NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Assessment report overview

The IN.PACT drug-coated balloon for peripheral arterial disease

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

Key issues for consideration by the Committee are described in section 6, following the brief summaries of the clinical and cost evidence.

This report contains information that has been supplied in confidence and will be redacted before publication. This information is highlighted in yellow. This overview also contains:

- Appendix A: Sources of evidence
- Appendix B: Comments from professional bodies
- Appendix C: Comments from patient organisations
- Appendix D: The company claims and decision problem

1 The technology

The IN.PACT drug-coated balloon (Medtronic) is an over-the-wire angioplasty catheter and drug delivery system for treating people with femoro-popliteal peripheral arterial disease (PAD). The IN.PACT device has a dual-lumen shaft, one lumen for the passage of the guidewire, and the other to allow contrast medium diluted with saline to inflate and deflate the balloon. Two radiopaque markers identify the working length of the balloon to aid the accurate positioning of the device across the target lesion during X-ray fluoroscopy. The balloon is placed using a standard percutaneous transluminal angioplasty (PTA) technique and when inflated stretches and widens the narrowed vessel lumen, leading to an increase in distal blood flow. The outer surface of the polyamide balloon is coated with paclitaxel at a dose of 3.5 µg/mm2, combined with a urea carrier which is delivered into the vessel wall at the time of balloon inflation. Paclitaxel reduces intimal smooth muscle cell proliferation that may subsequently lead to restenosis (recurrence of vessel narrowing). The IN.PACT drug-coated balloon is designed for a single inflation only, after which it is deflated and withdrawn. More than 1 IN.PACT devices may be used in the same patient for cases with long or multiple lesions.

IN.PACT is a Class III medical device available in a variety of balloon sizes and in 2 versions, depending on the diameter of the guidewire used: the IN.PACT Admiral is compatible with a 0.035” guidewire and the IN.PACT Pacific is compatible with a 0.018” guidewire.

2 Proposed use of the technology

2.1 Disease or condition

Peripheral arterial disease (PAD), also known as peripheral vascular disease, is a common condition in which a build-up of fatty deposits in the arteries (atheroma) encroaches on the lumen of the vessel and restricts blood supply to the tissues of the leg.

Many people with PAD have no symptoms but some develop a painful ache in their legs when they walk, which gradually resolves after a few minutes of rest. The medical term for this symptom is "intermittent claudication". In most people with intermittent claudication, the symptoms remain stable, but approximately 20% will develop increasingly severe symptoms as atheromatous narrowing increases and vascular insufficiency may ultimately lead to the development of critical limb ischaemia.

2.2 Patient group

The incidence of peripheral arterial disease increases with age, with around 20% of people aged over 60 years having some degree of peripheral arterial disease. Incidence is higher in people who smoke, who have diabetes and in people with coronary artery disease. In most people with intermittent claudication the symptoms remain stable, but approximately 20% will develop increasingly severe symptoms with the development of critical limb ischaemia[1].

2.3 Current management

Current treatment options for femoro-popliteal PAD include balloon percutaneous transluminal angioplasty (without drug coating), implantation of scaffolding devices called stents or surgical revascularization techniques (bypass surgery).

NICE guidance on peripheral arterial disease: diagnosis and management recommends that initial management should focus on preventative treatments and lifestyle changes to reduce symptoms and the risk of developing other forms of atheromatous cardiovascular disease. The management of people with intermittent claudication is described in section 1.5 of the guideline. People with intermittent claudication should be offered a supervised exercise programme: angioplasty can only be offered when exercise has not shown improvement, lifestyle changes have been reinforced and when suitability has been confirmed by imaging. Bypass surgery should only be offered to people

[1] Lower limb peripheral arterial disease. (2012) NICE guideline CG147

with severe lifestyle-limiting intermittent claudication when angioplasty has been unsuccessful or is unsuitable, and in the presence of appropriate patterns of vascular disease. People with critical limb ischaemia should be assessed by a vascular multidisciplinary team before angioplasty or bypass surgery is recommended. When angioplasty is indicated, NICE guidance recommends considering the use of primary stent placement in patients whose CLI is a result of complete aorto-iliac occlusion.

