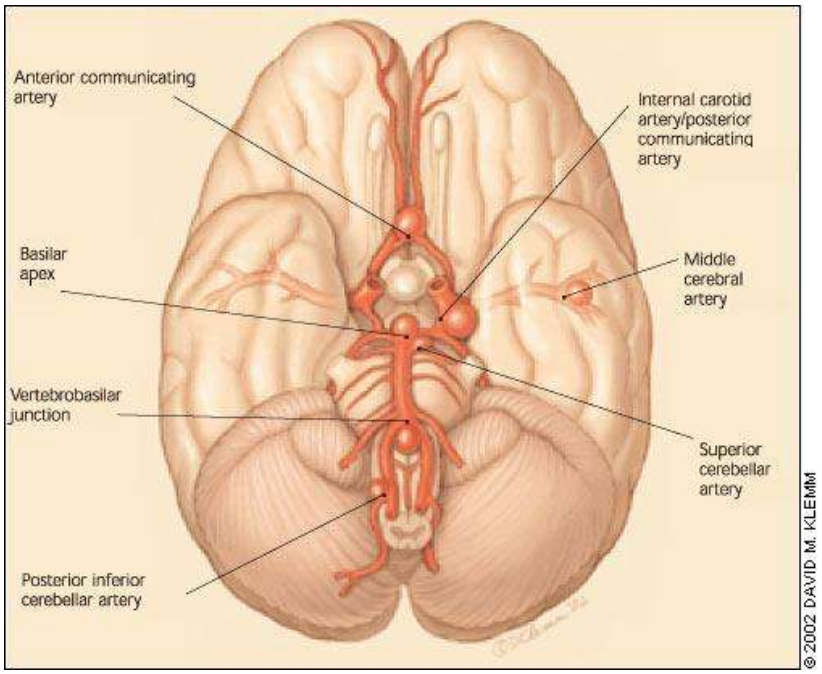
This scope considers complex IAs, specifically those that are large (10–25 mm in diameter) or giant (≥25 mm in diameter). Large or giant IAs can be saccular, where they are usually wide necked (≥4 mm), or fusiform in shape (i.e. they have no discernable necks).

Figure A2.1 Saccular and fusiform aneurysms



Source: http://neuro.wehealny.org/endo/cond_aneurysms.asp

Figure A2.2 Common locations of IAs (5)



IA, intracranial aneurysm

Symptoms of IAs

Small unruptured IAs are typically asymptomatic. When large and/or fusiform, an IA may press against nearby tissues or nerves, resulting in local symptoms of cranial-nerve or brain-stem compression (called mass effect). Symptoms can include: headache; seizures; visual disturbances, such as loss of vision, blurred vision, double vision due to inability to move the eyes in a conjugate fashion; dizziness resulting from nystagmus; facial paralysis or pain (5;6). The most common presentation of a giant aneurysm is mass effect on adjacent structures (7).

Ruptured IAs typically cause a sudden onset of severe headache, which may or may not be associated with a stiff neck, nausea and vomiting, slurred speech, photophobia, focal neurological defects, mental confusion and loss of consciousness (5;6). Approximately 50% of patients will present with milder symptoms suggestive of impending rupture, before full rupture of the aneurysm (5).

In most cases, unruptured IAs typically do not constitute a surgical emergency; however, they present a high morbidity and mortality risk if they are not treated. They have two major clinical consequences: mass effect and rupture (see Table A2.1).

Table A2.1 Major clinical consequences of IAs

Clinical consequence	Associated mortality and morbidity
'Mass effect' – where the IA begins to press against tissues or nerves inside the brain. Without treatment, these symptoms become worse over time	– Blindness, paralysis, other major neurological syndromes, headache (8) – Can be the source of embolic strokes (7)
Rupture, leading to SAH	– **Mortality** with SAH: approximately 30–40% of patients with a SAH die within one month (9) – **Morbidity** with SAH: 10–20% of patients who survive have long-term dependence due to brain damage (9); two-thirds of patients who *survive with an independent* functional status have a reduced QoL (9)

IA, intracranial aneurysm; QoL, quality of life; SAH, subarachnoid haemorrhage

Risk of rupture

Large and giant aneurysms have a greater risk of rupture than smaller aneurysms:

- Rinkel et al reported an annual risk of rupture of 0.7% for aneurysms <10 mm and 4% for those of ≥10 mm (10).
- In the retrospective cohort from the International Study of Unruptured Intracranial Aneurysms (ISUIA), large aneurysms (10–24 mm) or giant aneurysms (≥25 mm) were much more likely to rupture than small aneurysms (<10 mm; relative risk [RR]: 11.6, p=0.03 and 59.0, p<0.001; respectively) (11).
- Five-year rupture rates from the prospective cohort from ISUIA are summarised in Table A2.2, showing an increase in rupture rate with increasing aneurysm size regardless of location (12).

Table A2.2 5-year cumulative rupture rates according to size and location of unruptured aneurysms (12)

Aneurysm location	<7 mm Previous SAH	<7 mm No SAH	7–12 mm	13–24 mm	≥25 mm
Cavernous carotid artery (n=120)	0	0	0	3.0%	6.4%
AC/MC/IC (n=1037)	0	1.5%	2.6%	14.5%	40%
Post-P comm (n=445)	2.5%	3.4%	14.5%	18.4%	50%

AC, anterior communication or anterior cerebral artery; IC, internal carotid artery (not cavernous); MC, middle cerebral artery; Post-P comm, vertebrobasilar, posterior cerebral arterial system, or the posterior communicating artery; SAH, subarachnoid haemorrhage

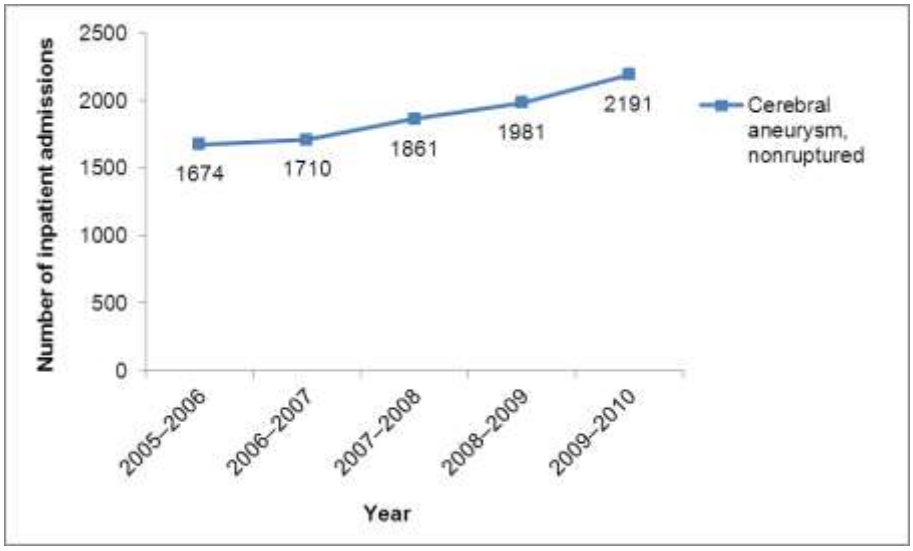
Summary: There is a need to treat IAs due to their high associated mortality and morbidity. Patients with larger IAs have a greater risk for rupture and SAH, and are more likely to experience aneurysm-related mass effect.

2.2 How many patients are assumed to be eligible for treatment in England and Wales? Present separate results for any groups and subgroups considered in the scope. How are these figures derived? Also present results for the subsequent 5 years.

Prevalence and incidence data from the literature varies according to the method of detection (autopsy vs. angiography studies) and collection (retrospective vs. prospective). Therefore, data from the NHS information service has been used to estimate the number of patients eligible for treatment with PED.

In 2009–2010 there were 2,191 inpatient admissions in England and Wales where the primary diagnosis was unruptured cerebral aneurysms (13;14). Although the number of inpatient admissions for unruptured cerebral aneurysms increased over the last 5 years (see Figure A2.3), we do not believe this trend can be extrapolated to the subsequent 5 years, due to compounding factors, such as improved imaging techniques (12), that may be causing this increase.

Figure A2.3 Number of admissions according to primary diagnosis in England and Wales (13;14)



In its retrospective cohort (n=1449), ISUIA reported that 26.5% of aneurysms were large (≥10–24 mm; 21.5%) or giant (≥25 mm; 5.0%) (11). Similar prevalence rates were found in the large ISUIA prospective cohort (n=4060), with 21% of aneurysms being large (13–24 mm; 16.3%) or giant (≥25 mm; 4.7%) (12). For the purposes of the estimate below, we have used prevalence range of 21–26.5% for large/giant aneurysms calculated from these two large studies.

We calculate that there are approximately 460–580 patients with unruptured IAs eligible for treatment annually with PED, based on the following assumptions:

- 2,191 patients in England and Wales are admitted with a primary diagnosis of unruptured IA.
- PED will be used primarily for large or giant aneurysms, of which the prevalence is approximately 21.0–26.5%.
- All patients with large or giant aneurysms require interventional treatment.
- All large and giant aneurysms have wide necks and/or are fusiform.

In practice, approximately 80% of PED cases will involve unruptured IAs, and 20% ruptured IAs (based on expert opinion); therefore the total number of patients eligible for treatment annually in England and Wales is estimated at 575–725.

Summary: There are approximately 575–725 patients annually in England and Wales eligible for treatment with PED.

2.3 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

The National Institute of Health and Clinical Excellence (NICE) has published several guidance documents concerning IAs (see Table A2.3). These guidance documents summarise basic information on safety and effectiveness of coil embolisation for ruptured and unruptured IAs and a microsurgical technique for IAs. A summary of the overall guidance issued in Interventional Procedure Guidance (IPG) 348 and IPG 233 have also been included because, although they are for atherosclerosis, procedures using similar techniques may be used when treating IAs.

Of note, none of these guidance documents specifically cover large and/or giant aneurysms. Also, the Interventional Procedure Overview documents that accompany IPG105 and IPG106 both state: “The technique is only suitable for people with aneurysms in which the entrance to the narrow part of the blood vessel (the aneurysms neck) is relatively narrow”. These are aneurysms for which PED is typically not used.

Table A2.3 Details of relevant NICE guidance and protocol for IAs

Protocol number and title	Guidance
IPG84 Supraorbital minicraniotomy for intracranial aneurysm (15)	• Current evidence for supraorbital minicraniotomy appears adequate to support the use of this procedure • The procedure involves a small incision made above the eyebrow and through the underlying skull. The aneurysm is then clipped or wrapped using conventional microsurgical instruments • **Efficacy**. No controlled studies were identified. In two studies the aneurysms were either successfully clipped or wrapped, but length of follow-up was not reported. In another study, 89% of patients showed good recovery on the Glasgow Outcome Scale; however, it was not clear how many of the patients were followed up for the entire study duration • **Safety**. In the three case series reviewed, adverse events were: – Rupture of aneurysm: 2–3% – Death within 8 days: 4% – CNS infection: 2% – Impaired cerebrospinal fluid circulation requiring shunting: 7% – Supraorbital nerve damage: 11% – Wound infection: 3%
IPG105 Coil embolisation of unruptured intracranial aneurysms (16)	• Coil embolisation is efficacious in obliterating unruptured intracranial aneurysms, and its safety is similar to that of surgical treatment • A thin tube containing the coil on a guidewire is inserted into a large artery and passed up into the skull. The coil is placed inside the aneurysm and detached from the guidewire. Once in position it cause clotting and stops blood from entering the aneurysm. Multiple coils may be inserted

Protocol number and title	Guidance
	• **Efficacy**. A large observational study reported that the overall morbidity and mortality associated with endovascular repair was 9% at 1 year compared with 12% for surgery. Similar results have been reported in two smaller studies. However, patient characteristics differed in these studies between groups. In the ISUIA trial, in patients undergoing endovascular repair by coil embolisation, obliteration was complete in 55% of patients, incomplete in 24%, unsuccessful in 18%, and unknown in 3%. At 1 year, less than 1% of patients had a moderate or severe disability. Other studies report a rate of permanent complications ranging from 5–8% • **Safety**. One retrospective study had a procedure-related complication rate of 23% after coil embolisation. Major complications were reduced functional status (8%) and prolonged hospitalisation (15%). AEs included: intra- or post-operative rupture (6%), and cranial neuropathy (11%). This large observational study reported peri-operative haemorrhage in 2% and cerebral infarction in 6% of patients undergoing endovascular repair
IPG106 Coil embolisation of ruptured intracranial aneurysms (17)	• Current evidence for coil embolisation appears adequate to support use of this procedure • The procedure is the same for unruptured IAs • **Efficacy**. One high-quality RCT showed a 7% absolute risk reduction in dependency (moderate to severe disability) or death in patients treated with coils compared with those treated by surgical clipping. However, long-term durability of coil embolisation has not been established • **Safety**. Complications associated with the procedure include: – Perforation of the aneurysm: 3% – Cerebral clot embolisation: 2% – Coil migration: 0.5%
IPG233 Endovascular stent insertion for intracranial atherosclerotic disease (18)	• There is currently inadequate evidence on the efficacy of endovascular stent insertion for intracranial atherosclerotic disease and the procedure poses some serious safety concerns. Therefore this procedure should only be used in the context of clinical research
IPG348 Extracranial to intracranial bypass for intracranial atherosclerosis (19)	• Current evidence is inconsistent and remains limited in quantity and quality. Therefore, the procedure should only be used with special arrangements to clinical governance, consent and audit or research

AE, adverse event; CNS, central nervous system; IA, intercranial aneurysm; IPG, Interventional Procedure Guidance; ISUIA, International Study of Unruptured Intracranial Aneurysms; NICE, National Institute of Health and Clinical Excellence; RCT, randomised controlled trial

Summary: There is guidance available for the endovascular and surgical treatment of IAs. However, these guidelines do not address wide-necked and/or fusiform aneurysms in which PED is typically used.

2.4 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

A variety of symptoms can lead to a diagnosis of IA. Once diagnosed, patients are cared for by neurological surgeons and interventional neuroradiologists.

The goal in caring for patients with unruptured IAs is to identify those at greatest risk of rupture and who would therefore merit an interventional procedure, and to identify the best treatment for those with debilitating symptoms caused by their IA. When making this decision there are several additional issues to consider (9):

- Current impact of aneurysm on quality of life (e.g. aneurysm-related mass effect).
- Risk of rupture.
- Potential risk of morbidity and mortality associated with treatments.
- Long-term efficacy of treatment.
- Patient-related factors such as age, presence of comorbidities.

Surgical clipping was the gold standard of therapy for over 50 years. However, since being introduced in 1991, the use of coils has substantially increased. Endovascular coiling is often considered for initial treatment, due to a somewhat lower associated morbidity and mortality, although clipping has a greater long-term efficacy (9).

Currently, there is an unmet clinical need in the treatment of unruptured fusiform and circumferential IAs that are not amenable to treatment with commercially available devices or conventional surgical techniques. Large or giant wide-necked aneurysms also pose an unmet need, as they are the most difficult IAs to treat safety and successfully with standard endovascular techniques (1) (see section 2.5 for further information on unmet needs). PED provides an alternative approach in these situations.

The context in which PED will be used is similar to currently existing technology, and will therefore not change the existing approach/pathway. Specialist physicians with expertise in endovascular procedures will be trained in the use of PED (training is provided by the device's manufacturer). The endovascular technique in which PED is used is similar to those in which other technologies (coils, stent-assisted coiling) are used. Patients undergoing both stent-assisted coiling and PED placement for IA are typically pre-treated with aspirin and clopidogrel (or ticlopidine) to diminish platelet response to the devices' metal components. Placement of PED is similar to placement of stents used for stent-assisted coiling. Post-operative care and follow-up are similar in patients treated with PED vs. other endovascular technologies.

Summary: The introduction of PED will not change the existing pathway of care. It will however provide an additional treatment choice for complex large or giant wide-necked and/or fusiform aneurysms, and may therefore lower the risk and improve the effectiveness of interventional treatments.

2.5 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

PED is intended for endovascular embolisation of cerebral aneurysms, specifically complex wide-necked and/or fusiform aneurysms that are large or giant (see section 2.1 for definitions). PED may also be useful in those aneurysms in which standard coiling and/or stent-assisted coiling is unsuitable, not possible or in which previous coiling/clipping procedures have previously failed. Although there are currently no satisfactory treatments for patients with such complex intracranial aneurysms, various strategies are attempted. These strategies include:

- **Reconstructive techniques (attempt to isolate the aneurysmal lumen from the intracranial circulation)**
  a) embolic coiling, often with a placement technique using a balloon (so-called balloon-assisted coiling)
  b) stent-assisted aneurysm coiling/multiple conventional stents
  c) neurosurgery (clipping or wrapping) +/- bypass procedures
  d) SILK artery reconstruction device, manufactured by Balt Extrusion and distributed in the UK by Sela Medical
- **Deconstructive techniques (occlude the parent artery)**
  e) parent vessel occlusion
- **Other**
  f) conservative management

The poor natural history of large/giant and other complex aneurysms means that conservative management is high-risk option for such patients. Without treatment, these aneurysms have a high probability of causing compressive symptoms and of rupturing. In the ISUIA study, five-year cumulative rupture rates of aneurysms in the anterior circulation were 2.6% for aneurysms 7–12 mm in diameter, 14.5% for those 13–24 mm, and 40% for those ≥25 mm. Rates were even higher for aneurysms located in the posterior circulation (see section 2.1 for more details). Rupture rates in ISUIA may be biased downwards because patients with large or giant aneurysms were preferentially selected for treatment; those who were offered conventional treatment may have been those identified by their physicians as having low risks of rupture. Compressive symptoms can be extremely debilitating, and aneurysm rupture is associated with a high risk of death and (in survivors) marked neurological sequelae.

However, very large and giant aneurysms present several technical challenges for surgical and endovascular repair, because of their physical size, incorporation of parent vessels and perforators, wide necks, and often poor tissue characteristics (e.g. thrombus, atheroma, calcification and thin tissue) (20;21). These difficulties are compounded where the aneurysm is located in a clinically difficult location or where access is limited (21). Furthermore, existing endovascular occlusion strategies result in low rates of complete occlusion, both initially and at follow up, for large/giant and wide-neck aneurysms (22).

Complete occlusion of the aneurysm is the goal of IA treatment. It implies a permanent and complete separation of the IA from the parent artery circulation, which results in reduced exposure of the thin aneurysm walls to systemic blood pressure, thereby decreasing the risk of aneurysm recurrence (and retreatment) and aneurysm rupture. Incomplete occlusion is a risk factor for retreatment and for haemorrhage (23;24). For example, Johnston et al (2008; CARAT study) showed that the more incomplete the occlusion of a target IA (varying sizes) using coil embolisation, the more likely the IA was to rerupture (24).The study reported that, compared to IAs that were completely occluded at the end of the placement procedure, aneurysms that had small residual necks (91–99% occlusion), large residual necks (70–90% occlusion) or partial occlusion (<70% occlusion) had relative risks for rerupturing of 2.9, 6.9 and 21.7, respectively (24). Therefore, lesions that are not completely treated the first time with existing reconstructive approaches often require additional retreatments and life-long surveillance (25;26).

