

# Impella 2.5 for haemodynamic support during high-risk percutaneous coronary interventions

Medtech innovation briefing

Published: 29 November 2016

[www.nice.org.uk/guidance/mib89](http://www.nice.org.uk/guidance/mib89)

## Summary

- The **technology** described in this briefing is the Impella 2.5 left ventricular assist device. It is used to temporarily support a patient's circulatory system during elective and urgent high-risk percutaneous coronary interventions (PCI).
- The **innovative aspects** are that it directly unloads the left ventricle, providing continuous forward flow in the ascending aorta, independent of the patient having any intrinsic cardiac output or rhythm. This is different to intra-aortic balloon pumps (IABPs), which provide pulsed therapy. This has the potential to increase overall cardiac output and improve oxygenation while protecting the heart muscle.
- The intended **place in therapy** would be as part of a comprehensive mechanical assist solution for people needing elective or urgent high-risk PCI.

- The **key points from the evidence** summarised in this briefing are from 1 meta-analysis, 1 large randomised controlled trial, 2 single-arm registry studies and 1 retrospective comparative single-arm study (involving a total of 1,586 patients). There were no statistically significant differences in 30-day major adverse events when using Impella 2.5 compared with IABP. Fewer major adverse events were reported at 90-day follow-up when using Impella 2.5. This was statistically significant using the per protocol analysis but not for the intention-to-treat analysis.
- **Key uncertainties** around the evidence are that a randomised controlled trial was terminated early because interim analysis showed that the primary clinical outcome was unlikely to be achieved. There are also currently no data from other studies directly comparing Impella 2.5 with IABP.
- The **cost** of a single-use Impella 2.5 catheter is approximately £15,000, although volume discounts are available. The reusable Automated Impella Controller, which is needed to use the device, costs approximately £35,000 for 2 units, excluding VAT. The unit cost of an IABP is estimated to be £600. Adopting Impella 2.5 is likely to pose an additional cost to the NHS.

## The technology

Impella 2.5 is a miniaturised, catheter-based, intravascular blood pump that supports a patient's circulatory system. It provides continuous forward flow to increase overall cardiac output, unload work from the ventricle (decreasing myocardial oxygen demand) and improve coronary flow (increasing oxygen supply). This action is designed to support systemic haemodynamics and protect the myocardium from ischaemic damage.

Impella 2.5 is indicated for clinical use in cardiology and cardiac surgery for a number of indications. The primary indication is for cardiovascular support before, during and after urgent or elective high-risk percutaneous coronary intervention (PCI).

Impella 2.5 comprises 3 main components:

- A sterile, single-use, intravascular catheter with an integrated blood pump that provides flow rates of up to 2.5 litres per minute.

- A sterile, single-use purge cassette with an in-line purge pressure transmitter which is connected to the catheter purge lumen. The purge fluid is typically 5% dextrose in water (the maximum recommended level of dextrose is 40%) containing heparin, and prevents blood from entering the motor.
- A reusable, external Automated Impella Controller (AIC), with a 10-inch colour display, which is the main user interface and is used to control the pump. The controller can be mounted on a 4-wheeled cart for use in the catheterisation laboratory, or on a bedside rail during patient transfer. The controller is powered by mains electricity or a rechargeable, lithium-ion battery for patient transfer, which lasts for at least 60 minutes when fully charged. The controller is provided in packs of 2, because the manufacturer's internal safety guidelines state that a backup controller should always be available in case the first controller fails.

An Impella setup and insertion kit contains all the single-use, sterile accessories needed: an introducer kit to gain arterial access, a 260 cm catheter placement guide-wire and a catheter-to-controller connection cable, as well as the Impella 2.5 catheter and purge cassette components. Hospitals must provide their own diagnostic catheter and a 5 to 8 French (Fr) introducer.

The operator follows the instructions shown on the AIC to setup the catheter. This includes inserting and auto-priming the purge cassette, connecting the Impella catheter cable and lumen luer connectors, auto-priming the catheter purge lumen and manually priming the catheter placement signal lumen with dextrose solution.

The operator then inserts the Impella catheter using fluoroscopy to guide placement across the aortic valve and into the ventricular chamber. A radiopaque marker on the catheter shaft will be level with the aortic valve when the catheter is properly positioned in the left ventricle, indicating that the pump is ready to be started. When the pump is started, blood from the pump inlet area, which sits inside the left ventricle, is delivered through the cannula to the outlet opening in the ascending aorta. Operators monitor the correct positioning and functioning of the Impella device using the AIC.

A number of versions of the Impella device are available. Impella CP (Cardiac Power) and Impella 5.0 have increased flow rates of 3.5 litres and 5 litres respectively. Impella CP can be used for the same indications as Impella 2.5. The 5.0 version is for use in patients with shock and acute myocardial infarction. Impella LD (Left Direct) and Impella RP (Right Percutaneous) are also available but are indicated for use during open chest surgery and for right heart failure respectively. These additional versions and indications are beyond

the scope of this briefing.