2.4 Proposed management with new technology

The IN.PACT drug-coated balloon is intended to deliver paclitaxel to the vessel wall in order to reduce re-stenosis. It is used in addition to plain balloon (without drug coating) angioplasty

3 Company claimed benefits and the decision problem

The company's claimed benefits and decision problem from the scope are attached as Appendix D. The company did not propose any variation from the scope. While the EAC agreed with the company it did note there was some variation arising from the fact that the evidence considered by the company included some patients with critical limb ischaemia and below the knee disease.

4 The evidence

4.1 Summary of evidence of clinical benefit

The company presented 23 studies, 16 published and 7 unpublished. The EAC carried out its own searches and identified 11 (7 published and 4 unpublished) studies

The EAC excluded studies where >10% of patients had a Rutherford score of 4 and above, which signifies critical limb ischaemia, and those which included below the knee lesions. The studies identified are summarised in Table 2 and further details can be found in section 3.3 of the assessment report.

Table 1: Included studies, company and EAC

Study	Type of publication	Type of study	Comment
Studies included by both EAC and company			
7 studies included by both	*Full paper*	*Multicentre prospective RCT*	*Krankenberg et al. 2015, Laird et al 2015, Werk et al. 2012*
		Multicentre prospective cohort	*Micari et al 2013, Micari et al 2017*
	Abstract	*Multicentre prospective RCT*	*Krishan et al. 2016*
		Multicentre prospective cohort	*Ansel et al. 2017*
Studies in submission excluded by EAC			
Micari et al. 2012	*Full paper*	*Prospective RCT single or multi-centre*	*overlap with Micari 2013*
Micari et al 2016			*overlap with Micari 2017*
Liistro et al. 2013, Fanelli et al. 2012, and Tepe et al. 2014			*included >10% patients with CLI*
Debing et al.2017			*included >10% patients with CLI and below the knee lesions*
Bague et al. 2017,		*Prospective multi-centre cohort*	*included >10% patients with CLI*
Grotti et al. 2016,		*Prospective or retrospective observational study*	*included >10% patients with CLI*
Schmidt et al. 2012,			
Stabile et al. 2012, and			
Virga et al. 2014			
Jaff et al. 2016, Scheinert et al. 2015, Tepe et al. 2014, and Fanelli et al. 2017	*Abstract*	*Prospective multi-centre cohort*	*Included >10% patients with CLI*
Brodmann et al. 2015			*Overlap with Brodmann et al. 2017*

Studies not in submission included by EAC			
Brodman et al. 2017	*Full paper*	*Prospective non comparative multicentre*	
Ott el al. 2017		*Prospective multi-centre RCT*	
Krishan et al. 2017 and Werk et al. 2014	*Abstract*	*Multicentre prospective RCT*	

EAC critical appraisal of the clinical evidence

The company conducted and reported a number of meta-analyses on freedom from target lesion revascularization and primary patency rates involving up to 11 studies, at 12 and 24 months. The EAC considered the company's meta-analysis to have a number of critical flaws; among which the company reported pooled results on the intervention ignoring any comparative evidence in the included studies, and reported proportions and not hazard ratios or relative risks. The EAC noted that the pooled analysis included retrospective and prospective cohort studies which is not advised by the Cochrane Collaboration, and that the company had also included results from a meta-regression but did not provide sufficient rationale for its choice of covariates. The EAC considered that no consideration had to been given to heterogeneity, and quality assessment undertaken, in the included studies, some of which it considered to be out of scope.

The EAC identified 4 RCT studies, 2 on de novo lesions (Werk et al. 2012 and Laird et al. 2015) and 2 on restenosis (Krackenberg et al. 2016 and Ott et al. 2017) which it considered were suitable for a meta-analysis. However since the studies contained no common outcome measures on which to synthesise results, the EAC concluded that a meta-analysis was not appropriate.

The EAC considered the IN.PACT SFA trial (Laird et al., 2015; Krishan et al., 2016) to be the pivotal evidence, a superiority multi-centre international RCT, which compared IN.PACT admiral DCB with standard PTA. The results

reported a statistically significant reduction in clinically-driven target lesion revascularization (CD-TLR), defined as reintervention at the target lesion due to symptoms or decrease in ankle-brachial index ≥ 20% or > 0.5 when compared to baseline, and in primary restenoses with IN.PACT compared with standard PTA. The two groups performed equally in terms of functional outcomes and target limb major amputations. There was a statistically significant higher mortality at 2 year in patients treated with IN.PACT, however the independent committee that assessed this outcome and the NICE expert advisers consulted by the EAC, considered that this was not attributed to the intervention. The EAC noted some potential sources of bias, mainly unclear risk of attrition bias and unclear risk of performance bias. The EAC also noted that the target lesion revascularization and safety benefits were also broadly supported by evidence from single-armed observational data. Although none of the included studies specific to the UK, the EAC considered the results should be generalisable to the UK setting.