The comparator strategies and the issues surrounding their use in the management of complex aneurysms are discussed in more detail in section 2.6. Their main advantages and disadvantages are summarised in Table A2.4.

Table A2.4 Advantage and disadvantages of current strategies used in an attempt to manage large/giant/complex unruptured IAs compared with PED

Strategy	Advantages	Disadvantages	How PED is different
Embolic coiling/balloon-assisted coiling	– Endovascular procedure, so no craniotomy required, and rapid recovery – Endovascular placement means that aneurysm location is less often an issue	– Not suitable for many complex aneurysms – Coils can migrate into the parent artery, resulting in parent artery blockage and stroke – Complete occlusion is uncommon, especially in large or giant aneurysms – Recanalisation (i.e. the aneurysm reopens and continues to fill with blood) and the need for retreatment are common in large or giant aneurysms – Coils in target IA represent a permanent mass in the aneurysm fundus, potentially worsening mass effect symptoms Balloon-assisted coiling exposes patient to risk of thromboembolic complications and vessel rupture	–Studies show that PED can be used in complex aneurysms –PED is placed in the parent artery not the IA fundus, minimising the potential for aneurysm-related mass effect postoperatively –Complete occlusion is more common in large or giant aneurysms –Retreatment is rare –Fundus shrinks after PED placement, potentially relieving symptoms of mass effect

Strategy	Advantages	Disadvantages	How PED is different
Stent-assisted aneurysm coiling/multiple conventional stents	– Endovascular procedure, so no craniotomy required, and rapid recovery – Endovascular placement means that aneurysm location is less often an issue – Technology more familiar to physicians. Works by known, proven mechanism of action (holding coils in place in the aneurysm fundus) – Can be used to treat wide-necked aneurysms as stents hold the coils in place so they are less likely to migrate into the parent artery	– Usually requires coils for treatment – Coils in target IA represent a permanent mass in the aneurysm fundus, potentially worsening symptoms of mass effect – Complete occlusion probably occurs in less than half of cases – Delivery and placement can be difficult as stents often buckle or kink when placed in tortuous vessels	–In most cases, coils are not required with PED –Fundus shrinks after PED placement, potentially relieving symptoms of mass effect –PED design avoids buckling and kinking –Complete occlusion is more common
Neurosurgery (clipping or wrapping) +/- bypass procedures	– Effective treatment for aneurysms that are conveniently placed and do not have complex anatomy – Is sometimes a feasible option for patients where an endovascular technique is not predicted to be successful	– Depending on aneurysm location, complex dissection required to access target IA, with associated risks and prolonged recovery – Not feasible for some complex aneurysms and technically very difficult for many	–Endovascular procedure, so no craniotomy required, and rapid recovery –Endovascular placement of PED means that aneurysm location is less often an issue
SILK artery reconstruction device	– May be more visible radiographically than PED and final wire recapture may be easier (limited data)	– MHRA review due to safety concerns – Requires coils for treatment – Reports of incomplete opening of the device	–Made from a different material –Coils not required –Differences in device design mean that PED is potentially able to open more fully and more consistently than SILK
Parent vessel occlusion (surgical or endovascular)	– Deconstruction thought to have high degree of effectiveness in occluding target aneurysms	– Not an option for many patients without adequate collateral circulation; otherwise, risky bypass operation required – Risk of delayed ischaemic complications, even following a successful balloon occlusion test	–PED can be used when collateral circulation is insufficient

Strategy	Advantages	Disadvantages	How PED is different
Conservative management	– No perioperative risk, by definition – Traditionally, the only option for some patients	– High risk of rupture, leading to SAH with 30–40% level of death or neurological disability – Does not address aneurysm-related mass effect – Does not reduce risk of progressive enlargement of aneurysm, which leads to increased risk of symptoms and rupture	– PED can be used in patients for whom clinicians have traditionally had no reasonable treatment option – Fundus shrinks after PED placement, potentially relieving mass effect symptoms

IA, intracranial aneurysm; MHRA, Medicines and Healthcare products Regulatory Agency; PED, Pipeline™ embolisation device; SAH, subarachnoid haemorrhage

In addition, a retrospective series presented by Darsaut et al (2011) clearly illustrates some of the unmet needs for patients with large/giant aneurysms in whom treatment strategies are attempted (21). The group reported on a cohort of 183 treated patients from Stanford with large/giant aneurysms (note that there were population differences between treatment methods and the study was not designed to directly compare treatments, but to present experiences). Table A2.5 summarises some of the key findings from this study. It should be noted that Darsaut showed that current 'best available' treatments commonly resulted in permanent neurological complications and had relatively low complete occlusion rates.

Table A2.5 Summary of outcomes from cohort of 183 treated patients from Stanford with large/giant aneurysms (21)

Outcome	Surgery (n=114)		Endovascular (n=60)		Combined (n=9)
	Clipping (n=84)	Flow modification (parent vessel occlusion, aneurysm trapping) (n=30)	Reconstructive (coiling alone, stent-assisted coiling) (n=27)	Deconstructive (parent vessel occlusion) (n=33)	
Permanent neurological complication	16%	14%	11%	33%	22%
Mortality within 31 days	13.1%	17%	19%	21%	33%
Total mortality	14%		20%		33%
Complete occlusion rates	85%	59%	26%	41%	67%
Need for retreatment	3.6%	13.3%	37%	21.2%	0%

Summary: There is an unmet clinical need for effective treatment of large, giant and other complex IAs. Patients with larger IAs have a greater risk for rupture, SAH and its associated mortality and morbidity, and are more likely to experience mass effect symptoms. At the same time, the feasibility, safety and effectiveness of current treatment strategies decreases as the complexity and size of IAs increases.

2.6 Please identify the main comparator(s) and justify their selection.

In the absence of a suitable alternative, various reconstructive and deconstructive techniques are attempted for the treatment of large/giant, wide necked and/or fusiform aneurysms for whom standard coiling and stenting is unsuitable, or where previous coiling/clipping procedures have failed. By definition, in some patients these strategies are not an option or have already failed. Therefore, these are not all direct comparators. Information about these techniques and how they compare to PED is provided below, and Table A2.5 in section 2.5 summarises the advantages and disadvantages of these techniques versus PED for use in large/giant/complex, unruptured aneurysms.

a. Embolic coils (used alone)

Placement of embolic coils into an aneurysm via a microcatheter (sometimes using balloon catheter assistance) is a well-established treatment for small intracranial aneurysms with narrow necks (16;17). However, this procedure is much less successful in large and giant aneurysms. Patients undergoing coiling usually have systemic heparinisation during, and for 48 hours after, the procedure.

A review by Parkinson et al (2006) of cohorts reporting outcomes for coiling alone for patients with giant aneurysms showed an overall permanent morbidity rate of 24% and mortality rate of 9%. They concluded that primary coiling is not a robust strategy for the majority of giant aneurysms (20). Large/giant aneurysms tend to have wide necks, fusiform shapes or other complex geometries that prevent treatment with coils alone. Coils placed into such aneurysms can prolapse into the parent artery, causing acute artery obstruction, thrombosis and distal embolisation. Even if coils are successfully placed in the aneurysm sac, complete sealing of the in-flow zone is rare, packing densities are often insufficient, complete occlusion is uncommon and recanalisation of aneurysms is exceedingly common (20;26-33). Parkinson et al (2006) reported an overall complete occlusion rate of approximately 43% and recanalisation rate of 55% following coiling of giant aneurysms (20). Incomplete occlusion is a risk factor for retreatment and haemorrhage. In a series of 39 giant aneurysms treated endovascularly, Jahromi et al (2008) reported that most patients with giant aneurysms who underwent coil placement were retreated at least once (34). Moreover, vast quantities of metal coils can exacerbate mass effect symptoms and necessitate additional treatment (7).

Balloon-assisted coiling is sometimes used to try to achieve long-term occlusion of giant cerebral aneurysms. In balloon-assisted coiling, a balloon catheter is placed in the parent artery close to the target aneurysm and inflated; inflation temporarily occludes the parent artery, making it technically easier to place coils into the aneurysm fundus. At least 40 to 50 coils are needed to fill a giant aneurysm, with multiple balloon inflations. Repeated

temporary balloon occlusion exposes the patient to an increased risk of cerebral ischemia resulting from thromboembolic complications (due to stasis of blood or temporary occlusion of local perforating end arteries), and vessel rupture (due to balloon design) (26). In many giant IAs where there is circumferential involvement of the vessel wall, it may not be possible to completely coil the neck of the aneurysm, even with balloon assistance. Continued placement of radiopaque coils into the aneurysm obscures the parent vessel and makes it difficult or impossible to completely coil the aneurysm.

The need for retreatment following endovascular coiling is such an important issue that some ongoing trials have focussed on this as a primary endpoint (e.g. Patients prone to Recurrence after Endovascular Treatment [PRET] study). In particular, retreatment after coiling of large/giant aneurysms is very common and patients should be aware that repeated efforts are commonly required (21;34). Follow-up data from the International Subarachnoid Aneurysm Trial (ISAT) confirms that late retreatment is common in patients treated with primary coiling, with younger age, larger lumen size and incomplete occlusion all being risk factors for retreatment (23). Ferns et al (2010) followed up patients with aneurysms that were incompletely occluded at 6 months post-coiling and found that 71% were re-treated (35).

Comparison to PED

PED can be used effectively in many situations in which coil embolisation alone is impossible. In the PUFS study, complete occlusion without major stenosis occurred in 70.8% of aneurysms at one year (n=106 IAs) (36). Retreatment is very rare with PED.

b. Stent-assisted aneurysm coiling and/or using multiple conventional stents

In patients with wide necked intracranial aneurysms, physicians often place stents designed for intracranial use (e.g. Neuroform, Enterprise) into the parent artery immediately before coil placement. These stents hold the coils in place in the target aneurysm. As with PED placement, patients undergoing stent-assisted coiling must be treated with dual antiplatelet therapy to prevent stent-associated parent artery thrombosis.

Several review articles have been published regarding stent-assisted coiling for large/giant aneurysms. Nelson et al (2006) reported thrombotic complications in around 10% of patients (449 aneurysms in 416 patients) (37). Follow-up angiograms were only reported for about half the patients, and in these patients, complete occlusion was noted in 69% and retreatment was required in 8.2%. Peruzzo et al (2005) reviewed stent-assisted coiling with the Neuroform stent (120 aneurysms) (38). Complete occlusion varied between studies; the combined complete occlusion rate from the studies reviewed was 40% (it is unclear whether this is acute or long-term occlusion). The combined permanent disability rate was 4.1% and mortality rate was 5%. Zenteno et al (2006) reviewed studies of stent-assisted coiling or stenting alone for wide necked or fusiform aneurysms (39). Total occlusion was seen in 45% of cases (again, not clear whether this represents acute or long-term occlusion). The combined permanent disability rate was 4% and the combined mortality rate was 4%.

Fiorella et al (2010) followed a cohort of 284 patients undergoing Neuroform stent-assisted aneurysm treatment for saccular (n=286) or fusiform (n=16) aneurysms (40). For saccular aneurysms, where follow-up imaging was available (166 out of 286), 48.2% demonstrated progressive thrombosis, and 27.7% showed recanalisation, 15.1% of which required retreatment. Most recanalisations were observed in large, giant or wide necked aneurysms. Complete occlusion at follow-up was observed in 33.1% of lesions, and nearly complete occlusion with small residual neck remnants in 27.7%. In this study, there were a cumulative total of 8.8% ischaemic strokes and 2.8% neurovascular deaths, but follow-up rates were poor (with nearly half of patients being lost to follow-up).

A retrospective study by Piotin et al (2010) reported outcomes from 1137 patients with 1325 aneurysms. Of these aneurysms 216 (16.5%) were coiled with stents, and 1109 (83.5%) without stents. A larger aneurysm sac and neck size were significantly associated with stent-use ($p=0.006$ and $p<0.001$, respectively). Immediate angiographic results in the stent-assisted coiling group showed that 46.3% of the aneurysms were totally occluded, 19.0% had a neck remnant and 34.7% had a sac remnant. Of the aneurysms that were not totally occluded in this group, 72.6% showed angiographic improvement at follow-up (41).

Whilst it is clear that stent assistance allows coil embolisation of aneurysms that would otherwise be difficult or impossible to embolise with coils, long-term complete aneurysm occlusion remains elusive. Stent delivery and placement can be very difficult, but is improving as newer generations of stents are developed (26). Delayed in-stent stenosis has been reported with Neuroform stents (42). In addition, the rate of long-term complete occlusion is not well-reported.

Comparison to PED

PED can be used in most aneurysms independent of size or shape, including some aneurysms that are not possible to treat with stent-assisted coiling. PED's mechanism of action is flow disruption and scaffolding for re-endothelialisation, so PED use does not require intrasaccular coils. The incidence of major stroke or deaths following PED placement in the PUFS study was 5.6% (see section 5.5 for detailed PED data).

c. Neurosurgery

Some patients with intracranial aneurysms undergo surgical approaches, primarily clipping (but also wrapping and/or complex high-flow bypass procedures), to treat the target aneurysm. However, these approaches require a craniotomy or minicraniotomy and are usually reserved for patients who cannot undergo an endovascular technique predicted to be successful. The size (particularly giant IAs), location (e.g. posterior circulation aneurysms or those involving multiple vessels) and poor tissue characteristics (e.g. thrombus, calcification and thin tissue) of aneurysms means that surgical treatment can be treacherous, requires much skill and expertise and is frequently limited by risks and complications (7;20). Furthermore, patients with giant IAs tend to be older, have multiple comorbid conditions, and are at higher risk for complications associated with prolonged general anaesthesia (26). Direct clip reconstruction is not possible for some aneurysms, especially some fusiform or serpentine aneurysms (20).

In the surgical cohort (n=1,971; varying sizes of aneurysm) of the ISUIA study, rupture during surgery was reported in 6% of patients, intracranial haemorrhage in 4% and cerebral infarction in 11% (12). Combined surgical morbidity and mortality at 1 year was 10.1% for patients without prior SAH and 12.6% for those with prior SAH. Predictors of poor surgical outcome included age ≥50 years, aneurysm diameter >12 mm, location in the posterior circulation, previous ischaemic cerebrovascular disease, and aneurysmal symptoms other than rupture. Among patients with large (13–24 mm) or giant (≥25 mm) aneurysms in the anterior circulation, 1-year surgical mortality/morbidity was approximately 4% and 22% for patients <50 years old and 24% and 32% for patients >50 years old (12).

To support the design of the PUFS investigational device exemption (IDE) study, Chestnut Medical performed a comprehensive literature search regarding surgical and endovascular treatment of large and giant IAs in 2008 (1,200 abstracts reviewed and data extracted from 250 full-text articles reporting relevant clinical experiences). This review provided strong evidence that surgical treatment for large and giant aneurysms carries a high risk of death and permanent disability. Mortality and stroke rates as high as 25% have been reported. Complete aneurysm occlusion after neurosurgery for large and giant IAs is rarely documented (43).

Comparison to PED

PED does not require an invasive craniotomy or minicraniotomy with its associated long recovery period. Aneurysm location within the brain is less of an issue with PED placement as it is delivered via an endovascular procedure.

d. SILK artery reconstruction device, manufactured by Balt Extrusion

The SILK artery reconstruction device is not a direct comparator to PED but is being used to manage IAs in some patients. SILK is similar in concept to PED (both are referred to as flow diversion devices in the literature) but it is a different device made from a different material. SILK is made primarily from nickel-titanium (nitinol) alloy wires braided more tightly than PED; PED is made from 25% platinum/tungsten and 75% cobalt-chromium-nickel alloy wires.

The SILK device is currently under review by the MHRA due to concerns about its safety. The manufacturer of SILK issued an urgent recall notice in March 2010 advising that the SILK device should not be used without embolisation coils. This was due to short- and mid-term (5–150 days) deaths due to a ruptured aneurysm in 8 patients (including 4 in the UK) with giant aneurysms (diameter size 18–31 mm) treated only with a SILK device. As a result of these safety concerns with SILK, a post-marketing multicentre, randomised trial started in 2010 comparing selective endovascular aneurysm occlusion with coils versus parent vessel reconstruction using the SILK flow diverter (MARCO POLO).

Additionally, there have been reports that SILK does not always open fully, and may require balloon opening (44;45). Failure to open correctly may lead to important flow changes or thrombosis of the treated vessel (46).

Following placement of a SILK device, Byrne at el reported that complete aneurysm occlusion occurred in 49% of patients at follow-up (range 9–528 days; median 119 days) (45).

Comparison to PED

PED is a different device, made of a different material. Unlike SILK, PED is typically used without coils in patients with giant aneurysms and to date has had few safety concerns. In the PUFS study, a single-arm study, PED was used alone (without coils) to treat patients with large or giant aneurysms. There was one early aneurysm rupture which caused a carotid-cavernous fistula that was subsequently successfully treated. Otherwise, there have been no aneurysm ruptures to date (mean 2.5 years cumulative follow-up data) (2).

PED has roughly twice the expansive radial strength of SILK which means that PED is potentially able to open more fully and more consistently than SILK. Additionally, there are differences in the foreshortening of the two devices which potentially makes PED more user-friendly. Within vessels, the PED device gives 50% more surface coverage than SILK, providing more contact points per mm^2, resulting in a denser mesh and a greater flow diversion effect. The platinum distribution in PED (12 wires versus 2 in SILK) gives PED greater homogenous visibility radiographically (47).

In the PUFS study, PED was successfully positioned in 99.0% of cases (in one of the 108 PUFS study subjects, the parent artery distal to the IA could not be catheterised and the PED procedure was abandoned). Whilst there have been no large-scale studies comparing SILK and PED, Wong et al (2010) reported a very small (8 patients) prospective evaluation of SILK versus PED. SILK positioning and deployment was reported to be more difficult than with PED, but SILK was more visible radiographically and final wire recapture was easier (48).

In the PUFS study of PED, complete occlusion without major stenosis occurred in 70.8% of aneurysms at one year (n=106 IAs) (36). (See section 5.5 for further details.)

e. Parent vessel occlusion (deconstructive approach)

Occlusion of the parent vessel proximal to the target aneurysm is an option for some patients with IAs. Lack of blood flow into the aneurysm effectively treats the aneurysm and is likely to prevent aneurysm rupture. Parent vessel occlusion can be performed surgically (i.e. ligation of the parent artery) or endovascularly (using coils or balloons to occlude the parent artery) (26). Parent vessel occlusion is usually reserved for aneurysms that cannot be treated by any other means (7;20).

Not all patients can receive parent vessel occlusion. It cannot be used in many patients due to lack of sufficient collateral circulation. Without sufficient collateral circulation, occluding the parent artery will cause a major stroke. Trial balloon occlusion is used to predict whether parent vessel occlusion is likely to be an option, but even after a successful balloon occlusion test, delayed ischaemic complications may appear (7). In patients with insufficient collateral circulation, a risky bypass procedure must be performed.

In a series by Clarencon (2010) of 22 patients with giant/large aneurysms who were able to tolerate balloon test occlusion, clinical symptoms disappeared in 75% of the patients, partially regressed in 10%, and remained unchanged in 15% at long-term follow-up (8). Another series by Elhammady et al (2010) of 27 patients with large/giant aneurysms who underwent carotid artery sacrifice, all surviving patients showed clinical improvement of presenting symptoms (49).

Treatment of internal carotid artery aneurysms with parent vessel occlusion requires increased flow from the contralateral carotid, which may not be desirable in patients with bilateral aneurysms.

Comparison to PED

PED is designed to preserve flow through the parent artery. PED use therefore does not depend on collateral circulation, so it can be used in patients in whom parent vessel occlusion is not a feasible option. The incidence of major stroke or deaths following PED placement in the PUFS study was 5.6% (see section 5.5 for detailed PED data). In addition, preserving the parent artery provides an opportunity to treat additional aneurysms that may occur, via endovascular methods. With parent vessel occlusion, endovascular access to subsequent distal aneurysms via collateral vessels may be difficult or impossible.

f. Conservative management

Without treatment, large or giant unruptured aneurysms present a risk of rupture, leading to SAH, which is associated with high level of mortality (30–40% at one month) or marked neurological disability (50) (9). The risk of rupture depends on the aneurysm size, aneurysm location, patient age, previous history of haemorrhage from an IA, and patient-specific factors such as smoking and hypertension. In the ISUIA study, five-year cumulative rupture rates of aneurysms in the anterior circulation were 2.6% for aneurysms 7–12 mm in diameter, 14.5% for those 13–24 mm, and 40% for those ≥25 mm (12). Rates were even higher for aneurysms located in the posterior circulation (see section 2.1 for more details). In the 51 patients who had unruptured aneurysms at baseline, but had a subsequent haemorrhage, 65% died (12). ISUIA is the only source of information for rates of aneurysmal haemorrhage in conservatively managed patients. However, spontaneous aneurysmal haemorrhage rates from ISUIA may be biased as ISUIA was not randomised, and therefore patients at high risk for haemorrhage may have been preferentially selected for surgical or endovascular treatment, leaving a relatively ‘low-risk’ cohort selected for conservative treatment.

Unruptured large/giant aneurysms often cause a compressive mass effect as they press against tissues or cranial nerves. This can cause various symptoms of cranial nerve compression (e.g. blindness, paralysis, muscle weakness, deafness) and headache (8). Without treatment, this mass effect becomes worse over time. Unruptured aneurysms can also be the source of embolic strokes (7). In the ISUIA study, reasons for diagnostic angiography in untreated patients (with a variety of sizes of aneurysms) included cranial nerve palsies in 8.0%, headaches in 23.7%, and transient ischaemic attacks in 10.6% of patients (12).

Comparison to PED

PED is an active treatment option for patients with large, giant or complex IAs. With PED, occlusion is achieved in 75–93% of aneurysms. It is assumed that the high aneurysm occlusion rate reduces the risk of rupture. Clinical studies show a low incidence of stroke and death following PED placement (incidence of major stroke or death following PED placement was 5.6% in the PUFS study). Furthermore, following PED placement in the parent artery, the aneurysm fundus shrinks, potentially relieving mass effect symptoms. This was assessed using thorough neurological assessments in the PUFS study (see section 5.5 for detailed PED data).

2.7 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

The potential risks of PED placement are similar to those of coil embolisation and stent-assisted coiling. Patients undergoing these techniques have a risk of embolic or thrombotic stroke, which can be managed interventionally or via standard medical techniques. Intracranial haemorrhage from aneurysm perforation (not seen in the PUFS study and rarely reported with PED use), aneurysm rupture (seen in stent-assisted coiling and infrequently with PED placement) or distal intracranial haemorrhage can be managed using standard neurosurgical and intensive care techniques. No aspect of PED use gives rise to complications unfamiliar to the practicing interventional neuroradiologist/neurosurgeon.

Consistent with the placement of other neurovascular stents, patients require appropriate dual anti-platelet therapy prior to PED placement, administered in accordance with standard medical practice. Patients participating in the PUFS study were pre-treated with 325 mg aspirin for at least 2 days and 75 mg clopidogrel for at least 7 days (or a 600 mg loading dose of clopidogrel the day prior to the procedure). Intravenous heparin was used during the procedure. Patients were asked to take dual antiplatelet therapy (aspirin 325 mg daily for at least 6 months and clopidogrel 75 mg daily for at least 3 months) after PED placement.

Summary: No aspect of PED use requires therapies or gives rise to complications that are unfamiliar to the practicing interventional neuroradiologist/neurosurgeon.

2.8 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

The cost of the Pipeline Device is £10,171 per unit. Patients may require more than one implant per procedure. Consumables include one each of: microcatheter through which PED is delivered (e.g., Marksman catheter, ev3), guidewire, distal access catheter and guide catheter, at a cost of £1,030 and £160, £500 and £290 respectively.

Pipeline is used in a hospital inpatient setting and is inserted by a surgeon under fluoroscopic guidance in an angiography suite. The procedure may require the patient to spend time in a rehabilitation clinic following the treatment. NHS Reference Costs 2009–2010 and PSSRU Unit Costs of Health and Social Care 2010 will be used to identify these staff and ward costs. Additional drugs may be required such as anaesthetics, pain killers etc. The British National Formulary will be used to provide costs for these drugs. Following treatment, patients may undergo a cerebral angiogram to monitor the occlusion status of the aneurysm.

2.9 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

In addition to the costs of the technology, other significant costs are the tariff for the procedure, payable by the commissioner to the healthcare provider.

3 Equity and equality

3.1 Identification of equity and equalities issues

3.1.1 Please specify any issues relating to equity or diversity in NICE guidance, or protocols for the condition for which the technology is being used.

IAs are more common in women than men; not surprisingly therefore, in clinical trials to date approximately 80–90% of trial participants have been women. No evidence suggests that safety or effectiveness varies by gender.

3.1.2 Are there any equity or diversity issues anticipated for the assessment of this technology (consider issues relating to current legislation and any issues identified in the scope for the assessment)?

No equity or equality issues have been identified to date associated with use of PED.

3.1.3 How have the clinical and economic analyses addressed these issues?

There are no issues anticipated for the assessment of this technology.

Note: the ratio of males to females in the clinical trials described in section 5, reflect those in the general IA population: 80.6% of patients in the PITA (Pipeline^{TM} for Intracranial Treatment of Aneurysms) study, and 88.9% in the PUFS (Pipeline^{TM} for Uncoilable or Failed Aneurysms Study) were female.

4 Statement of the decision problem

	Final scope issued by NICE	**Decision problem addressed in the submission**	**Rationale if different from the scope**
Population	Patients with complex intracranial aneurysms, specifically large/giant, wide necked and fusiform aneurysms	N/A	N/A
Intervention	Pipeline™ embolisation device	N/A	N/A
Comparator(s)	Stent-assisted coiling Parent vessel occlusion Neurosurgical techniques Conservative management	In section 2.6 of this submission document SILK has been discussed because, although not a direct comparator, it is being used to manage IAs in some patients	Although it is not required by the scope we have addressed SILK to highlight and clarify the differences between this device and PED
Outcomes	The outcome measures to consider include: • successful device deployment • successful occlusion of the aneurysm, with and without preservation of flow through the parent vessel • size of collective aneurysm-thrombus mass • resolution of symptoms (i.e. headache, diplopia, nystagmus or other neurological dysfunction), relief of pain and quality of life outcomes • resource-use outcomes for example re-admission rates, re-interventions and duration of hospital stay • stroke (all causes, but specifically when caused by blood clot or bleed related to the interventional procedure) • delayed parent vessel occlusion, • subarachnoid haemorrhage and/or other major bleeding events requiring hospitalisation and/or transfusion or active treatment • neurovascular death • device-related adverse events	N/A	N/A

Continued…

	Final scope issued by NICE	**Decision problem addressed in the submission**	**Rationale if different from the scope**
Cost analysis	Three cost analyses to be undertaken. <u>Analysis 1</u> Population: Patients with complex intracranial aneurysms for whom stent-assisted coiling is considered feasible (*de novo* or repeat treatment). Intervention: Pipeline™ embolisation device Comparator: Percutaneous interventional techniques including stent-assisted coiling and parent vessel occlusion <u>Analysis 2</u> Population: Patients with complex intracranial aneurysms for whom stent-assisted coiling is not considered feasible (de novo or repeat treatment) Intervention: Pipeline embolisation device Comparator: Neurosurgical techniques (including bypass) <u>Analysis 3</u> Population: Patients with complex intracranial aneurysms for whom stent-assisted coiling and neurosurgical techniques are not considered feasible (de novo or repeat treatment) Intervention: Pipeline embolisation device Comparator: Conservative treatment Costs will be considered from an NHS and Personal Social Services perspective. Both the analyses should take into account hospital care (surgical time and recovery), and the long term management of the aneurysm including drug costs, for example, antiplatelet therapy. Additional training required to use the device should be accounted for. Adverse events and complications relating to the use of the device (including re-intervention) and treatment required for these complications should also be considered (for example, the costs associated with social care if the patient has a stroke) The time horizon for the economic evaluation should be based on the appropriate time period over which costs and benefits can reasonably be expected to be experienced given the chronic nature of the condition The sensitivity analysis should address uncertainties in the model parameters, which should include scenarios in which different numbers and combinations of devices are required	N/A	N/A

Continued…

	Final scope issued by NICE	**Decision problem addressed in the submission**	**Rationale if different from the scope**
Subgroups to be considered	None identified	N/A	N/A
Special considerations, including issues related to equity or equality	The natural history of the disease should be considered and presented	N/A	N/A

Section B – Clinical effectiveness and cost

5 Clinical evidence

5.1 Identification of studies

5.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data. 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. Exact details of the search strategy used should be provided in section 7.2, appendix 2.

A range of databases indexing published research were searched for studies about the clinical effectiveness and safety of the Pipeline™ Embolisation Device (PED) for cerebral aneurysm. The databases searched included the minimum required by NICE: MEDLINE, MEDLINE In-Process, EMBASE and the Cochrane Library. The searches were limited to human studies in the MEDLINE and EMBASE databases. No date or language limits were applied. Study design search filters were not included to ensure that studies with adverse events data were found. Searches (including *ad hoc* internet searches) for systematic reviews and technology assessments, guidelines, patient pathways and epidemiological information relating to cerebral aneurysm were also undertaken. All clinical study protocols and reports conducted by Chestnut Medical Technologies, ev3 and Covidien were made available for inclusion in this submission. Publically available data from the PUFS (Pipeline™ for Uncoilable or Failed Aneurysms) trial were sourced from the US FDA website. A subset of the information available on the FDA's website is currently being prepared for publication in peer-reviewed medical literature.

Full details of the search strategies, databases and resources searched are provided in appendix 2, section 7.2.

5.2 Study selection

5.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

The eligibility criteria for study selection are described in Table B5.1.

Table B5.1 Eligibility criteria used in search strategy

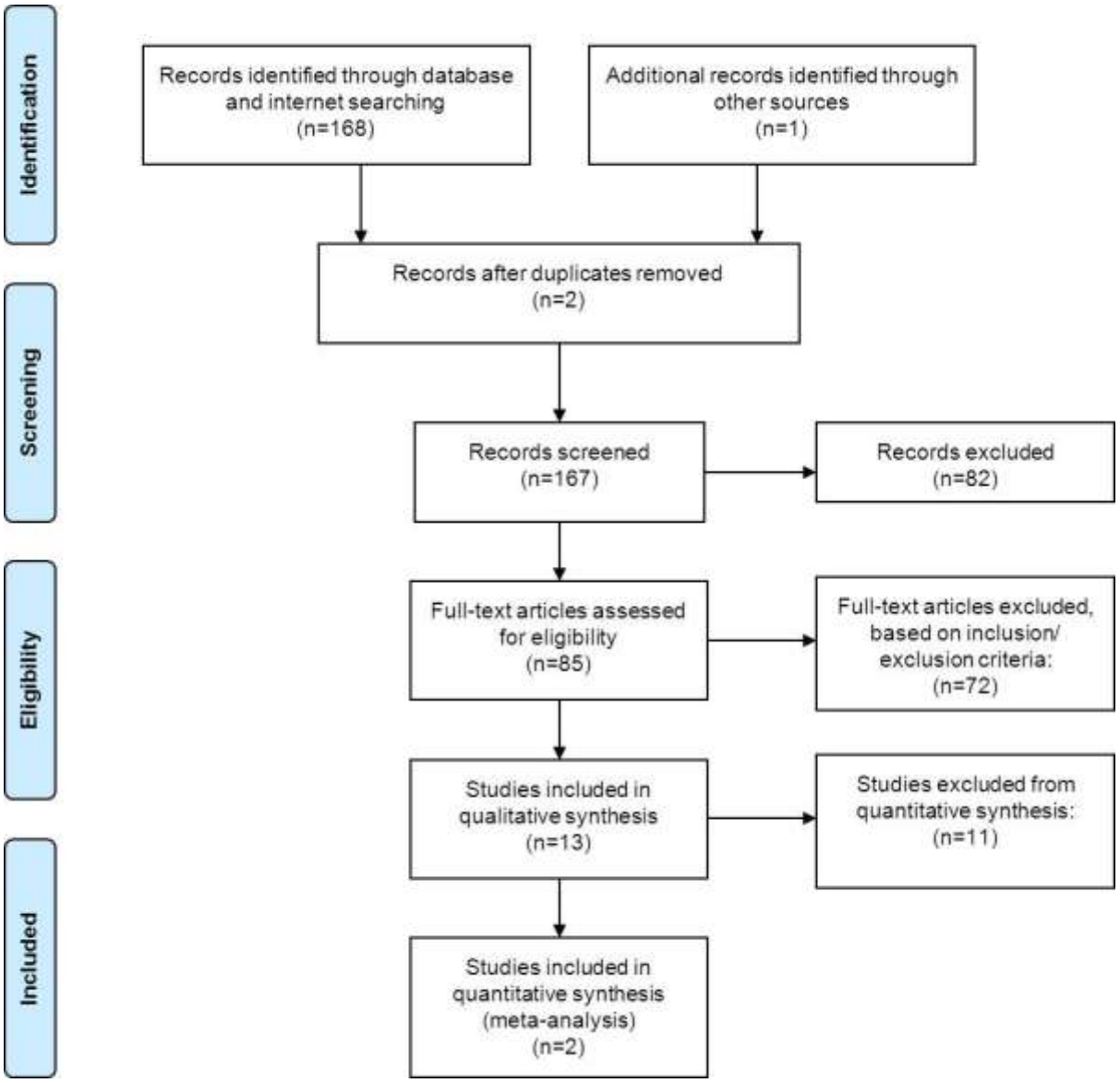
	Clinical effectiveness
Inclusion criteria	Population: large and giant IAs Interventions: PED Outcomes: safety and efficacy Study design: RCTs, interventional, multi-centre, single-centre, single-arm, double-arm, prospective, retrospective, case studies Language restrictions: English
Exclusion criteria	Population: non-cerebral aneurysms, small IAs Interventions: SILK, coiling, clipping/surgery, balloon-assisted embolisation Outcomes: MR imagery, rupture mechanisms, complication management, haemodynamics, technical use Study design: None

IA, intracranial aneurysm; PED, Pipeline™ Embolisation Device

5.2.2 The numbers of studies included and excluded at each stage should be reported

The search strategy identified 168 published articles. The number of studies excluded at each stage is reported in Figure B5.1. Ultimately, there were 13 studies included in the qualitative analysis, 2 of which have been used for the quantitative assessment.

Figure B5.1 Number of studies included and excluded at each stage



Complete list of relevant studies (RCTs and non-RCTs)

5.2.3 Provide details of all studies that compare the intervention with other therapies in the relevant patient group. Highlight which of these studies compare the intervention directly with the appropriate comparator(s) referred to in the decision problem. If there are none, please state this. The list must be complete and will be validated by independent searches conducted by the External Assessment Group. This should be presented in tabular form. A suggested format is presented below.

There are no comparator studies for PED.

During the clinical development of PED it has not been possible to carry out a comparative clinical study (versus existing treatments) for the indication discussed in this document since historical information clearly indicated that a concurrent control group was not practical or feasible:

- Clinical equipoise would limit a randomised trial to those patients in whom the investigator was indifferent to the treatment arms. The PUFS population did not have acceptable alternative treatments. To limit the investigation to randomised patients would have resulted in a population different from the one discussed in this document.
- The target IA population was likely to include many IAs that could be treated by PED but not by any particular single alternative treatment. This would have resulted in heterogeneity in a comparative arm and would have made outcomes difficult to interpret.
- Neurosurgery for IAs near the skull base is extremely difficult and available in a limited number of study centres. Moreover, neurosurgery for large and giant IAs was already known to be associated with high rates of morbidity and mortality.
- The current standard for treatment, coil embolisation, was predicted to be infeasible in many patients.
- Historical information was sufficient to show that the likelihood of long-term complete occlusion of the target IA with coils was low.
- The target population for PED of large and giant aneurysms is very small (for example, estimates suggest approximately 575–725 patients per year in England and Wales), which means that subgroup analysis would have been very difficult in such small cohorts of patients.

Following the study selection process (see section 5.2 following) two single-arm studies with PED (Table B5.2) are used as support for this NICE submission:

- The first is the Pipeline™ for Intracranial Treatment of Aneurysms (PITA). PITA was a multicentre prospective study of patients with untreatable or recurrent aneurysms not suitable for treatment with coils. This study provided support for the granting of PED's CE mark in June 2008.
- The primary support for reasonable assurance of safety and effectiveness of the PED device comes from the ongoing Pipeline™ for Uncoilable or Failed Aneurysms (PUFS). PUFS is a study of PED in the treatment of wide-necked large and giant IAs of the internal carotid artery. It is being conducted in the US under an approved investigational device exemption (IDE) application, and in Hungary and Turkey.

Both studies involved patients with difficult-to-treat IAs with results that revealed a high rate of complete occlusion of the target aneurysm with a low rate of stroke.

Table B5.2 List of relevant studies

Study no. (acronym)	Intervention/Aim	Comparator	Population	Primary study ref.
PITA study CE mark study	To assess the safety and effectiveness of PED in minimally invasive endovascular treatment of intracranial aneurysms	None	Wide neck IAs unsuitable for treatment with coils	Nelson et al. 2011(22)
PUFS Pivotal Study	To assess the safety and effectiveness of PED in endovascular treatment of wide-neck, large and giant intracranial aneurysms localised in the cavernous and paraclinoid segments of the internal carotid artery	None	Wide-neck, large and giant IAs localised in the petrous, cavernous and the paraophthalmic (hypophyseal, ophthalmic or paraclinoid) segments of the internal carotid artery	Follow-up of patients in this study is ongoing (2)

PED, Pipeline™ embolisation device; PITA, Pipeline™ for Intracranial Treatment of Aneurysms; PUFS, Pipeline™ for Uncoilable or Failed Aneurysms

Case study series are also relevant for the support for PED, and are described in Table B5.3.