Table 2: Pivotal studies in the EAC assessment report, reproduced from Table 4 in the assessment report

Study and design	Participants/ population	Intervention & comparator	Outcome measures and follow up	Results	Withdrawals	Funding	Comments
Laird et al. 2015	331 (65% male) age 67.5±9.5 Multi-centre USA and Europe	IN. PACT Admiral with or without stenting PTA with or without stenting	At 2 years follow-up: Primary patency CD-TLR Major amputations Functional improvement Device related deaths Mortality	IN.PACT had significantly better outcomes than PTA with the exception of mortality: <u>Primary patency</u> DCB 42 (78.9%) vs. PTA 54 (50.1%) (p<0.001) <u>CD-TLR</u> DCB 18, 9.1% vs. PTA 30, 28.3% (p<0.001) <u>MAE</u> DCB 38, 19.2% vs. PTA 33, 31.1% (p=0.023) <u>Functional improvement</u> DCB 133, 76.9% vs. PTA 61, 59.2% (p=0.003)	11 (10 intervention and 1 comparator) 6 lost to follow-up (3 in each group)	Company funded	Good methodological quality Powered to detect clinically significant TLR at 1 year follow-up, however results presented for follow-up up to 3 years (Krishan et al 2016)

				Device related deaths None Major amputations None Mortality DCB 16, 8.1% vs. PTA 1, 0.9% (p=0.008)			
Krishan et al 2016	As above	As above	Primary patency and CD-TLR at 3 years	Primary patency DCB 42 (69.5%) vs. PTA 54 (45.1%) (p<0.001) CD-TLR DCB 15.2% vs. PTA 31.1% (p=0.002)	Not reported	Company funded	As above
Abbreviations used: PTA = Percutaneous Transluminal Angioplasty; DCB = Drug coated balloon; CD-TLR = Clinically Driven Target Lesion Revascularization; MAE = Major Adverse Events							

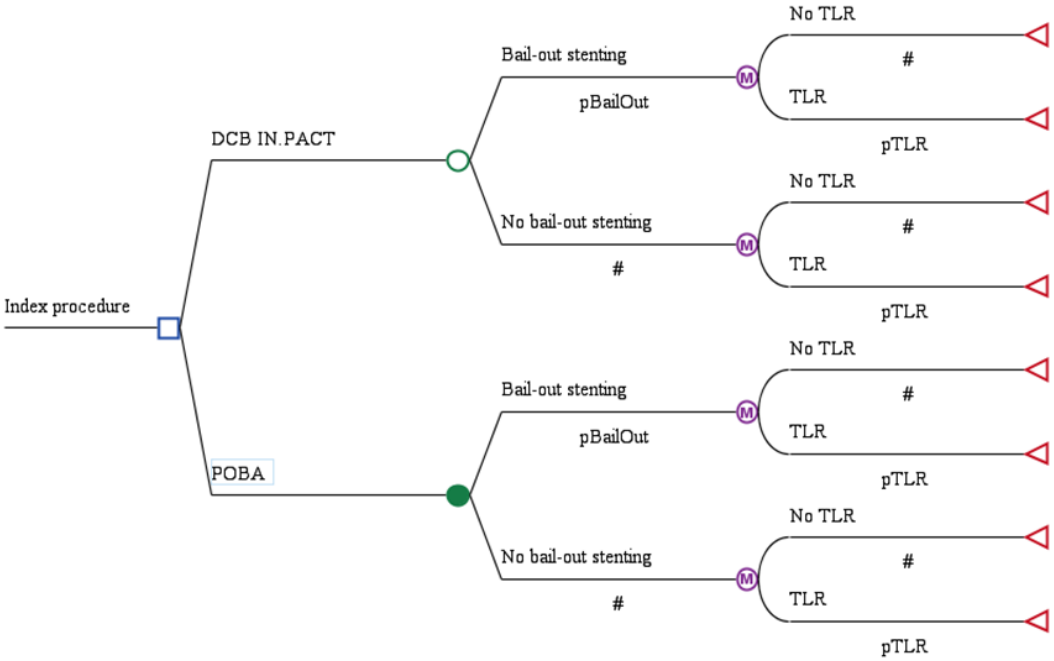
4.2 Summary of economic evidence

The company conducted literature searches for economic evidence that identified 7 studies. The EAC considered the company's searches to be appropriate but noted it included economic studies that included drug coated balloons as a class of devices and just 2 of the included studies (Salisbury et al 2016; Katsanos et al 2016) looked specifically at IN.PACT. The EAC conducted its own searches which identified no further evidence. For a full description of the EAC's consideration of the economic evidence see section 4.1 of the assessment report.

De novo analysis

The company submitted a decision tree model with INPACT and plain old balloon angioplasty (POBA) at the decision node as the 2 interventions of choice in patients eligible for PTA, and the need, or otherwise, for target lesion revascularisation as the endpoint in both treatment arms. To reflect current clinical practice, a certain proportion of patients receiving INPACT or POBA were assumed to require a bare metal stent ("bail out stenting") when the lesion showed either an inadequate post-treatment flow or a significant dissection. The model captures the cost of bail out stenting in these cases, and allows the option to apply a different target lesion revascularization (TLR) rate in these patients. The probability of TLR is modelled over 3 years in the base case, and total costs for the initial procedure and any TLR are estimated. A schematic representation of the model is shown in Fig 1.

Figure 1: Company model schematic, reproduced from Figure 1 in the assessment report



The EAC considered the company's model structure to be appropriate. It noted that the company had used a cycle length of 3 months, on the basis that the TLR proportions of 7 to 21% per year necessitated a shorter cycle length. The EAC considered that these proportions did not necessitate a short cycle length, it noted that the TLR was assumed to be constant over time, and concluded that while a shorter cycle length did not present any issues, a cycle length of 1 year was more appropriate.

Model parameters

The EAC used the relative risk from Laird et al (2015) to revise the company's parameter for the probability of a TLR but otherwise left the model inputs unchanged. The changes made by the EAC, and the costs of INPACT and POBA are reported in Table 3 below, with full details of the model parameters reported in Table 12 in the assessment report.

Table 3: Company model parameter values and EAC changes (reproduced from Table 12 in the assessment report)

Parameter	Company's value	Source	EAC value
Probabilities			
36 month TLR risk after DCB (primary)	17.8%	Company's meta-analysis	18.6%
36 month TLR risk after DCB (restenosis)	34.1%	Company's meta-analysis	36.3%
Unit Costs			
IN.PACT DCB (balloon only)	£603	Sales data, Medtronic	No change (base case)
BMS (stent only)	£384.00	Katsanos et al 2016	No change
POBA	£2,213.82	2015/16 NHS Ref. costs	No change

Results

The company reported a cost utility analysis, combining utilities accrued with costs, resulting in an ICER of £665 per QALY in the base case, and IN.PACT being dominant (lower costs, higher QALYs) at 4 years. The approach expected to be appropriate for most technologies is a cost consequence analysis, and the EAC used this approach. See pages 70 and 71 of the assessment report.

Table 4: The company's base case, reproduced from Table 11 in the assessment report

	Expected cost (£)	Cost difference (£) per patient
IN.PACT DCB with BMS bailout TLR (Technology)	3,947	-
PTA (POBA) with BMS bailout TLR (Comparator)	3,936	11

The company's base case reported costs at 3 years and showed a marginal cost increase from the adoption of IN.PACT compared with PTA. Within this time frame the additional cost of the technology was greater than the costs saving of target lesion revascularisations avoided. The company extended the model to a 4 year time horizon by which point savings through target lesion revascularisations were realised and a cost saving of £95 per patient was realised for IN.PACT.

The EAC accepted the principles of the company's model and made minor changes to a small number of parameters based on minor adjustment made to the relative risk of a TLR, using data from Laird et al (2015). When the EAC reran the model with their changes IN.PACT remained cost incurring at 3 years, but by the larger amount of £106 per patient.