Table B5.3 Further relevant experiences with PED

Study no. (acronym)	Description	Population	Primary study ref.
US compassionate use cases	Compassionate use cases treated in the US met the criteria for treatment with an unapproved device and did not qualify for inclusion in open studies. These patients were seriously ill and did not have other reasonable alternative treatments	23 patients with IA of the ICA (21 of which were with large/giant wide-necked IAs) 14 patients with IAs of the posterior circulation	Some of these cases have been published as case reports • Fiorella et al, 2008 (51) • Fiorella et al 2009 (52) • Fiorella et al 2010 (53)
Buenos Aires experience with PED	Prospective, single-centre evaluation Study/case series to produce the results of implantation safety/efficacy for PED use in ruptured and unruptured aneurysms	180 patients (217 IAs) • 50% were large/giant • 81% unruptured • 84% in ICA	First results (n=53, 63 IAs) published in: Lylyk et al. 2009 (54) 6 of these patients were also included in PITA

Continued…

Study no. (acronym)	Description	Population	Primary study ref.
Canadian special access cases	Cases performed in Canada under the Special Access provision of Canadian medical device law	2 series totalling 55 patients • 16 IAs in the carotid and vertebral-basilar circulation • 39 IAs, 28 of which were in the anterior circulation and 12 were in the posterior circulation	No published data available
Mass effect study	Study to demonstrate the effect of flow modification of mass effect caused by large and giant aneurysms (PED intervention) Patients were monitored up to 12 months	42 aneurysms (patient number not reported) Patients with large and giant aneurysms causing mass effect	Szikora et al, 2010 (55)
Budapest experience with PED Single-centre trial	Study/case series to summarise midterm results for PED in the treatment of aneurysms Carried out between February 2007 and July 2008 Patients were followed up for 2 years	n=18	Szikora et al, 2010 (56) 9 of these patients were included in the PITA trial
Australian single-centre experience with PED	Carried out from September 2009 to April 2010	n=10 Aneurysms considered to be difficult to treat with coiling or stent-assisted coiling	Phillips et al 2010 (57)
German case series	Case series of initial experience with PED Carried out between October 2009 and March 2010 Patients were followed up for a mean of 2 months	n=8 Non-ruptured, large and giant wide-necked aneurysms	Hartmann et al 2010 (58)

Continued…

Study no. (acronym)	Description	Population	Primary study ref.
Additional case reports	Published case reports	Case reports (n=5), as follows: • 38-year-old female with small ruptured aneurysm • 30-year-old male with ruptured fusiform aneurysm • Two patients with very large fusiform basilar trunk aneurysms • 68-year-old female with large dumbbell aneurysm located on the left A1 segment	Matouk et al, 2010 (59); Klisch et al, 2011 (60); Van Rooij 2010 (61)

FDA, Food and Drug Administration; IA, intracranial aneurysm; PED, Pipeline™ embolisation device

5.2.4 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of study data required, this should be indicated.

Whilst results from individual case reports and case study series are relevant, they have not been considered as providing a robust enough evaluation, in terms of design and execution, to be included in the main body of supporting evidence for this submission. There is also some duplication of patients between the case studies and the PITA trial.

Note also that a PED study, The Complete Occlusion of Coilable Aneurysms (the COCOA study) has been recruiting since October 2008. COCOA is a randomised trial of coil embolisation alone vs. PED alone for the treatment of small, unruptured, saccular aneurysms along the internal carotid artery. Since this patient population is not the focus for this current NICE submission, interim evidence (which is currently very limited) from this trial has not been included in the main body of supporting evidence.

5.3 Summary of methodology of relevant studies

5.3.1 As a minimum, the summary should include information on the study(s) under the subheadings listed in this section. It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE.

Methods

5.3.2 Describe the study(s) design and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one study.

Table B5.4 provides a comparative summary of the methodology for the PITA and PUFS studies.

PITA methods:

- PITA was a multicentre, prospective interventional cohort of 31 patients with IAs that were either wide-necked (neck ≥4 mm or dome/neck ratio <2) or had failed previous attempts at treatment.
- PITA was conducted in four centres in Europe and South America between January and November 2007.
- Patients were treated with PED, with or without adjunctive placement of coils.
- Clinical follow-up was performed 30 days and 180 days after PED placement. At 180 days, all patients also underwent repeat angiography.
- Angiographic images were interpreted by a core radiology laboratory. The scale of Raymond (62) was used to judge the level of occlusion as complete, residual neck and residual aneurysm.
- All patients took standard dual antiplatelet therapy (aspirin and clopidogrel) for 3–6 months after PED placement.
- A post-study follow-up at 2 years was performed to assess the degree of complete occlusion, either by catheter angiography or MRI.

PUFS methods:

- The PUFS study is a prospective, multicentre, single-arm interventional study (10 centres in the United States, Europe and Middle East).
- Patients were treated with PED, with no alternative treatment performed.
- Clinical follow-up was performed at 180 days (primary endpoint) after PED placement. At 180 days, and at 1 year, patients also underwent repeat angiography. Late follow-up clinic visits and cerebral angiograms are scheduled for 3 and 5 years.
- Sites contacted the patients by telephone at 90 days after PED placement to assess medical status and the occurrence of AEs. Phone calls are also scheduled for 2 and 4 years.

- Angiographic images were interpreted by a core radiology laboratory. The Raymond scale was used to judge the level of occlusion as complete, residual neck and residual aneurysm.
- The first patient was enrolled on November 3, 2008 and the last on July 17, 2009.
- The study is expected to end in July 2014. One year data are available and described in this document.
- All patients received the standard pre- and post-procedure aspirin and clopidogrel.

Table B5.4 Comparative summary of methodology of the studies

Study no. (acronym)	**PITA**	**PUFS**
Location	Four centres, Europe and South America, conducted between January 2007 and November 2007	Ten centres (8 USA, 1 Europe, 1 Middle East)
Design	Prospective, single-arm, feasibility study	Prospective, single-arm, open-label interventional trial
Duration of study	180 days (A post-study follow-up was conducted at 2 years)	180 days, with up to 5-year follow-up
Method of randomisation (if applicable)	N/A	N/A
Method of blinding (care provider, patient and outcome assessor) (if applicable)	N/A	N/A
Intervention(s) (n) and comparator(s) (n)	Interventions: n=31 Comparators: n=0	Interventions: n=108 Comparators: n=0
Primary outcomes (including scoring methods and timings of assessments)	Device-placement success, defined as the successful deployment and placement at the target site Incidence of death or ipsilateral stroke at 30 days post-procedure	**Efficacy**: percentage of patients with complete occlusion of the target IA and ≤50% stenosis in the parent vessel on 180-day angiogram, without using any other devices in the IA; trial considered as successful from the effectiveness perspective if the percentage of patients is statistically >50% **Safety**: percentage of patients experiencing major ipsilateral stroke or death by 180 days following the procedure; trial considered as successful from the safety perspective if the percentage of patients is statistically <20%

Continued…

Study no. (acronym)	PITA	PUFS
Secondary outcomes (including scoring methods and timings of assessments)	Device-deployment success, defined as the successful introduction of PED through the guide catheter and its release Clinical procedure success, defined as the successful delivery of the device without procedural in-hospital death or ipsilateral stroke	Complete occlusion at 1, 3 and 5 years (3 and 5 year results not yet available) Incidence of major ipsilateral stroke at 180 days Changes in the modified Rankin scale ≥2 points at 180 days compared to the start of the study (assessment of the state of dependence) Changes in neurological symptoms linked to the aneurysm at 180 days compared to the start of the study Incidence of adverse events associated with the device at 180 days, 1, 3 and 5 years
Additional outcome measures	Occlusion of the aneurysm at 180 days post-PED placement Incidence of new neurological deficits Neurological assessment Rate of neurological and non-neurological complications Distal device migration Stenosis with PED	Change in the eye test at 180 days Distal migration of PED Stenosis with PED
Duration of follow-up	Clinical follow-up assessment immediately post-procedure/prior to hospital discharge, and 30 days and 180 days post procedure	Assessment prior to hospital discharge, and clinic visits at 30 days, 180 days, and 1, 3 and 5 years after the procedure Phone calls at 90 days, 2 and 4 years after the PED placement

IA, intracranial aneurysm; PED, Pipeline™ embolisation device; N/A, not applicable; PITA, Pipeline™ for Intracranial Treatment of Aneurysms; PUFS, Pipeline™ for Uncoilable or Failed Aneurysms; USA, United States of America

Participants

5.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the study. The following table provides a suggested format for the eligibility criteria for when there is more than one study. Highlight any differences between the studies.

Eligibility criteria for the studies are provided in Table B5.5.

Table B5.5 Eligibility criteria in the studies

Study no. (acronym)	Inclusion criteria	Exclusion criteria
PITA	a) Age 21 to 85, inclusive b) In the opinion of the physician, placement of the Pipeline™ Embolisation Device is technically feasible and clinically indicated in at least one IA c) Patient has provided written informed consent using a form that has been approved by the reviewing Ethics Committee d) Patient has mental capacity and is willing and able to comply with protocol requirements e) Angiographic inclusion criteria (candidate must meet at least ONE of the following): • Patient has a wide-necked intracranial aneurysm defined as a neck length of ≥4 mm, or a dome to neck ratio of less than 2 • Patient has an aneurysm that has failed previous attempts at treatment as evidenced by aneurysm regrowth, coil compaction, or incomplete coiling	a) Unstable neurological deficit (condition worsening within the last 90 days) b) SAH within the last 60 days c) Irreversible bleeding disorder d) Platelet count <100 x 10^3 cells/mm^3 e) Inability to tolerate, adverse reaction or contraindication to taking aspirin or clopidogrel f) Contraindication to CT scan or MRI g) A history of contrast allergy that cannot be medically controlled h) Relative contraindication to angiography (e.g. serum creatinine >2.5 mg/dL) i) Woman with child-bearing potential who cannot provide a negative pregnancy test j) Evidence of active infection (fever with temperature >38°C and/or WBC >15,000) k) Other conditions of the heart, blood, brain or intracranial vessels that carry a high risk of neurological events l) Evidence of disease or condition expected to compromise survival or ability to complete follow-up assessments during the 180-day follow-up period m) Extracranial stenosis greater than 50% in the carotid artery for anterior circulation aneurysms or vertebral artery for posterior circulation aneurysms n) Intracranial stenosis greater than 50% in the treated vessel
PUFS	a) Age 21 to 75 years, inclusive b) Patient has a single large or giant target IA that: i) Is located in the following regions of the internal carotid artery: • Petrous • Cavernous • Paraophthalmic (including paraclinoid, ophthalmic and hypophyseal segments)	a) More than one IA requires treatment in the next 6 months b) Subarachnoid haemorrhage in the past 60 days c) Any intracranial haemorrhage in the last 42 days d) Major surgery in the last 42 days e) Unstable neurological deficit (i.e. any worsening of clinical condition in the last 30 days) f) History of irreversible bleeding disorder g) Platelet count <100 x 10^3 cells/mm^3 or known platelet dysfunction h) Inability to tolerate, documented evidence of adverse reactions or contraindication to study medications i) Stent in place at the target IA j) Contraindication to CT scan or MRI

Continued…

Study no. (acronym)	Inclusion criteria	Exclusion criteria
	ii) Has a neck >4 mm or no discernible neck AND a size (maximum fundus diameter) >10 mm iii) Has a parent vessel with diameter 2.5–5.0 mm distal/proximal to the target IA c) Patient has provided written informed consent using the IRB-approved consent form d) Patient has the necessary mental capacity to participate and is willing and able to comply with protocol requirements	k) Known allergy to contrast used in angiography that cannot be medically controlled l) Known severe allergy to platinum or cobalt/chromium alloys m) Relative contraindication to angiography (e.g. serum creatinine >2.5 mg/dL) n) Woman of child-bearing potential who cannot provide a negative pregnancy test o) Evidence of active infection at the time of treatment p) Other known conditions of the heart, blood, brain or intracranial vessels that carry a high risk of neurological events (e.g. severe heart failure, atrial fibrillation, known carotid stenosis) q) Current use of cocaine or other illicit substance r) Any comorbid disease or condition expected to compromise survival or ability to complete follow-up assessments to 180 days s) Extracranial stenosis greater than 50% in the carotid artery t) Intracranial stenosis greater than 50% in the treated vessel

CT, computed tomography; IA, intracranial aneurysm; IRB, institutional review board; MRA, magnetic resonance imaging; PITA, Pipeline™ for Intracranial Treatment of Aneurysms; PUFS, Pipeline™ for Uncoilable or Failed Aneurysms; SAH, subarachnoid haemorrhage

In terms of eligibility criteria, PITA differed from PUFS in the following ways:

- PITA patients did not necessarily have giant and wide-necked aneurysms and a carotid location was not required.
- PITA was primarily a safety and feasibility study, with inclusion and exclusion criteria that are similar but not identical to those of the pivotal PUFS study.
- The adjunctive use of coils was allowed in PITA but not in PUFS.

5.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups.

Since the studies were non-comparative, ‘differences between study groups’ is not relevant.

In general, there were few differences between the two studies. Of note is that in the PITA study there were a significant number of smaller aneurysms than in PUFS. In the PUFS trial aneurysm location was restricted to the internal carotid artery. Aneurysms were most common in the cavernous (41.7%) or paraophthalmic (32.4%) regions of the internal carotid artery. In the PITA study most aneurysms were in the ICA, but a small number were in the posterior circulation (vertebral artery or vertebrobasilar artery).

The greater number of female patients in both trials reflects the higher incidence of IAs in females than in males in the general population.

PITA patient characteristics

In total, 32 patients were enrolled in the PITA study between January 2007 and May 2007. Of these patients, one patient was removed from all analyses because a prior (and no longer manufactured) version of the PED was used, thus the study population is 31. The average age of patients is 54.6 years and the majority of patients were female (80.6%). The demographic characteristics of the patients are shown in Table B5.6.

The average size of the aneurysms treated was 11.5 mm. Nine aneurysms were large (29.0%) and 2 (6.5%) were giant. The characteristics of the target IAs are shown in Table B5.7.

In total, 47 PEDs were implanted. A single PED was placed in 18 (58.1%) procedures; two PEDs in 11 (35.5% of procedures); three PEDs in one procedure (3.2%) and four PEDs in one procedure (3.2%). Coils were used in 16 patients (51.6%) and a Neuroform® stent was used in one patient to form a bridge between the proximal end of the PED and the internal carotid artery, since the aneurysmal sac was larger than expected making a stent necessary. The entire neck of the target IA was covered by PED in 30 procedures (96.8%).

Table B5.6 Demographic characteristics of the patients in the PITA study (n=31)

Characteristics		**Value**
Female		25 (80.6%)
Mean age ± SD (range)		54.6 ± 9.3 (35–76) years
Mean height ± SD (range)		166 ± 8.4 (150–183) cm
Mean weight ± SD (range)		72.9 ± 13.8 (49–105) kg
Medical history	Stroke	4 (12.9%)
	Myocardial infarction	1 (3.2%)
	Diabetes	1 (3.2%)
Other significant illnesses		13 (41.9%)
Previous treatment of target intracranial aneurysm	Yes	12 (38.7%)
	No	19 (61.3%)
Previous treatment of intracranial aneurysm	Coil embolisation	13 (41.9%)
	Stent	6 (19.4%)
	Surgery	0
	Other	0

SD, standard deviation

Table B5.7 Characteristics of the target aneurysms in the PITA study (n=31)

Category		Value
Side affected	Left	13 (41.9%)
	Right	10 (32.3%)
	Not known	8 (25.8%)
Location of target aneurysm	Cavernous segment – ICA	5 (16.1%)
	Paraophthalmic segment – ICA	15 (48.4%)
	Superior hypophyseal segment – ICA	4 (12.9%)
	Posterior communicating segment – ICA	4 (12.9%)
	Proximal segment – MCA	1 (3.2%)
	Vertebral artery	1 (3.2%)
	Vertebrobasilar junction – vertebral artery/PICA	1 (3.2%)
Neck of aneurysm	<4 mm	9 (29.0%)
	≥4 mm	22 (71.0%)
Maximum aneurysm dimension*, average ± SD (min–max)		11.51 ± 7.52 (2.5–26.6) mm
Maximum aneurysm dimension*	<10 mm	20 (64.5%)
	10–25 mm	9 (29.0%)
	>25 mm	2 (6.5%)

*greater of width or height
ICA, internal carotid artery; MCA, middle cerebral artery; PICA, posterior inferior cerebellar artery; SD, standard deviation

PUFS patient characteristics

In total, 111 patients were included in the PUFS study between November 2008 and July 2009. Of these patients, three were withdrawn from the study before treatment (exclusion criteria, suspicion of cancer, scheduling issues) and were not included in the analyses.

Therefore, 108 patients were treated with PED. The average age of the patients was 57 years and the majority of patients were female (88.9%). The demographic characteristics of the patients are shown in Table B5.8.

The average size of the aneurysms treated was 18.2 mm. Eighty five intracranial aneurysms were large (78.7%) and 22 were giant (20.4%). The average neck width was 8.8 mm and the average size of the aneurysmal sac was 14.6 mm. The target IA characteristics are shown in Table B5.9.

In total, 341 PEDs were placed in the target IA. Two patients also had treatment with a total of 8 PEDs in a contralateral qualifying IA, thus the total number of PEDs implanted was 349. On average, 3.1 PEDs were used per IA (median 3, range 1–13). Note that the implantation of 13 PEDs in one particular patient (with a highly unusually configured aneurism) was atypical.

Table B5.8 Demographic characteristics of the patients included in the PUFS study (n=108)

Characteristics		Value
Mean age ± SD (min–max)		57 ± 11.3 (30.2–75.1) years
Females		96 (88.9%)
Race	White	99 (91.7%)
	Black	6 (5.6%)
	Not reported	3 (2.8%)
Medical history	Subarachnoid haemorrhage	8 (7.4%)
	Stroke	7 (6.5%)
	Coronary artery disease	6 (5.6%)
	Hypertension	60 (55.6%)
	Diabetes	7 (6.5%)
	Past history of cocaine use	1 (0.9%)
Smoker	Never	46 (42.6%)
	Current	31 (28.7%)
	Past history	31 (28.7%)
Endovascular infection		1 (0.9%)
Previous treatment of target aneurysm	Coil embolisation	6 (5.6%)
	Surgery	1 (0.9%)
	Other	1 (0.9%)

SD, standard deviation

Table B5.9 Target aneurysm characteristics in PUFS (n=108)

Characteristics		Value
Side affected	Left	57 (52.8%)
	Right	51 (47.2%)
Location of target aneurysm	Petrous segment	4 (3.7%)
	Cavernous segment	45 (41.7%)
	Carotid cave	2 (1.9%)
	Superior hypophyseal segment	10 (9.3%)
	Lateral clinoidal segment	2 (1.9%)
	Paraophthalmic segment	35 (32.4%)
	Supraclinoid segment	9 (8.3%)
	Posterior communicating segment	1 (0.9%)*

Continued…

Characteristics		Value
Max size fundus diameter, mean ± SD (range)		18.2 ± 6.4 (6.2–36.1) mm
	Small aneurysm (<10 mm)	1 (0.9%)†
	Large aneurysm (10–25 mm)	85 (78.7%)
	Giant aneurysm (>25 mm)	22 (20.4%)
Neck of aneurysm, mean ± SD (range)		8.8 ± 4.3 (4.1–36.1) mm
Dome, mean ± SD (range)		14.6 ± 5.5 (4.4–29.5) mm
Dome/neck ratio, mean ± SD (range)		1.8 ± 0.6 (0.6–4.1)
Partially thrombosed target aneurysm		17 (15.7%)

*This non-qualifying aneurysm was excluded from the effectiveness analysis
†This small aneurysm was excluded from the effectiveness analysis

Outcomes

5.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the study protocol as primary or secondary, and whether they are relevant with reference to the decision problem. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one study.