Table 5: Base case with EAC corrections (reproduced from Table 13 in the assessment report)

	Index cost per patient	TLR cost per patient	Total cost per patient
PTA with BMS bailout	£2,694	£1,200	£3,894
IN.PACT DCB with BMS bailout	£3,504	£496	£4,000
Difference			£106

The EAC extended the model to 4 years, at which point IN.PACT remained cost incurring but by the smaller amount of £36.

The EAC conducted a number of sensitivity analyses and identified key parameters as the number of DCB devices used; the cost of IN.PACT DCB; and the relative risk of TLR with IN.PACT DCB. In most instances IN.PACT DCB remained cost incurring at 3 years, but was cost saving in each case at 4 years when the lower bounds of the sensitivity analyses were used, the cost saving scenario results are reported in Table 4 below:

Table 6: Cost saving scenarios in sensitivity analyses conducted by the EAC, reproduced from Tables 15 to 23 in the assessment report

Scenario	Saving at 3 years	Saving at 4 years
Assuming the same rate of bail-out stenting (12.6%) and no DCB used where stenting is indicated	N/A	£32
Assuming the TLR rate after bailout stenting is the same as rate with POBA (49.4% at 3 years instead of 36.3%)	N/A	£6
Assuming TLR rate after bailout stenting is the same as rate with POBA (49.4% at 3 years instead of 36.3%) and no difference in rates of bailout stenting between DCB and POBA	N/A	£32
Assuming 1.2 IN.PACT devices are used	£14	£108
Assuming IN.PACT costs £500	£39	£131
Assuming RR of TLR with IN.PACT of 0.21 (TLR risk 11.3% at 36 months)	£63	£193

The EAC undertook a subgroup analysis in patients with restenosis. This assumed a 3 year TLR rate of 32.0% for DCB and 67.5% for PTA, and found a slight cost increase of £7 for IN.PACT at 3 years but a cost saving of £29 at 4 years.

The EAC explored break-even values for the key parameters. It found that in patients undergoing a first procedure the relative risk for TLR with IN.PACT would have to fall from the EAC's estimate of 0.35 to 0.26 for savings in avoided TLRs to offset increased initial device costs at 3 years, and a rate of 0.34 would represent the breakeven point at 4 years. It found the breakeven price point for IN.PACT to be £527 at 3 years, and £593 at 4 years. It noted that further savings are likely to be realised beyond 4 years from reductions in TLRs, and resultant reductions in amputations, and that while these had not been modelled, this meant the estimates of the cost benefit of IN.PACT at 4 years are likely to be conservative.

5 Ongoing research

2 ongoing studies were identified by the EAC, both of which are funded by the company (INPACT SFA I - NCT01175850 and INPACT SFA II - NCT01566461). The INPACT SFA I study is shown as completed, there is data reported on changes in EQ5D scores at 12 months compared to baseline, but no data on the primary or secondary clinical outcomes.

6 Issues for consideration by the Committee

Key issues for consideration by the committee include:

What is the most appropriate measure of relative risk for TLR to use in the cost modelling? The EAC changed this parameter in the company's model based on data from Laird et al. 2015 increasing the relative risk of a TLR for IN.PACT compared with POBA. It decided to change this and the probability since the company's estimate had included some studies where >10% of the study population had critical limb ischaemia.

The cost modelling shows that IN.PACT is likely to be cost incurring at 3 years but moving from cost neutral to cost releasing at 4 years. There are a number of uncertainties and assumptions in the model as discussed and explored by the EAC. Does the committee consider that overall the technology is likely to represent a cost neutral option? What are the most relevant key parameter assumptions which must be considered?

There is evidence that IN.PACT has quality of life benefits, and the company calculated ICER is low at £665 per QALY in the base case. Does the committee consider that there are significant quality of life benefits not captured in the cost modelling?

7 Authors

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February 2018

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

A Details of assessment report:

- Bourmpaki, E; Bunce, C, Chalkidou, A et al. The IN.PACT drug-coated balloon for femoro-popliteal peripheral arterial disease (December 2017)

B Submissions from the following sponsors:

- Medtronic

C Related NICE guidance

- Cardiovascular disease: risk assessment and reduction, including lipid modification (2014; updated 2016) NICE guideline CG181
- Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease (2014; updated 2016) NICE guideline CG181
- Peripheral arterial disease: diagnosis and management (2012) NICE guideline CG147
- Type 1 diabetes in adults (2015; updated 2016) NICE guideline NG17.
- Type 2 diabetes in adults: management (2015; updated 2016) NICE guideline NG28
- Cardiovascular disease prevention (2010) NICE guideline PH25