It is important to note that an initial structured literature review was carried out to determine realistic safety and efficacy endpoints for the PUFS study (see following box for details).

Structured literature review used to support the objective performance criteria in PUFS

Justification for effectiveness success threshold. The manufacturers performed a comprehensive literature review of the effectiveness and safety of surgical and endovascular approaches to large and giant aneurysm treatment. This was used to determine the safety and effectiveness success thresholds for PED performance in the PUFS trial.

The review, which summarised 250 published clinical cohorts, showed that effectiveness of coil embolisation - the current treatment standard for large/giant IAs - was poor with long-term effectiveness rates substantially less than 50%. The long-term complete occlusion rate for large and giant IAs treated with surgical or endovascular approaches was <30%. Thus, a 6-month complete occlusion rate statistically exceeding 50% represents a marked advance for these patients.

Justification for safety success threshold. The sample comprehensive literature review also examined the safety of surgical and endovascular approaches to IA treatment. The review showed a 10-15% risk of stroke from large/giant IA treatment, and the risk of perioperative neurological death was in the same range.

It should be noted that **most studies reported only perioperative outcomes**; very few reported morbidity and mortality through to 6 months after treatment. Moreover, most published studies have poor rates of long-term follow-up and use vague measures of occlusion effectiveness. Therefore, a procedure with an associated long-term stroke/neurological death rate with an upper confidence limit of <20% would represent a treatment that, in the setting of a high rate of complete occlusion, would be seen as having a positive benefit-risk balance for the target patient population.

Table B5.10 provides details of the primary and secondary outcomes of the studies. Table B5.11 provides details of other additional outcomes.

Table B5.10 Primary and secondary outcomes of the studies

	Primary outcome(s) and measures	**Reliability/validity/ current use in clinical practice**	**Secondary outcome(s) and measures**	**Reliability/validity/ current use in clinical practice**
PITA efficacy	Device placement success	Feasibility of delivering device to the target area and functioning correctly	Device deployment success	Feasibility of investigator being able to pass a PED through the guide catheter and release it into the target site

Continued…

	Primary outcome(s) and measures	**Reliability/validity/ current use in clinical practice**	**Secondary outcome(s) and measures**	**Reliability/validity/ current use in clinical practice**
PITA safety	Death and ipsilateral stroke at 30-days after post-implantation	The primary risks of either surgery or endovascular approaches: – stroke resulting from ischaemia or stenosis – intracranial bleeding resulting from aneurysm rupture or procedure-related perforation	Clinical procedure success	Indicates if the device can be delivered successfully without in-hospital neurological death or ipsilateral stroke
PUFS efficacy	Complete angiographic occlusion of the target IA at 180 days with PED in the absence of >50% stenosis or the use of other devices (e.g. coils) in the target aneurysm IA occlusion and parent artery stenosis were judged by an independent radiology committee on 180-day angiography Considered successful if the percentage of patients is statistically >50%	Studies with conventional interventions† show that incomplete IA occlusion increases the risk of rupture and retreatment. Therefore, PUFS was designed with a “high bar” for effectiveness, namely complete occlusion of the target IA in the absence of newly developed stenosis	– Complete occlusion at 1, 3 and 5 years (3 and 5 year results not yet available) – Changes in the modified Rankin scale ≥2 points at 180 days compared to the start of the study (assessment of the state of dependence) – Changes in neurological symptoms linked to the aneurysm at 180 days compared to the start of the study	In contrast to most literature reports, PUFS focused on long-term effectiveness and used an unequivocal effectiveness measure (complete occlusion)

Continued…

	Primary outcome(s) and measures	**Reliability/validity/ current use in clinical practice**	**Secondary outcome(s) and measures**	**Reliability/validity/ current use in clinical practice**
PUFS safety	Proportion of patients who experienced either death due to neurological reasons or major ipsilateral stroke* by 180 days after the last IA treatment procedure Considered as successful if the percentage of patients is <20%	The primary risks of either surgery or endovascular approaches are: – stroke resulting from ischaemia or stenosis – intracranial bleeding resulting from aneurysm rupture or procedure-related perforation Therefore, meeting the primary safety endpoint in PUFS included: – any major ipsilateral stroke or neurological death occurring within 180 days of device placement (Note: when comparing stroke rates, most published studies of available therapies† report only perioperative strokes)	– Incidence of major ipsilateral stroke at 180 days (a component of the primary safety endpoint) – Incidence of adverse events associated with the device at 180 days, 1, 3 and 5 years	In contrast to most literature reports, PUFS focused on long-term safety, i.e. the cumulative rate of major ipsilateral stroke or death by 180 days

*Major stroke was defined as a stroke present after 7 days that increases the NIH Stroke Scale score by at least 4 points. Whether an adverse event met the definition for the primary safety endpoint was adjudicated by an independent clinical events committee (CEC).

†Results from the comprehensive, structured review of literature on the effectiveness and safety of surgical and endovascular approaches to large and giant aneurysm treatment.

Table B5.11 Other additional outcomes of the studies

	PITA	PUFS
Additional outcome measures	– Occlusion of the aneurysm at 180 days post-implantation – Incidence of new neurological deficits – Neurological assessment – Rate of neurological and non-neurological complications – Distal migration of the device – Stenosis with PED	– Change in various eye function tests at 180 days. (These were performed because large/giant aneurysms in the internal carotid artery often cause mass effect on local cranial nerves that mediate eye function) – Distal migration of PED – Stenosis within PED – Technical success – IA occlusion ranking at 180 days – Complete occlusion rate including salvage treatment – Incidence of neurological death by 180 days – Change in mean deviation index (MDI) of the visual field examination at 180 days – Frequency of worsened eye alignment by clinical examination by the ophthalmologist – Frequency of >2 lines lost in visual acuity by Snellen chart – Frequency of >2 lines gained in visual acuity by Snellen chart – Incidence of secondary treatments for the target IA

Statistical analysis and definition of study groups

5.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew. The following table provides a suggested format for presenting the statistical analyses in the studies when there is more than one study.

The study hypotheses and an outline of the statistical analyses for PITA and PUFS are provided in Table B5.12.

Table B5.12 Summary of statistical analyses in studies

Study acronym	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
PITA	The primary endpoint, device placement success should be achieved in at least 80% of device placement attempts and death and ipsilateral stroke should not exceed 10%	Sample size was sufficient to draw initial conclusions regarding the safety and effectiveness of PED placement for patients with complex IAs Confidence intervals for continuous outcomes were calculated using standard methods	Feasibility study, therefore not powered for analysis	Of the 32 patients taking part, one was not analysed as a prior (not currently manufactured) version of the device was used instead. Data from 31 patients were analysed
PUFS	The statistical goal of the study was to show that: – the rate of complete occlusion of the target IA without stenosis of the parent artery on 180-day angiography is at least 50% – the rate of neurological death or major ipsilateral stroke by 180 days is at most 20% Major stroke was defined as a stroke present after 7 days that increased the NIH Stroke Scale score by at least 4 points	Used a Bayesian approach to statistical analysis and interpretation of clinical trial success for primary endpoints. The study was interpreted as a success if the following two conditions were met: Pr(pE >0.50 | Trial Data) >0.975 AND Pr(pS <0.20 | Trial Data) >0.975 i.e. the posterior probability that: – effectiveness rate (pE) exceeds 50% given trial data is at least 0.975 – the safety rate (pS) is less than 20% given trial data is at least 0.975 A non-informative beta (1,1) prior distribution was used for both calculations. The 0.975 probability values are analogous to one-sided p-values of 0.025. The approach carefully preserved overall Type 1 error rate.	A power analysis prior to study initiation showed that a sample size of 100 patients had a high chance of showing study success given the then current knowledge of safety and efficacy	In total, 111 patients were enrolled in the study Of these, 3 were withdrawn before treatment (exclusion criteria, suspicion of cancer, scheduling issues) Data from108 patients were analysed

5.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

There was no relevant subgroup analysis in the PITA study.

The PUFS study protocol included four pre-planned subgroup analyses of the primary effectiveness and safety endpoints for the following subgroups:

- IA maximum dimension ≥25 mm vs. <25 mm.
- IA neck size ≥6 mm vs. <6 mm.
- IA partially thrombosed at baseline or not.
- Current/former smoker vs. never smoker.

These subgroups were selected because they were known to be predictive of long-term success in patients treated with coil embolisation. Fisher's exact test was used to compare proportions reaching the primary effectiveness or safety endpoints for each subgroup. Adjustment for multiplicity was performed using the Holm step-down procedure (63). No subgroup analysis showed statistically significant differences.

Participant flow

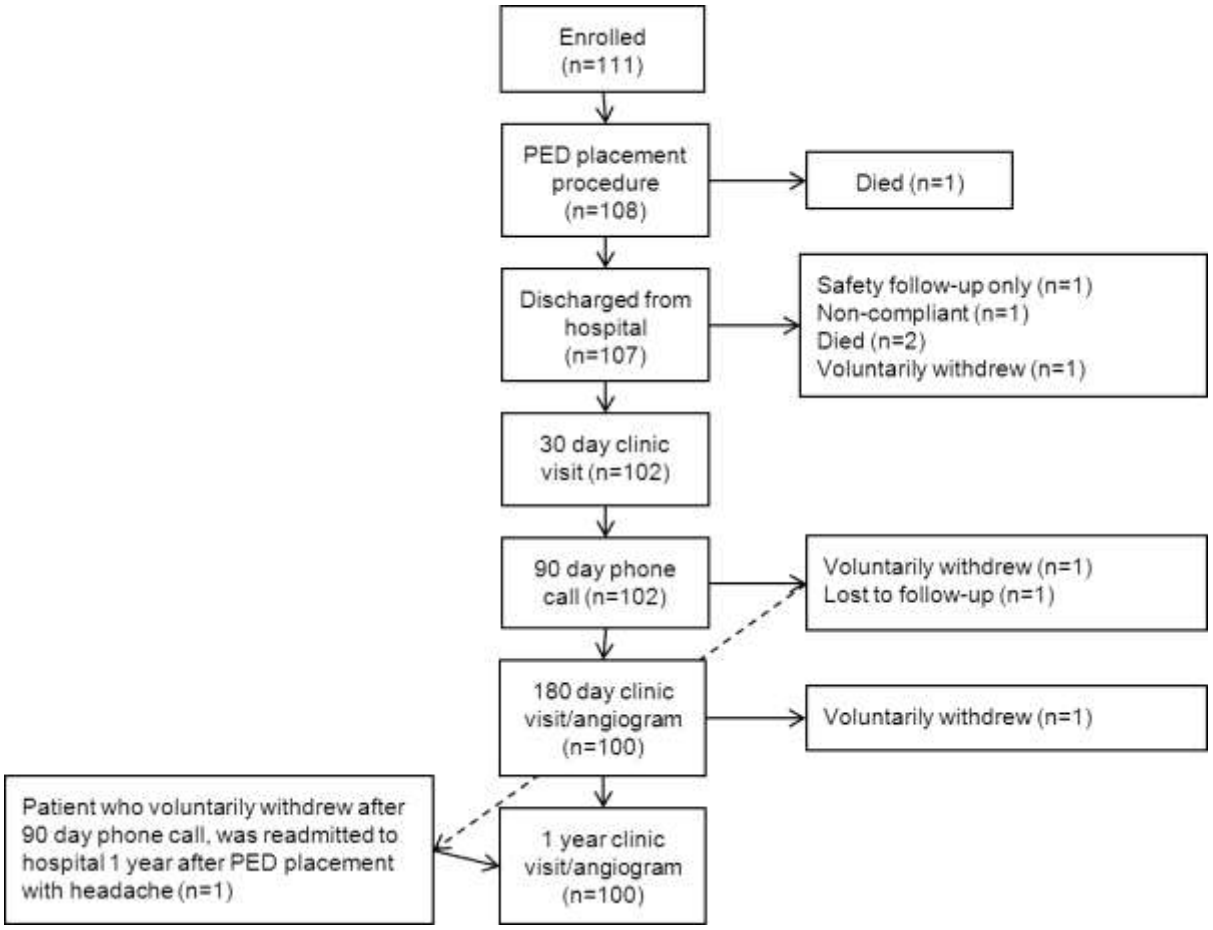
Where applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who were lost to follow-up or withdrew from the study.

Details for PITA and PUFS – regarding the numbers of patients who were eligible to enter, and who were randomised, and allocated to each treatment – is not applicable.

No patients were lost to follow up or withdrew from PITA.

For PUFS, patient losses to follow-up and withdrawal were minimal (see Figure B5.2). The number of patients available for post-procedure outcomes are described in Table B5.13.

Figure B5.2 Participant flow in PUFS



PED, Pipeline™ embolisation device

Note that:

- One patient refused to attend the 30-day visit and subsequently withdrew from the study (non-compliant). Informal contact with the patient by the study investigator showed that the patient is currently doing well. She had normal neurological status at last telephone contact.
- One patient voluntarily withdrew from the study at approximately Day 30. She had two ‘house calls’ from a study site physician primarily to assess safety outcomes. She had stroke associated with thrombosis of the parent artery, likely due to non-compliance with antiplatelet medication.
- One patient’s parent artery could not be catheterised distal to the target IA; this patient did not undergo PED placement but rather underwent repacking of the IA with coils. (Interestingly, coil embolisation caused a serious adverse event, confusion and hydrocephalus, which resolved after lumbar puncture.) This patient was therefore excluded from the efficacy and safety evaluation.

Table B5.13 Number of patients in PUFS who underwent post-procedure assessments

Assessment	Number of patients	Number of IAs
Enrolled and underwent PED placement procedure • Two patients received bilateral IA treatment	108	110
Safety cohort • PED treatment was aborted in one patient who was excluded from the efficacy and safety cohort	107	109
Efficacy cohort • In three patients the IA did not meet the eligibility criteria (in two cases the location of the IA was incorrect; in one case the size of the IA was too small). These patients are excluded from the efficacy cohort	104	106
180 day efficacy assessment (out of 104 patients, 106 IAs)		
Angiography • 3 patients died prior to Day 180 • 4 withdrew/lost to follow-up/refused the angiogram	97	99
Neurological examination • 3 patients died prior to Day 180 • 1 patient's eye assessment was incomplete thus excluded from analysis	100	102
Ophthalmological examination	89	91
180 day safety assessment (out of 107 patients, 109 IAs)		
Modified Rankin Scale was carried out for 101 patients at Day 180 • 3 patients died (and were assigned a Rankin score of 6) • 3 patients withdrew from the study (and scores were recorded as 'not defined')	101	103
1 year efficacy assessment (out of 104 patients, 106 IAs)		
Angiography • 3 patients died prior to Day 180 • 4 withdrew/lost to follow-up/refused the angiogram • 2 had insurance difficulties preventing obtaining a 1 year angiogram • 2 had carotid occlusion at 180 days (1 year angiogram is not indicated in these cases) • 4 refused the 1 year angiogram • 1 patient who refused the angiogram at Day 180, agreed to the procedure at 1 year. Therefore of the 97 patients who had an angiogram at Day 180, 89 had an angiogram at 1 year	89	91

5.4 Critical appraisal of relevant studies

5.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should

therefore be critically appraised. Whenever possible, the criteria for assessing published studies should also be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the External Assessment Group.

5.4.2 Please provide as an appendix a complete quality assessment for each study. See section 7.3, appendix 3 for a suggested format. For the quality assessments use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd).

5.5 Results of the relevant studies

5.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. If there is more than one study, tabulate the responses

5.5.2 For each outcome for each included study, the following information should be provided.

The unit of measurement.
The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.
A 95% confidence interval.
Number of participants in each group included in each analysis and whether the analysis was by 'intention to treat'. State the results in absolute numbers when feasible.

When interim study data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that study. Analytical adjustments should be described to cater for the interim nature of the data.

Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.

Discuss and justify definitions of any clinically important differences.

Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.

The results for PITA and PUFS are provided in Table B5.14.

Table B5.14 Results of PITA and PUFS

Study acronym	Outcome	Results
PITA	**Primary outcomes**	
	Device-placement success, defined as the deployment and placement at the target site	A total of 47 PEDs were placed in 31 IAs. They were successfully positioned in 97.9% (95% CI: 88.7–99.9%) of cases (46/47 PED devices). In one case, a PED was successfully delivered to the location, but placement was judged as failed due to slow flow in the ICA
	Incidence of death and ipsilateral stroke at 30 days post-procedure	There were no deaths at PED placement or during 30 days post-implantation follow-up. Two patients (6.5%; 95% CI: 0.8–21.4%) had an ipsilateral stroke within 30 days: • In one patient, the stroke caused right-sided hemiparesis and motor aphasia immediately upon awakening. These consequences were resolved and the stroke was thought to be possibly linked to PED and/or the placement procedure • In the second patient, the stroke was caused by iatrogenic rupture of the supraclinoid carotid artery. PED and the coils had to be removed. The patient underwent rehabilitation therapy and remained hospitalised at the time of the 30 day follow-up. The stroke was considered likely to be a result of the placement procedure rather than PED itself

Continued…

Study acronym	Outcome	Results
PITA (cont.)	**Secondary outcomes**	
	Device-deployment success, defined as the introduction of PED through the guide catheter and its release	PED was successfully deployed in 87% (95% CI: 75.1–94.6%) of cases (47/54 deployments). In 6 cases (5 patients) the physician was unable to insert the delivery wire all the way through the microcatheter. In one additional case, the position of the delivery wire was unfavourable and as a result the device was removed. In all of these patients, subsequent deployment of PED was successful (Note that the problems with PEDs, resulting in non-deployment in 13% of cases in PITA, were identified and resolved before PEDs were used subsequently)
	Clinical procedure success, defined as the successful delivery of the device without death or ipsilateral stroke	The implantation procedure was successful for 29 of 31 patients (93.5%; 95% CI: 78.6–99.2%). The two failures were a result of strokes
	Additional outcome measures	
	Occlusion of the aneurysm at 180 days post-implantation	A total of 28/30 patients (93.3%; 95% CI: 77.9–99.2%) had complete occlusion of the target aneurysm at 180 days. It was not possible to assess occlusion in one patient who had an arterial ligation
	Incidence of new neurological deficits	Excluding the two incidences of stroke, no other patients reported any new neurological deficits during follow-up
	Neurological assessment	Excluding the two strokes, there was no deterioration in neurological status. At 30 days, 3/31 patients (9.7%) (one of whom previously had a stroke) experienced an improvement in their IA-related symptoms