D References

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Appendix B: Comments from professional bodies

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

Dr James Lenton

Vascular & Interventional Radiology Consultant, nominated by British Society for Interventional Radiology

Dr Trevor Cleveland

Consultant Vascular Radiologist, ratified by British Society for Interventional Radiology

Prof Andrew Bradbury

Consultant Vascular and Endovascular Surgeon, nominated by Vascular Society

Ms Jane Todhunter

Vascular Nurse Practitioner, nominated by Society of Vascular Nurses

Dr Peter Holt

Reader/Consultant Vascular Surgeon, ratified by The Vascular Society of Great Britain and Ireland

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Consultant Vascular & Interventional Radiologist, nominated by British Society for Interventional Radiology

Mr Dan Carradice

Consultant Vascular & Endovascular Surgeon, ratified by The Vascular Society of Great Britain and Ireland

Mr Kevin Varty

Consultant Vascular Surgeon, nominated by British Society for Interventional Radiology

Dr Robert Morgan

Specialist vascular and interventional radiologist, ratified by British Society for Interventional Radiology

Dr Stephen Butterfield

Consultant Vascular Interventional Radiologist, nominated by British Society for Interventional Radiology

Ms Janice Tsui

Consultant Vascular Surgeon, ratified by The Vascular Society of Great Britain and Ireland

- The experts considered that IN.PACT DCB sat within a class of DCB technologies and therefore could not be considered to be novel in itself but that overall drug coated balloons are a significant innovation
- The experts considered that either no or minimal training was required to use the technology
- All of the experts were familiar with the technology, and with the exception of 2 experts all had direct experience of using the technology and were using it currently.
- The majority of experts considered that the technology would improve patient outcomes, principally by reducing restenosis and re-intervention rates.
- In terms of the system impact of the technology while the experts acknowledged that it is more expensive than plain balloon it may reduce costs through reductions in readmissions and reinterventions.
- All experts considered that no changes in facilities or infrastructure would be needed if this technology were adopted
- One expert considered that the technology would not save costs and 3 were unsure. The remaining experts considered it would save costs with one adding that this would be realised in the long term and one that the savings would be minor

Appendix C: Comments from patient organisations

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

- British Heart Foundation
- Cardiovascular Care Partnership (UK)
- Lindsay Leg Club Foundation
- The Circulation Foundation
- UK Health Forum (formerly National Heart Forum)

Appendix D: decision problem from scope

Claimed benefits

The benefits to patients claimed by the company are:

- A significant improvement in primary patency
- A significant decrease in rates of repeat interventions
- An improvement in target lesion revascularisation
- A reduction in claudication symptoms and scores
- An improvement in quality of life and function.

The benefits to the healthcare system claimed by the company are:

- A reduction in hospitalisations
- Cost savings through the avoidance of complications and subsequent hospitalisation and re-intervention

	Scope issued by NICE	
Population	People with femoro-popliteal peripheral arterial disease undergoing revascularization for intermittent claudication	
Intervention	Percutaneous transluminal angioplasty (PTA) with IN.PACT drug coated balloon (Pacific or Admiral versions) (with or without bailout stenting)	
Comparator(s)	Percutaneous transluminal angioplasty (PTA) with a non-drug coated balloon (with or without bailout stenting)	
Outcomes	The outcome measures to consider include: • Intermittent claudication symptom severity (including scores) • Quality of life and functional capability • Rate of hospitalization • Target lesion revascularisation rates • Primary patency rates • Repeat intervention rates • Rates of vessel thrombosis • Angiographically determined late lumen loss • Device-related adverse events	
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.	
Subgroups to be considered	• people presenting with in-stent restenosis • people with restenosis or recurrence	
Special considerations, including those related to equality	PAD is more common in older people and men and people with diabetes. Diabetes is more common in people from certain ethnic groups and race is a protected characteristic under the Equalities Act. Some people with PAD may have symptoms severe enough to limit their mobility and may be considered disabled under the Equalities Act.	
Special considerations, specifically related to equality issues	The technology is contraindicated in pregnant or breast-feeding women	
	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristics?	Yes
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure MTAC will have relevant information to consider equality issues when developing guidance?	No