Continued…

<table>
<tr><th>Study acronym</th><th>Outcome</th><th>Results</th></tr>
<tr><td rowspan="6">PITA (cont.)</td><td colspan="2">Additional outcome measures (cont.)</td></tr>
<tr><td>Rate of neurological and non-neurological complications</td><td>A total of 18 AEs were reported in nine patients (see Table below). Sixteen of the 18 events were not related to the study device. One patient had bleeding at the puncture site in the groin. Two patients experienced allergic reactions to medications and/or contrast medium. Six additional patients had other events, none of which were device related. No patient experience significant bleeding with use of aspirin and clopidogrel
<table>
<tr><th rowspan="2">Category</th><th rowspan="2">Number of occurrences</th><th rowspan="2">Number of patients (%) n=31</th><th colspan="3">Time of occurrence</th></tr>
<tr><th>Procedure-discharge</th><th>1–30 days</th><th>1–6 months</th></tr>
<tr><td>Headache</td><td>3</td><td>3 (9.7%)</td><td>3</td><td>0</td><td>0</td></tr>
<tr><td>Allergic reaction</td><td>2</td><td>2 (6.5%)</td><td>2</td><td>0</td><td>0</td></tr>
<tr><td>Stroke</td><td>2</td><td>2 (6.5%)</td><td>2</td><td>0</td><td>0</td></tr>
<tr><td>Vomiting</td><td>2</td><td>2 (6.5%)</td><td>2</td><td>0</td><td>0</td></tr>
<tr><td>Back pain</td><td>1</td><td>1 (3.2%)</td><td>1</td><td>0</td><td>0</td></tr>
<tr><td>Dizziness</td><td>1</td><td>1 (3.2%)</td><td>1</td><td>0</td><td>0</td></tr>
<tr><td>Fever</td><td>1</td><td>1 (3.2%)</td><td>1</td><td>0</td><td>0</td></tr>
<tr><td>Hair loss</td><td>1</td><td>1 (3.2%)</td><td>0</td><td>1</td><td>0</td></tr>
<tr><td>Hypertension</td><td>1</td><td>1 (3.2%)</td><td>1</td><td>0</td><td>0</td></tr>
<tr><td>Hypotension</td><td>1</td><td>1 (3.2%)</td><td>1</td><td>0</td><td>0</td></tr>
<tr><td>Nausea</td><td>1</td><td>1 (3.2%)</td><td>1</td><td>0</td><td>0</td></tr>
<tr><td>Postural pain</td><td>1</td><td>1 (3.2%)</td><td>1</td><td>0</td><td>0</td></tr>
<tr><td>Puncture site injury</td><td>1</td><td>1 (3.2%)</td><td>1</td><td>0</td><td>0</td></tr>
<tr><td>Total</td><td></td><td>18</td><td>17</td><td>1</td><td>0</td></tr>
</table></td></tr>
<tr><td>Distal device migration</td><td>No distal migration of the device was observed in 29 patients. The assessment was not possible for two patients (one due to insufficient imaging and one patient did not undergo the radiographic examination because the PED had been removed)</td></tr>
<tr><td>Stenosis</td><td>For 28/30 patients (93%; 95% CI: 77.9–99.2%) stenosis was judged as not significant (<25%). Stenosis in one patient was considered mild (26–50%) and for the final patient, assessment was not possible because of interference from the presence of coils</td></tr>
<tr><td colspan="2">Post study follow-up (2 years)</td></tr>
<tr><td>Occlusion of the aneurysm at 2-year follow-up</td><td>All patients who had complete occlusion at 180 days also had complete occlusion at 2 years as assessed by either catheter angiography or MRI. In addition, one patient who was incompletely occluded at 180 days progressed to complete occlusion</td></tr>
</table>

Continued…

Study acronym	Outcome	Results
PUFS	**Primary outcomes**	
	Efficacy: percentage of patients with complete occlusion of the target IA at 180 days and ≤50% stenosis in the parent vessel, without using any other devices in the IA; considered as successful if the percentage of patients is >50%	Effectiveness (complete occlusion and absence of stenosis >50% at 180 days) was achieved in 78 of the 106 aneurysms treated (73.6%; posterior credible interval: 64.4–81.0%) For 28 aneurysms, effectiveness was not achieved: • 7 patients/IAs did not receive an angiogram • 8 aneurysms had a residual IA neck • 6 aneurysms had a residual aneurysm • 3 aneurysms had occlusion of the parent vessel • 2 aneurysms were completely occluded but patients presented with >50% parent vessel stenosis • 1 aneurysm was completed occluded but coils had been inserted into the target IA fundus (did not meet study's success criteria) • 1 patient had a carotid-cavernous fistula The posterior probability that the primary effectiveness endpoint exceeded 50%, the pre-determined success threshold, was 0.999999. This probability value exceeds the pre-determined success probability of 0.975 and is therefore considered statistically significant. (An analogous one-sided p-value vs. the 50% null hypothesis was p<0.0001) There was no significant site treatment effect for the primary effectiveness endpoint across site (exact chi-squared p-value 0.8287). Inter-rater reliability of core laboratory assessments of IA occlusion was excellent with kappa values of 0.7732, 0.6038 and 0.8019, respectively, amongst the 3 core laboratory radiologists In the protocol, a subgroup analysis for the primary efficacy criteria had been specified, according to the size of the aneurysm, the size of the neck, partial or complete embolisation of the aneurysm and smoking status. All subgroup analyses showed no association between subgroup membership and the rate of complete occlusion of the target aneurysm

Continued…

Study acronym	Outcome	Results
PUFS (cont.)	**Primary outcomes (cont.)**	
	Safety: percentage of patients in whom the incidence of major ipsilateral stroke or death was observed in the 180 days following the procedure; considered as successful if the percentage of patients is <20%	Of the 108 patients enrolled and treated, one patient was excluded from the safety analysis because the clinician was unable to insert the micro-catheter. Consequently, PED treatment had to be aborted and the patient was retreated with coils The primary safety endpoint (ipsilateral major stroke or neurological death as judged by the clinical events committee) occurred in 6 patients (5.6%, 95% posterior credible interval: 2.6–11.7%). The posterior probability that the major safety endpoint rate was less than 20% (the predetermined safety success threshold) was 0.999979. This probability value exceeds the pre-study probability threshold of 0.975 and is therefore considered statistically significant. (An analogous one-sided p-value vs. the 20% null hypothesis was p<0.0001) Out of 107 patients analysed, the primary criteria regarding safety observed in 6 patients included: • 3 ischaemic events • 2 haemorrhagic events • 1 event of unknown cause Three patients died as a result of the adverse events, as described below: • Of the three patients experiencing an ischaemic event, one did not follow the antiplatelet treatment, another had stenosis in both the target aneurysm's parent vessel and in a contralateral vessel treated with stent-assisted coiling, indicating a possible predisposition to intimal hyperplasia. The third patient had suspected non-response to the antithrombotic treatment, leading to an ipsilateral stroke which brought about the patient's death • Out of the two haemorrhagic patients, one underwent a prolonged procedure due to the complexity of the vessels and was given antithrombotic treatment probably causing the haemorrhage, and the other patient presented with multiple haemorrhagic risk factors. • For the event with an unknown cause, the patient had a medical history of cardiomyopathy Three of these six events were considered as being probably or definitely linked to PED

Continued…

Study acronym	Outcome	Results
PUFS (cont.)	**Secondary outcomes**	
	Complete occlusion at 1, 3 and 5 years (3 and 5 year results not available)	One-year follow-up data is complete One-year angiography was performed in 89 patients (91 IAs), see Table B5.13 for details. Among these patients: • Complete occlusion was seen in 78 IAs (85.7%) • Residual neck was seen in 5 IAs (5.5%) • Residual aneurysm was seen in 5 IAs (5.5%) • Other, in 3 IAs (3.3%) Of the 104 patients (106 IAs) in the efficacy cohort, effectiveness success (complete IA occlusion without major stenosis) was seen in 75 IAs (70.8%) at 1 year Of the 71 patients with complete occlusion at 180 days and who also had an angiogram at 1 year, 1-year angiography showed continued complete occlusion in 69 (97%) Using a Bayesian approach to assess outcomes among the 9 patients who had not have an angiogram at 1 year but did at 180 days and taking into account known failures: • The 1-year predicted complete occlusion rate was 80.7% (95% posterior credible interval 72.7–87.7%) • The 1-year predicted effectiveness rate was 78.0% (95% CI 69.5–85.3%) The Bayesian posterior probabilities that the 1-year complete occlusion and effectiveness rates exceeded 50% were >0.999999
	Incidence of major ipsilateral stroke at 180 days	Out of the 107 patients assessed, 6 (5.6%, 95% CI 2.6–11.7%) had a major ipsilateral stroke at 180 days, as adjudicated by the CEC. To date, there have been no additional major stokes

Continued…

<table>
<tr><th>Study acronym</th><th>Outcome</th><th>Results</th></tr>
<tr><td rowspan="3">PUFS (cont.)</td><td colspan="2">Secondary outcomes (cont.)</td></tr>
<tr><td>Changes in the modified Rankin scale ≥2 points at 180 days compared to the start of the study (assessment of the state of dependence)</td><td>At 180 days, assessment of the modified Rankin score (a general measure of neurological functions) was carried out for 101 patients (3 patients did not continue with the study and 3 patients died). A Rankin score of 6 was assigned for the deceased patients at 180 days

The Rankin score improved at 180 days for 21 patients (19.6%), remained the same for 70 patients (65.4%) and deteriorated for 10 patients (9.3%; grey boxes in Table below) and could not be assessed for 6 patients (5.6%). 94 patients (87.9%) had a Rankin score of 1 or 0 at 180 days. The main reasons for deterioration in the scores were the death of 3 patients, headaches in 2 patients, secondary effects of stroke in 2 patients, diplopia in 1 patient and hearing problems in 1 patient. Three of these cases were rated as probably or definitely PED-related

<table>
<tr><th colspan="2" rowspan="2">Frequency</th><th colspan="8">Rankin score at 180 days</th></tr>
<tr><th>Not defined</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="7">Score at baseline</td><td>Not defined</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>
*Patients withdrew from study</td></tr>
<tr><td>Changes in neurological symptoms linked to the aneurysm at 180 days compared with baseline</td><td>Analysis of change from baseline in neurological signs/symptoms related to the target IA involved 100 of the 108 patients undergoing attempted PED placement (see Table)

<table>
<tr><th>Changes</th><th>Nº (%)</th></tr>
<tr><td>Normal at baseline and follow-up, no symptoms</td><td>24 (24%)</td></tr>
<tr><td>Improvement</td><td>31 (31%)</td></tr>
<tr><td>Improvement but not linked to aneurysm treatment</td><td>3 (3%)</td></tr>
<tr><td>Probable improvement</td><td>5 (5%)</td></tr>
<tr><td>Mixed</td><td>9 (9%)</td></tr>
<tr><td>No change</td><td>19 (19%)</td></tr>
<tr><td>Not clearly specified</td><td>1 (1%)</td></tr>
<tr><td>Deterioration</td><td>6 (6%)</td></tr>
<tr><td>Deterioration but probably not linked to aneurysm treatment</td><td>2 (2%)</td></tr>
<tr><td>Total</td><td>100 (100%)</td></tr>
</table></td></tr>
</table>

Continued…

<table>
<tr><th>Study acronym</th><th>Outcome</th><th>Results</th></tr>
<tr><td rowspan="5">PUFS (cont.)</td><td colspan="2">Secondary outcomes (cont.)</td></tr>
<tr><td>Incidence of AEs associated with the device at 180 days, 1, 3 and 5 years</td><td>180 days and 1-year follow-up data is complete

At 1 year, 21 adverse events (19.6%) were observed (15 SAEs [14%] and 6 non-SAEs [5.6%]) which were considered as probably or definitively linked to PED treatment (see Table). 18 events occurred prior to Day 180, and a further 3 events occurred between Day 180 and 1 year
<table>
<tr><th colspan="2"></th><th colspan="2">Relatedness</th></tr>
<tr><th>SAE</th><th>Event</th><th>Probably</th><th>Definitely</th></tr>
<tr><td rowspan="3">No</td><td>Headache</td><td>4</td><td>0</td></tr>
<tr><td>Diplopia</td><td>1</td><td>0</td></tr>
<tr><td>Nausea</td><td>1</td><td>0</td></tr>
<tr><td rowspan="6">Yes</td><td>Amaurosis fugax</td><td>5</td><td>0</td></tr>
<tr><td>Carotid cavernous fistula</td><td>1</td><td>0</td></tr>
<tr><td>Carotid occlusion</td><td>1</td><td>0</td></tr>
<tr><td>Diplopia</td><td>0</td><td>1</td></tr>
<tr><td>Headache</td><td>1</td><td>2</td></tr>
<tr><td>Ischaemic stroke</td><td>1</td><td>3</td></tr>
<tr><td colspan="2">Total</td><td>15</td><td>6</td></tr>
</table></td></tr>
<tr><td colspan="2">Additional outcome measures</td></tr>
<tr><td>Change in mean deviation index (MDI)* at 180 days</td><td>At 180 days, 101 patients had an eye examination. Visual field sensitivity improved in 19 patients from the start of the study. 65 patients did not observe any changes and 5 patients saw their eye function deteriorate
<table>
<tr><th>Side of aneurysm</th><th>Improvement</th><th>No change</th><th>Deterioration</th><th>Test not performed</th><th>Total</th></tr>
<tr><td>Right</td><td>9</td><td>33</td><td>2</td><td>6</td><td>50</td></tr>
<tr><td>Left</td><td>10</td><td>32</td><td>3</td><td>6</td><td>51</td></tr>
<tr><td>Total</td><td>19 (21.3%)</td><td>65 (73.0%)</td><td>5 (5.6%)</td><td>12</td><td>101</td></tr>
</table></td></tr>
<tr><td>Distal migration of PED</td><td>Migration is defined as movement of more than 5 mm of one or several PEDs in the parent vessel as per the angiography at 180 days compared with that of post-placement of PED

Angiography revealed no observable migration in 99 IAs viewed</td></tr>
<tr><td>Stenosis with PED at 180 days</td><td>In total, 97/99 IAs in patients who had an angiogram, had either mild (<25%) or moderate (25–<50%) stenosis at the level of the PED. One of the 2 patients with >50% stenosis was not symptomatic. The other had a major ipsilateral stroke</td></tr>
</table>

Continued…

<table>
<tr><th>Study acronym</th><th>Outcome</th><th>Results</th></tr>
<tr><td rowspan="8">PUFS (cont.)</td><td colspan="2">Additional outcome measures (cont.)</td></tr>
<tr><td>Technical success</td><td>Technical success, as defined by the study protocol, was achieved in 100% of patients</td></tr>
<tr><td>IA occlusion ranking at 180 days</td><td>At 180 days, out of 99 IAs, IA occlusion was ranked as:
– Complete occlusion: 81 (81.8%)
– Residual neck: 8 (8.1%)
– Residual aneurysm: 6 (6.1%)
– Other: 4 (4.0%)</td></tr>
<tr><td>Complete occlusion rate including salvage treatment</td><td>Complete occlusion rate, including salvage treatment was 73.6%</td></tr>
<tr><td>Incidence of neurological death by 180 days</td><td>Three patients out of 107 patients (2.8%) had neurological death by 180 days</td></tr>
<tr><td>Change in mean deviation index (MDI)* of the visual field examination at 180 days</td><td><table><tr><th>Change</th><th>N (%)</th></tr><tr><td>Improved</td><td>19 (21.3%)</td></tr><tr><td>Same</td><td>65 (73.0%)</td></tr><tr><td>Worsened</td><td>5 (5.6%)</td></tr></table>In 4 of the 5 patients who showed worsening of visual fields, test reliability was low, making interpretation of worsening difficult; in addition, some patients had apparent worsening of pre-existing eye diseases (glaucoma, cataracts). In 1 case, worsened MDI was due to cilioretinal artery embolism</td></tr>
<tr><td>Frequency of worsened eye alignment by clinical examination by the ophthalmologist</td><td>Not analysed</td></tr>
<tr><td>Frequency of >2 lines lost in visual acuity by Snellen chart</td><td>Five of 91 patients (5.5%) had >2 lines lost in visual acuity by Snellen chart</td></tr>
</table>

Continued…

Study acronym	Outcome	Results
PUFS (cont.)	**Additional outcome measures (cont.)**	
	Frequency of >2 lines gained in visual acuity by Snellen chart	Eight of 91 patients (8.8%) had >2 lines gained in visual acuity by Snellen chart
	Incidence of secondary treatments for the target IA	There were no secondary treatments for the target IA

*MDI is a measure of visual field. MDI is reduced in patients with optic neuropathy resulting from aneurysm-related mass effect or retinal problems.

5.6 Meta-analysis and evidence synthesis

5.6.1 Describe the technique used for meta-analysis and/or evidence synthesis, the steps undertaken and results of the analysis including methodology. For example, when direct comparative evidence is not available, indirect treatment comparison methods can be used. The following descriptions should be included if indirect or mixed treatment comparisons are undertaken.

Identification, selection, methodology and quality assessment of relevant studies

Summary of the studies used to conduct the indirect comparison. For the selected studies, provide a summary of the data used in the analysis.

Indirect/mixed treatment comparison methodology.

Results of the analysis.

The statistical assessment of heterogeneity and any **sensitivity analyses**

Not applicable

5.6.2 If evidence synthesis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

Not applicable

5.7 Adverse events

5.7.1 If any of the main studies are designed primarily to assess safety outcomes, please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection, methodology and quality of the studies, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each study should be provided in sections 7.4 and 7.5, appendices 4 and 5.

The searches as described in section 5.1 were devised to identify clinical studies regarding the use of PED for cerebral aneurysm. Study design search filters were not included in the strategies so that RCTs and non-RCTs studies would be identified from the searches. As no study design filters were used the searches also identified studies with adverse events data. Full details of the search strategies, databases and resources searched are provided in appendix 2, section 7.2. All the relevant information has been included in section 5.1–5.5.

5.7.2 Please provide details of all important adverse events. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

Adverse events in PITA

In total, 18 adverse events were reported by 9 patients. Among these events, 16 were not considered to be linked with the PED. The most common events were headaches, allergic

reactions, strokes and vomiting, which were considered to be possibly or probably linked with the procedure.

One patient reported bleeding at the puncture site. Two patients had allergic reactions linked to the medication used or the contrast medium. No patients experienced any significant bleeding linked to taking aspirin and clopidogrel.

The two strokes were characterised as severe. No other patient experienced any new neurological deficits during the follow-up.

The adverse events observed during the study are shown in Table B5.15.

Table B5.15 Adverse events during PITA classified by MedDRA body system and term (n=31)

MedDRA category	MedDRA term	Number of patients (%)
Headaches NEC	Headache	3 (9.7%)
Allergic conditions NEC	Immediate post-injection reaction	2 (6.5%)
Central nervous system haemorrhages and cerebrovascular accidents	Ischaemic stroke	2 (6.5%)
Nausea and vomiting	Procedural vomiting	2 (6.5%)
Musculoskeletal and connective tissue pain and discomfort	Back pain	1 (3.2%)
Neurological signs and symptoms NEC	Dizziness	1 (3.2%)
Disorder characterised by fever	Postoperative fever	1 (3.2%)
Alopecias	Application site alopecia	1 (3.2%)
Vascular hypertensive disorders NEC	Procedural hypertension	1 (3.2%)
Vascular hypotensive disorders	Procedural hypotension	1 (3.2%)
Nausea and vomiting	Procedural nausea	1 (3.2%)
Pain and discomfort NEC	Discomfort	1 (3.2%)
Haemorrhages NEC	Vessel puncture site haemorrhage	1 (3.2%)
Total		**18**

MedDRA, Medical Dictionary for Regulatory Activities; NEC, Not elsewhere classified

All adverse events except one (hair loss) occurred during the procedure or hospitalisation.

Adverse events in PUFS

Sections 5.5 reported on:

- Serious adverse events meeting the primary safety endpoint definition (major ipsilateral stroke or neurological death) up to Day 180
- Adverse events that were device-related (a secondary endpoint) up to Day 180.

Serious Adverse Events in PUFS

An adverse event was considered a serious adverse event if it met the ISO14155 definition for serious adverse events. All serious adverse events were reviewed by the clinical events committee (CEC).

In total, 44 serious adverse events have been reported in PUFS to 1 year (Table B5.16).

- The most common neurological events were amaurosis fugax, headache, and stroke resulting from intracranial haemorrhage or ischaemia.
- The most common non-neurological events were non-neurological bleeding and cardiac arrhythmias.

Of these serious adverse events, 15 were judged as probably or definitely related to PED, 8 were judged as probably or definitely related to the placement procedure, 10 events were judged as probably or definitely related to the use of antithrombotic medications and 15 were judged as probably or definitely related to a pre-existing condition.

Table B5.16 Serious adverse events in the PUFS study by MedDRA body system and term cumulative to 1 year (n=107)

MedDRA category	MedDRA term	Cumulative to 1 year
Arteriosclerosis, stenosis, vascular insufficiency and necrosis	Carotid artery occlusion	1 (0.9%)
	Compartment syndrome	1 (0.9%)
Cardiac arrhythmias	Atrial fibrillation	1 (0.9%)
	Sinus bradycardia	1 (0.9%)
	Sudden cardiac death	1 (0.9%)
Central nervous system vascular disorders	Cerebral haematoma	1 (0.9%)
	Haemorrhage intracranial	4 (3.7%)
	Ischaemic stroke	3 (2.8%)
	Thrombotic stroke	1 (0.9%)
Decreased and nonspecific blood pressure disorders and shock	Procedural hypotension	1 (0.9%)
Ear and labyrinth disorders	Tinnitus	1 (0.9%)
Embolism and thrombosis	Deep vein thrombosis postoperative	1 (0.9%)
	Retinal artery thrombosis	1 (0.9%)
Gastrointestinal haemorrhages	Colitis (excluding infective)	1 (0.9%)
	Rectal haemorrhage	1 (0.9%)
Infections – pathogen unspecified	Urinary tract infection	1 (0.9%)
Neoplasms benign, malignant and unspecified	Breast cancer recurrent	1 (0.9%)
Nervous system disorders	Amaurosis fugax	5 (4.7%)
	Headache	5 (4.7%)
Neurological disorders NEC	Dizziness	2 (1.9%)
Pulmonary vascular disorders	Post procedural pulmonary embolism	1 (0.9%)
Reproductive system and breast disorders	Female genital tract fistula	1 (0.9%)
Respiratory tract neoplasms	Lung squamous cell carcinoma stage I	1 (0.9%)
Vascular disorders	Aneurysms and dissections site specific NEC	1 (0.9%)
Vascular disorders NEC	Arteriovenous fistula	2 (1.9%)

Continued…

MedDRA category	MedDRA term	Cumulative to 1 year
Vascular haemorrhagic disorders	Epistaxis	1 (0.9%)
	Retroperitoneal haemorrhage	1 (0.9%)
Vision disorders	Diplopia	1 (0.9%)
Visual field disorders	Visual field defect	1 (0.9%)
Total		**44 (41.1%)**

MedDRA, Medical Dictionary for Regulatory Activities; NEC, not elsewhere classified

Non-Serious Adverse Events in PUFS

In total, 126 non-serious adverse events have occurred to 1 year in PUFS. Headache was the most common event.

Non-serious adverse events are shown in Table B5.17. Six events were probably or definitely related to PED, 15 were probably or definitely related to the PED placement procedure, and 18 were probably or definitely related to an underlying condition. Most events resolved completely.

Table B5.17 Non-serious adverse events in PUFS by MedDRA body system and term to 1 year (n=107)

MedDRA category	MedDRA term	Cumulative to 1 year
Allergic conditions	Drug eruption	1 (0.9%)
Anxiety disorders and symptoms	Panic attack	1 (0.9%)
Blood and lymphatic system disorders	Anaemia	2 (1.9%)
Body temperature conditions	Postoperative fever	2 (1.9%)
Ear and labyrinth disorders	Tinnitus	1 (0.9%)
Embolism and thrombosis	Deep vein thrombosis postoperative	2 (1.9%)
Epidermal and dermal conditions	Pruritis	1 (0.9%)
Eye disorders NEC	Eye pain	1 (0.9%)
Gastrointestinal disorders	Constipation	1 (0.9%)
Gastrointestinal haemorrhages	Lower gastrointestinal haemorrhage	1 (0.9%)
Gastrointestinal signs and symptoms	Nausea	5 (4.7%)
	Procedural nausea	7 (6.5%)
	Procedural vomiting	1 (0.9%)
General system disorders	Discomfort	1 (0.9%)
	Facial pain	1 (0.9%)
	Peripheral oedema	1 (0.9%)
Infections – pathogen unspecified	Acute sinusitis	1 (0.9%)
	Bronchitis	1 (0.9%)
	Pharyngitis	2 (1.9%)
	Puncture site infection	1 (0.9%)
	Urinary tract infection	2 (1.9%)
Injuries NEC	Corneal abrasion	1 (0.9%)
Musculoskeletal and connective tissue disorders NEC	Back pain	1 (0.9%)
	Pain in extremity	1 (0.9%)

Continued…

MedDRA category	MedDRA term	Cumulative to 1 year
Nervous system disorders	Headache	18 (16.8%)
	Post-traumatic headache	1 (0.9%)
Neurological disorders NEC	Dizziness	2 (1.9%)
	Hyperaesthesia	1 (0.9%)
	Hypoaesthesia	1 (0.9%)
	Hypoaesthesia facial	1 (0.9%)
Ocular neuromuscular disorders	Eyelid ptosis	4 (3.7%)
	IIIrd nerve disorder	1 (0.9%)
	IVth nerve disorder	1 (0.9%)
	VIth nerve disorder	4 (3.7%)
Procedural and device related injuries and complications NEC	Procedural headache	16 (15.0%)
Reproductive system and breast disorders	Menometrorrhagia	1 (0.9%)
	Menorrhagia	1 (0.9%)
Skin and subcutaneous tissue disorders	Skin bacterial infection	1 (0.9%)
Skin appendage conditions	Application site alopecia	1 (0.9%)
Vascular disorders	Ecchymosis	4 (3.7%)
Vascular haemorrhagic disorders	Conjunctival haemorrhage	1 (0.9%)
	Epistaxis	3 (2.8%)
	Subcutaneous haematoma	1 (0.9%)
	Urogenital haemorrhage	2 (1.9%)
	Vessel puncture site haemorrhage	7 (6.5%)
	Vitreous haemorrhage	1 (0.9%)
Vision disorders	Diplopia	6 (5.6%)
	Photopsia	4 (3.7%)
	Vision blurred	1 (0.9%)
Visual field disorders	Visual field defect	3 (2.8%)
Total		**126 (118%)**

MedDRA, Medical Dictionary for Regulatory Activities; NEC, not elsewhere classified

5.7.3 Give a brief overview of the safety of the technology in relation to the decision problem.

In summary, the studies presented are able to demonstrate the safety of PED for the endovascular treatment of large and giant aneurysms and those with a complex form, which are difficult to treat using existing techniques such as coils or stents combined with coils. The studies showed that the serious adverse events rate after PED placement was low given the complexity of cases. These AEs occurred primarily in the periprocedural setting. In PUFS AEs were uncommon between Day 180 and 1 year, and were typically unrelated to PED.

The PITA and PUFS studies provide good scientific evidence of a low adverse events rate with PED use, particularly in complex IA cases.

5.8 Interpretation of clinical evidence

5.8.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

Two international studies have been conducted in support of PED for the treatment of IAs.

- PITA was a multicentre prospective study in Europe and Argentina of difficult-to-treat or failed wide-necked IAs of varying sizes in which PED was used with or without adjunctive coils. The 180-day aneurysm occlusion rate was 93% and the stroke rate was 6.5%.
- PUFS was a multicentre study in the US, Europe and Turkey of PED use alone for the treatment of wide-necked or fusiform large and giant IAs of the internal carotid artery. The 180-day complete aneurysm occlusion rate without major stenosis was 73.6% and the stroke/death rate was 5.6%. At 1-year, the complete aneurysm occlusion rate without major stenosis was 70.8%.

The target IA population in PUFS is commonly acknowledged to be either untreatable with current methods or have a very low success rate. Moreover, there is a high rate of procedure-related morbidity and mortality. Several PUFS cases had already failed coil treatment and one had failed Onyx treatment.

PUFS showed that the PED primary effectiveness success rate (complete occlusion without major stenosis) at 180 days was 73.6% and the 180-day major ipsilateral stroke/neurological death rate was 5.6%. At 1 year, the effectiveness success rate was 70.8%. The study's primary effectiveness and safety endpoints met their predetermined thresholds for success with very high degrees of statistical certainty. In addition, neurological assessments showed that many PUFS patients with severe baseline symptoms due to mass effect from the target IA showed improvements at 180 days.

PITA and PUFS provide strong evidence of safety and effectiveness to support the use of PED in the treatment of patients with IAs. This evidence is strongly supported by results from use of PED in compassionate and special access cases in the US and Argentina.

The degree of effectiveness success for the use of PED in the PUFS target population provides strong evidence that this device can meet an important unmet clinical need. The level of evidence for safety met the study's predetermined goals and appeared to meet or exceed that of other approved devices. Overall, the risks of PED use in the intended patient population appear to be strongly outweighed by the benefits.

Summary: In conclusion, the PUFS study constitutes valid scientific evidence and provides reasonable assurance that the PED device is effective and safe for its intended use.

5.8.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

The limitations of the two main studies underpinning PED's clinical evidence data base are chiefly those associated with the non-comparative nature of these data. For reasons listed above (see section 5.2.3), it has not been possible to carry out a clinical study versus existing treatment primarily because clinicians lacked equipoise: most patients in the two PED studies presented had either already failed current treatment or had aneurysms that were not feasibly treated with current technologies. Nonetheless, PITA and PUFS do provide strong evidence of safety and effectiveness to support the use of PED in IA treatment.

The strength of evidence from the PUFS study is particularly compelling. The observed effectiveness success rate evidence in PUFS appears to be robust because its methodology addresses some important potential strong biases present in the medical literature for existing IA treatment:

- In PUFS a core laboratory of independent neuroradiologists judged target IA occlusion, rather than relying on self-adjudicated reporting by the authors. It is therefore likely that the study avoids any overestimation of the true rate of completely occluded aneurysms.
- PUFS used a simple, binary, easily interpreted effectiveness endpoint: complete IA occlusion without major stenosis.
- PUFS determined the number of angiographic successes amongst **all** patients in whom PED placement was attempted; if the patient did not return for follow-up, the patient was not dropped (as is common in most published studies) but was instead treated as an effectiveness failure. Moreover, the rate of angiographic follow-up in PUFS was very high compared to most published articles.
- PUFS determined success at a long-term time point. In contrast, many reports of 'success' in the published literature are based on complete occlusion of an aneurysm immediately after placement of coils. This approach ignores the high chance of aneurysm recurrence that has been documented for wide-necked aneurysms.
- Selection bias was minimised in PUFS since no IA was 'rejected' on the grounds that the IA's geometry was too complex. In contrast, reports in the literature provide information on those patients selected for the particular treatment. These are not 'all comers' studies.
- Whilst PED is radiopaque, it remains in the parent vessel and not inside the aneurysm and thus allows sensitive and accurate evaluation of the aneurysm at follow up. In contrast, occlusion assessment of IAs with coils in place is difficult as coils interfere with assessment of contrast opacification of the aneurysm.

5.8.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical studies to the clinical benefits experienced by patients in practice.

Intracranial arterial aneurysms are a severe pathology likely to lead to poor quality of life and a high risk of death. Larger aneurysms have a greater risk of rupture than small aneurysms, with the risk of rupture and associated high mortality rates being greatest for untreated giant aneurysms.

There is good evidence, particularly from PUFS, to show that PED can provide important benefits in patients with aneurysms that have large dimensions (giant, wide-neck, etc.) and/or a complex morphology (fusiform, dissecting, etc.), and which are unable to be treated by existing therapies. In the majority of cases, complete occlusion of the aneurysm is achieved with PED and the occurrence of life-threatening events is avoided.

Summary: The expected benefit of PED is likely to be substantial in patients with intracranial aneurysms that are unable to be treated using other existing techniques (coils or stents combined with coils).

5.8.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the study, issues relating to the conduct of the study compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted.

Both PUFS and PITA were ‘real-world’ studies and did not ‘select’ patients. Although PUFS did not formally capture the number of patients who may have been briefly considered for the study and not enrolled, personal communications between study investigators and the sponsor indicate that nearly all patients who were eligible for the study were eventually enrolled and treated. This is primarily because no reasonable alternatives were available to such patients. Therefore, the experience of patients in PITA and PUFS is likely to represent the real-world situation.

A key factor that is highly likely to influence the external validity of the study results is the experience of the specialist who implants PED. These specialists should be neurosurgeons or interventional neuroradiologists who are qualified in intravascular and percutaneous techniques, and in procedures within medical infrastructures equipped with suitable fluoroscopy equipment. It is important that they receive specific PED placement training prior to patient implantation.

Procedures used to place PED are similar in many respects to those used for stent-assisted coiling. The degree of training required for physicians prior to using PED is moderate.

Published instructions for use and a user manual are available.

6 Cost

[To be completed with economic submission]

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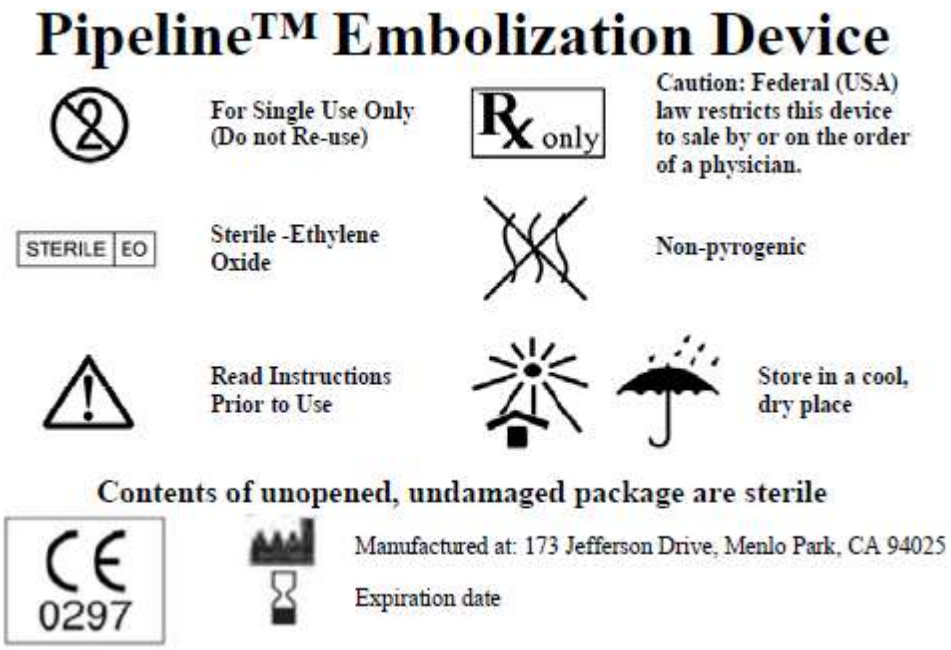
(63) Holm S. A Simple Sequentially Rejective Multiple Test Procedure. Scandinavian Journal of Statistics 1979;6(2):65-70.

7 Appendices

7.1 Appendix 1

Instruction for Use (IFU)



1. CAUTION

This device should be used only by physicians trained in percutaneous, intravascular techniques and procedures at medical facilities with the appropriate fluoroscopic equipment. PED should be used by physicians who have received appropriate training for this device.

Carefully inspect the sterile package and the Pipeline Embolisation Device prior to use to verify that neither has been damaged during shipment. Do not use kinked or damaged components.

The PED is not to be used after the expiration date imprinted on the product label.

2. DEVICE DESCRIPTION

The Pipeline™ Embolisation Device (PED) consists of a flexible mesh-like device designed for placement in a parent vessel across the neck of an aneurysm.

The Pipeline Embolisation Device is an endoluminal implant placed across the neck of an aneurysm which facilitates repair of the affected parent artery. The PED can be used alone or in combination with other aneurysm embolisation devices. Clinical data demonstrates a satisfactory level of safety and efficacy when the PED were utilised alone or adjunctively with embolisation coil. The comparative safety profile data between these specific populations is not yet available.

The PED is packaged in a delivery system (an introducer and a flexible tapered delivery wire) and is designed to be introduced into a microcatheter of 0.027 inch (0.69 mm) inside diameter.

A platinum coil at the distal end provides fluoroscopic visibility. A retaining mechanism at the proximal end of this platinum coil facilitates insertion of the PED through the lumen of a microcatheter.

A platinum marker is located on the delivery wire proximally to the PED. This marker provides fluoroscopic visibility of the proximal location of the PED.

3. INDICATION FOR USE

The PED is intended for endovascular embolisation of cerebral aneurysms.

4. CONTRAINDICATIONS

- Patients with active bacterial infection.
- Patients in whom antiplatelet and/or anticoagulation therapy is contraindicated.
- Pipeline Embolisation Device should not be used alone as sole therapy for acutely ruptured aneurysms.
- Patients who have not received antiplatelet agents prior to the procedure.

5. POTENTIAL COMPLICATIONS

Possible complications include but are not limited to the following:

Adverse reaction to antiplatelet/ anticoagulation agents or contrast media
Blindness
Coma
Death
Device fracture
Device migration or misplacement
Dissection of the parent artery
Distal embolisation including to a previously uninvolved territory
Embolism
Groin injury
Headache
Hemorrhage
Hematoma or hemorrhage at the puncture site
Hydrocephalus
Infection
Intracerebral bleeding
Ischemia
Mass effect
Neurological deficits
Parent artery stenosis
Perforation
Perforator occlusion
Post-procedure bleeding
Ruptured or perforated aneurysm
Seizure
Stroke
Thromboembolism
Transient Ischemic Attack (TIA)
Vasospasm
Vessel occlusion
Vessel perforation
Vision impairment

6. PRECAUTIONS:

- Do not use in patients in whom the angiography demonstrates the anatomy is not appropriate for endovascular treatment, due to conditions such as severe intracranial vessel tortuosity or stenoses.
- Do not attempt to re-position the Pipeline Embolisation Device after deployment.
- Placement of multiple PEDs may increase the risk of ischemic complications.
- The appropriate anti-platelet and anti-coagulation therapy should be administered in accordance with standard medical practice.
- A thrombosed aneurysm may aggravate pre-existing, or cause new, symptoms of mass effect and may require medical therapy.

7. COMPATIBILITY

PED is compatible with a 0.027 (0.69mm) inside diameter microcatheter. Unconstrained diameter of the PED is 0.25mm greater than the labeled diameter (on the packaging). Do not use PED in vessel diameters that are larger than the labeled diameter.

8. MAGNETIC RESONANCE IMAGING

Non-clinical testing has demonstrated that the PED is MR Conditional. It can be scanned safely under the following conditions:

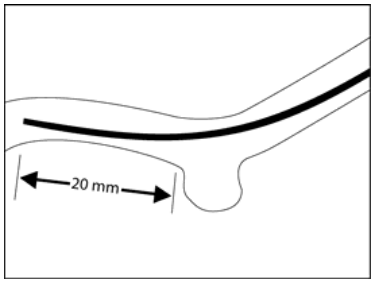
- Static magnetic field of 3 Tesla or less.
- Spatial gradient field of 720 Gauss/cm or less.
- Maximum whole-body-averaged specific absorption rate (SAR) of 4.0 W/kg for 15 minutes of scanning.

In non-clinical testing, the PED produced a temperature rise of less than 0.6°C at a maximum whole body averaged specific absorption rate (SAR) of 4.0 W/kg for 15 minutes of MR scanning in a 3 Tesla MR system.

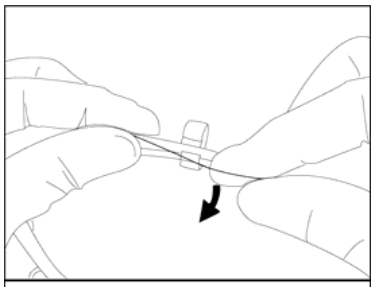
The PED may create local field inhomogeneity and susceptibility artifacts which may degrade the diagnostic quality of the MRI images. Based on the non-clinical testing of the 5.0 mm device using standard views, the worst case maximum artifact was <3mm when subjected to 3.0 Tesla. Local field artifact from the PED may decrease the accuracy of MR angiogram in assessing vessel luminal patency.

MR image quality may be compromised if the area is in the exact same area or relatively close to the position of the PED. Therefore, it may be necessary to optimise MR imaging parameters for the presence of this metallic implant.

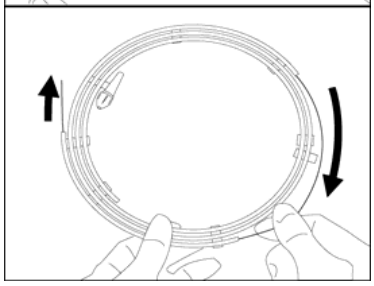
9. DIRECTIONS FOR USE



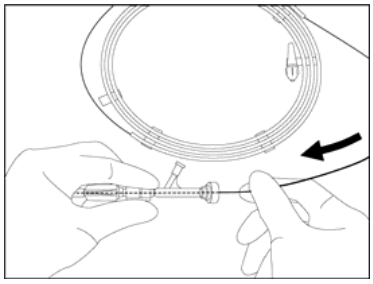
a. Using standard interventional radiographic technique, place the microcatheter tip at least 20mm past the distal edge of the aneurysm.



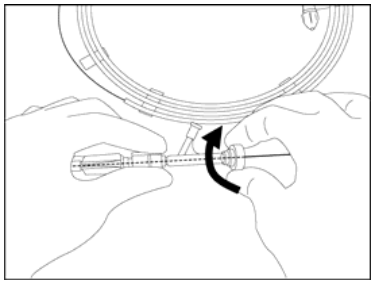
b. Detach wire from the white rubber holder.



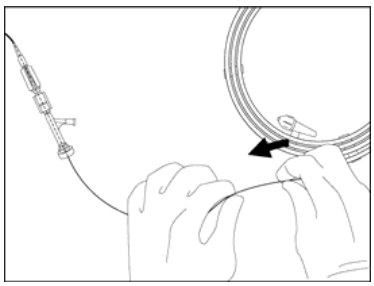
c. Push wire and introducer sheath out of the packaging coil.



d. Insert the introducer sheath into the microcatheter hub.



e. Secure introducer sheath to the hub by locking down the RHV.

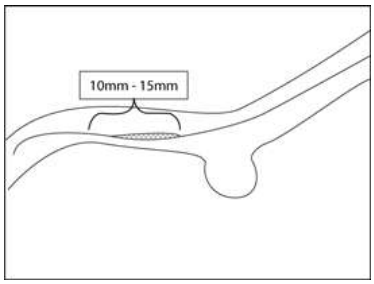


f. Advance the PED into the microcatheter by pushing the delivery wire.

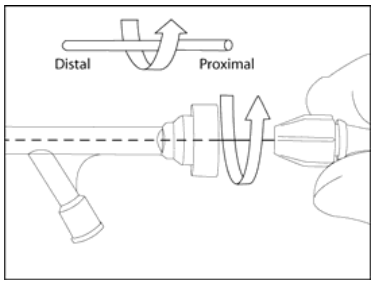
Caution: Do not torque wire or pull back wire during insertion.

Caution: If excessive resistance is noted during the use of the Pipeline Embolisation Device or microcatheter at any time during the procedures, discontinue the delivery of the Pipeline Embolisation Device and identify the cause of the resistance. Advancement of the Pipeline Embolisation Device against resistance may result in device damage or patient injury.

Caution: The presence of other indwelling endovascular stents may interfere with proper deployment and function of the Pipeline Embolisation Device.



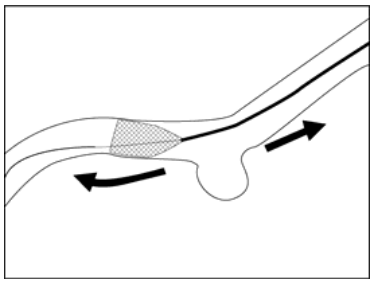
g. Once the tip of delivery system and microcatheter align, to facilitate PED deployment, unsheath 10mm to 15mm of the packaged PED by slowly retracting the catheter.



h. After distal segment of PED is exposed, rotate the proximal end of the delivery wire clockwise to facilitate the expansion of PED.

i. Deploy the PED slowly under direct fluoroscopic observation. If the device becomes kinked around a curve you may need to relax the tension on the microcatheter before deploying the rest of the PED.

Warning: Never rotate the delivery wire for more than 10 full turns. If PED does not open after 10 turns, remove the entire system (microcatheter and PED delivery system).

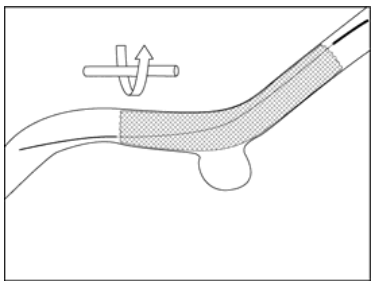


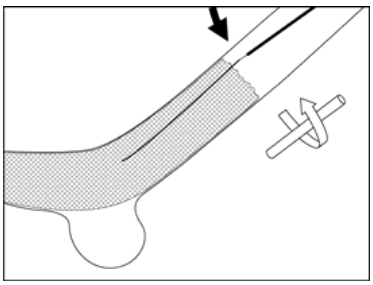
j. After the distal end of the PED has expanded, deploy the remainder of PED by advancing the delivery wire and maintaining forward motion on the catheter. Watch the tip of the delivery wire on fluoroscopy while advancing the PED.

Caution: Under fluoroscopy, carefully monitor the tip of the core wire during PED deployment. The core wire can be rotated and maneuvered as needed after the distal end for the PED is detached.

k. Carefully advance the delivery catheter through the deployed PED under fluoroscopy making sure not to dislodge the PED.

l. Remove the delivery wire back into the microcatheter while gently rotating the delivery wire clockwise to prevent entanglement with the PED.





Caution: If the catheter cannot be advanced through the PED remove the delivery wire carefully to avoid entangling the capture coil on the PED construct.

Caution: If the delivery wire cannot be retracted into the microcatheter, carefully remove the delivery core wire and microcatheter simultaneously.

m. A second PED can be placed inside another PED. Position the microcatheter at the desired location. Select a new appropriate PED and deploy it as normal.

Caution: Placement of multiple PEDs may increase the risk of ischemic complications.

7.2 Appendix 2: Search strategy for section 5.1 (Identification of studies)

The following information should be provided.

7.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

The following databases were searched using the specified data providers:

- MEDLINE (OvidSP)
- MEDLINE In-Process (OvidSP)
- EMBASE (OvidSP)
- Cochrane Database of Systematic Reviews (CDSR) (Cochrane Library/Wiley Interscience)
- Cochrane Central Register of Controlled Trials (CENTRAL)(Cochrane Library/Wiley Interscience)
- Database of Abstracts of Reviews of Effects (DARE) (Cochrane Library/Wiley Interscience)
- Health Technology Assessment Database (HTA) (Cochrane Library/Wiley Interscience)
- NHS Economic Evaluation Database (NHS EED) (Cochrane Library/Wiley Interscience)

- National Institute for Health and Clinical Excellence (NICE) (http://www.nice.org.uk/)
- NHS Evidence (http://www.evidence.nhs.uk/)
- US National Guideline Clearinghouse site (http://www.guidelines.gov/)
- Clinical Knowledge Summaries (CKS) (http://www.cks.nhs.uk/)
- NHS Scotland (http://www.show.scot.nhs.uk/)
- Best Practice (http://bestpractice.bmj.com/best-practice/welcome.html)
- TRIP (Turning Evidence into Practice) (http://www.tripdatabase.com/)
- Hospital Episode System (HESonline) (http://www.hesonline.nhs.uk/)
- Office of National Statistics: mortality data (http://www.statistics.gov.uk/)
- PubMed (www.ncbi.nlm.nih.gov/pubmed/)

7.2.2 The date on which the search was conducted.

All searches were conducted between the 3rd and 6th June 2011.

7.2.3 The date span of the search.

- MEDLINE (1948-2011/May week 4)
- MEDLINE In-Process (6th June 2011)
- EMBASE (1980-2011/week 22)
- Cochrane Database of Systematic Reviews (CDSR) (2011 Issue 5)
- Cochrane Central Register of Controlled Trials (CENTRAL) (2011 Issue 2)
- Database of Abstracts of Reviews of Effects (DARE) (2011 Issue 2)
- Health Technology Assessment Database (HTA) (2011 Issue 2)
- NHS Economic Evaluation Database (NHS EED) (2011 Issue 2)
- National Institute for Health and Clinical Excellence (NICE) (3rd June 2011)
- NHS Evidence (3rd June 2011)
- US National Guideline Clearinghouse site (3rd June 2011)
- Clinical Knowledge Summaries (CKS) (3rd June 2011)
- NHS Scotland (3rd June 2011)
- Best Practice (3rd June 2011)
- TRIP (Turning Evidence into Practice) (3rd June 2011)
- Hospital Episode System (HESonline) (5th June 2011)
- Office of National Statistics: mortality data (5th June 2011)

- PubMed (6th June 2011)

7.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

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$).ti,ab. (402)
7 (berry adj3 aneurysm$).ti,ab. (225)
8 (basilar adj3 aneurysm$).ti,ab. (906)
9 (saccular adj3 aneurysm$).ti,ab. (1856)
10 (fusiform adj3 aneurysm$).ti,ab. (727)
11 or/1-10 (21724)
12 pipeline.ti,ab. (2955)
13 PED.ti,ab. (890)
14 (chestnut or EV3 or covidien).ti,ab. (966)
15 (flow diverter$ or flow diversion$).ti,ab. (129)
16 emboli?ation device$.ti,ab. (30)
17 or/12-16 (4952)
18 11 and 17 (50)
19 (PUFS or (Pipeline for Uncoilable adj Failed Aneurysm$)).ti,ab. (23)
20 (PITA or (Pipeline for Intracranial Treatment adj Aneurysm$)).ti,ab. (77)
21 (Complete Occlusion adj Coilable Aneurysm$).ti,ab. (0)
22 or/18-21 (149)
23 animals/ not (humans/ and animals/) (3505641)
24 22 not 23 (133)

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$).ti,ab. (1102)
10 (saccular adj3 aneurysm$).ti,ab. (2065)
11 (fusiform adj3 aneurysm$).ti,ab. (893)
12 or/1-11 (26072)
13 pipeline.ti,ab. (4178)
14 PED.ti,ab. (1184)
15 (chestnut or EV3 or covidien).ti,ab. (1362)
16 (flow diverter$ or flow diversion$).ti,ab. (190)
17 (emboli?ation adj2 device$).ti,ab. (283)
18 or/13-17 (7134)
19 12 and 18 (107)
20 (PUFS or (Pipeline for Uncoilable adj Failed Aneurysm$)).ti,ab. (40)
21 (PITA or (Pipeline for Intracranial Treatment adj Aneurysm$)).ti,ab. (97)
22 (Complete Occlusion adj Coilable Aneurysm$).ti,ab. (0)
23 or/19-22 (243)
24 Animal/ or Animal Experiment/ or Nonhuman/ (5521487)
25 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,sh. (4307813)
26 24 or 25 (5912420)
27 exp Human/ or Human Experiment/ (12416698)
28 26 not (26 and 27) (4647774)
29 23 not 28 (185)

Cochrane Library: CDSR, CENTRAL, DARE, HTA, and 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 (saccular NEAR/3 aneurysm*):ti,ab,kw (6)
#11 (fusiform NEAR/3 aneurysm*):ti,ab,kw (3)
#12 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11) (509)
#13 (pipeline) (53)
#14 (ped) (86)
#15 (chestnut or EV3 or covidien) (192)
#16 "flow diverter*" or "flow diversion*" (3)
#17 (emboli?ation NEAR/3 device*) (9)
#18 (#13 OR #14 OR #15 OR #16 OR #17) (343)
#19 (#12 AND #18) (1)
#20 (PUFS or (Uncoilable NEXT "Failed Aneurysm*")) (0)
#21 (Pipeline NEXT "Intracranial Treatment " NEXT Aneurysm*) (0)
#22 "Complete Occlusion" NEXT "Coilable Aneurysm" (0)
#23 (#19 OR #20 OR #21 OR #22) (1)

Systematic reviews and technology assessments, guidelines, patient pathways and epidemiological information were identified from the following sources

National Institute for Health and Clinical Excellence (NICE)

aneurysm

NHS Evidence

aneurysms

US National Guideline Clearinghouse site

cerebral aneurysm

intracranial aneurysm

Clinical Knowledge Summaries (CKS)

cerebral aneurysm

NHS Scotland

cerebral aneurysm

Best Practice

cerebral aneurysm

TRIP (Turning Evidence into Practice)

cerebral aneurysm

Hospital Episode System (HESonline)

The data on inpatient admissions and finished consultant episodes (2009-2010) for main procedures and interventions categorised by 4 character OPCS-4 were identified for the treatment of cerebral aneurysms:

http://www.hesonline.nhs.uk/Ease/servlet/ContentServer?siteID=1937&categoryID=215

Office of National Statistics: mortality data

Table 5.9 Deaths1: underlying cause, sex and age-group, 2009: Chapter IX Diseases of the circulatory system, England and Wales

www.statistics.gov.uk/downloads/theme_health/dr2009/Table5.9.xls

PubMed

Cerebral aneurysm AND Great Britain/epidemiology

7.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

NICE web site clinical guidelines stroke

DoH The National Service Framework

FDA site for stents

Search general internet search for

- SILK device
- Neuroform stent
- Enterprise stent
- Onyx in intravascular surgery

7.2.6 The inclusion and exclusion criteria.

Articles were immediately excluded if they were irrelevant due to the search picking up a different definition of the study acronym.

Inclusion criteria were:

- Large and giant IA population
- PED as the intervention
- Study designed to assess safety and/or efficacy
- Case studies with PED
- English language

Exclusion criteria were:

- Non-cerebral aneurysms
- Small IAs
- Interventions other than PED: SILK, coiling, clipping/surgery, balloon-assisted embolisation
- Studies designed to assess MR imagery, rupture mechanisms, complication management, haemodynamics, technical use

7.2.7 The data abstraction strategy.

Two independent investigators reviewed the title and abstract (where available) of all articles found in the search to determine if the article met the inclusion criteria. Where the abstract was not sufficient, full-text articles were sought. All disagreements were discussed and resolved.

Full-text articles for review were obtained, and data abstracted by a single investigator. All abstracted data were verified by a second investigator.

7.3 Appendix 3: Quality assessment of RCT(s) and non-RCT(s) (section 5.4)

7.3.1 A suggested format for the quality assessment of RCT(s) is shown below.

The studies included were single-armed trials. The quality assessment has been based on the following paper: Carey TS, Boden SD. A critical guide to case series reports. Spine 2003;28:1631-4.

	PUFS	**PITA**
Did the study address a clearly defined question?	Yes. The study objective was to determine the safety and effectiveness of PED placement in the endovascular treatment of large or giant wide necked intracranial aneurysms in the petrous, cavernous or paraophthalmic segments of the internal carotid artery	Yes. The study objective was clearly defined to assess the safety and performance of the PED in the minimally invasive endovascular treatment of intracranial aneurysms
Is the study population well described?	Yes. Clearly stated inclusion and exclusion criteria were used	Yes. Clearly stated inclusion and exclusion criteria were used
Is the intervention well described?	Investigational procedure was clearly defined in the study protocol	Investigational procedure was clearly defined in the study protocol
Were the outcome measures validated?	Yes. Hard primary safety outcome measures were used (death due to neurological reasons or major ipsilateral stroke). Primary efficacy outcome was complete occlusion of the target intracranial aneurysms and ≤50% stenosis of the parent artery at the target IA location, judged by an independent radiology committee, on Day 180-antiography. This is a high-quality, rigorous measure of treatment of IA. Incomplete occlusion after PED treatment is easily detected. Outcome thresholds were based on success rates supported by a structure literature review	Yes. Study used hard outcome measures (device deployment success to the target site, death and ipsilateral stroke at 30-days post-procedure
Were statistical analyses appropriate?	Yes, appropriate statistical analyses were used. Modelling showed that the sample size had ample statistical power to	Study is a feasibility study. Therefore it is not powered for statistical analysis

	PUFS	PITA
	achieve the study's goals. A Bayesian statistical approach was used to evaluate the study's primary endpoint	
Are the results well described?	As the study is ongoing limited data are currently available. Day 180 and 1 year follow up data are available and clearly summarised in the 1 year data interim report	Study report describes the results in detail
Is the conclusion and discussion supported by data?	Conclusions are supported by 180 day (primary endpoint) and 1 year data	The conclusion and discussion is supported by the study data

7.4 Appendix 4: Search strategy for section 5.9 (Adverse events)

The following information should be provided.

7.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

The same search strategy was used as for the identification of studies, see section 7.2, appendix 2.

7.4.2 The date on which the search was conducted.

See section 7.2.2.

7.4.3 The date span of the search.

See section 7.2.3.

7.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

See section 7.2.4.

7.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

See section 7.2.5.

7.4.6 The inclusion and exclusion criteria.

See section 7.2.6.

7.4.7 The data abstraction strategy.

See section 7.2.6.

7.5 Appendix 5: Quality assessment of adverse event data in section 5.9 (Adverse events)

7.5.1 Please tabulate the quality assessment of each of the non-RCTs identified.

See section 7.3.