## The innovation

Impella 2.5 directly unloads the left ventricle, providing continuous forward flow in the ascending aorta. This is different to an intra-aortic balloon pump (IABP), which is used in current practice. Unlike Impella 2.5, the IABP is not a mechanical left ventricular assist device; it is a volume displacement device that provides pulsed therapy by inflating and deflating the balloon in time with the patient's heart rate.

The pulsed therapy of IABP relies on there being adequate time between triggers (electrocardiogram [ECG] or pulse pressure wave) to inflate and deflate the balloon. This can be problematic if the patient has tachycardia, and can result in failure if cardiac output stops altogether. The continuous flow support from Impella 2.5 is independent of the patient having any intrinsic cardiac output or rhythm.

## Current NHS pathway

Currently, no national guidance exists in the UK for the use of haemodynamic support devices, such as Impella 2.5, in high-risk PCI procedures.

Haemodynamic support devices can be used during some PCI procedures to maintain blood flow. This may be necessary for some high-risk procedures, such as those in patients with complex coronary artery disease (unprotected left main disease, last remaining vessel or multi-vessel disease), compromised left ventricular function or ongoing ischaemia ([Jones et al. 2012](#)). The specialist commentators who contributed to this briefing estimated that between 0.2% and 5.0% of patients having PCI need a haemodynamic support device.

IABPs are the most common device used to provide haemodynamic support during PCI, although intra-corporeal or extra corporeal pumps may also be used. Impella 2.5 could be used to provide haemodynamic support for suitable patients instead of IABPs.

NICE is aware of another CE-marked device which fulfils a similar purpose as the Impella 2.5:

- [Thoratec HeartMate PHP](#).

## Population, setting and intended user

Impella 2.5 would be used in patients needing haemodynamic support before, during or after elective or urgent high-risk PCI procedures, instead of an IABP. It is also indicated for patients with reduced left ventricular function, such as in post-cardiotomy, low output syndrome, cardiogenic shock after acute myocardial infarction, or myocardial protection after acute myocardial infarction. These indications are beyond the scope of this briefing.

Impella 2.5 is contraindicated in patients with certain conditions, as detailed in the [instructions for use](#).

Impella 2.5 and IABP have different mechanisms of action and safety profiles. They are both considered to be parts of a comprehensive mechanical assist solution, with the most appropriate device being used based on the clinical scenario.

Impella 2.5 would be used by interventional cardiologists trained in cardiac catheterisation who have appropriate training in all Impella system components.

In some clinical scenarios, Impella 2.5 could be used for up to 5 days in patients who need prolonged haemodynamic support. In these cases interventional cardiologists would be responsible for the implant and removal, while general intensivists and advanced heart failure cardiologists would be responsible for ongoing care.

## Costs

### Device costs

The reusable controller has an anticipated lifespan of 7 years. The Impella 2.5 catheter is designed to provide circulatory support for up to 5 days.

The controller needs scheduled maintenance and safety checks once a year. Three service options are available:

- Service on call – Charged at a rate of £1,676 (€2,000) per service.

- Maintenance agreement – In place for 3 years and includes preventative maintenance, maintenance parts and software and hardware updates, costing £2,386\* (€2,850) per system per year.
- Full service with extended warranty – In place for 3 years, in addition to services provided under the maintenance agreement, all repairs and spare parts for repair and loaner units during repair are covered, costing £3,014\* (€3,600) per system per year.

The manufacturer provides 2 training programmes with the purchase of the system, included with the purchase cost. Initial training lasts a few hours, introducing the science of haemodynamic support and providing an overview of the Impella system and procedure. A 1-day advanced training programme is also available, which provides more hands-on experience and case reviews.

**Table 1 Current costs of Impella 2.5 system components**

Description	Cost (excluding VAT)*	Additional information
Automated Impella Controller	€42,000 (£35,049)	Includes 2 reusable units
Impella 2.5 setup and insertion kit	€8,000 to €18,000€ (£6,676 to £15,022): discount available based on quantity purchased per year	Single-use, containing all sterile accessories including the Impella 2.5 catheter and purge cassette
Full service agreement for the AIC	€3,600 (£3,004)	Pricing per year, minimum 3 years. Includes an extended warranty
Abbreviation: AIC, Automated Impella Controller. * Note that prices were converted from euros to pounds using the <a href="#">XE currency converter</a> in July 2016.		

## Costs of standard care

IABPs are the most common device used to provide haemodynamic support during PCI. The unit cost of an IABP is estimated to be £603 (taken from the appendices of NICE's guideline on [acute heart failure](#)).

## Resource consequences

Impella 2.5 is likely to be used instead of an IABP for suitable patients in the current clinical pathway. The unit cost for Impella 2.5 is considerably greater than that for an IABP so the technology would pose an additional expense to the NHS.

The literature review identified 3 economic studies ([Roos et al. 2013](#), [Gregory et al. 2013](#) and [Wohns et al. 2014](#)) which reported that Impella 2.5 was cost effective compared with IABPs. However, the cost savings were based on treatments and care pathways offered outside of the UK and so these results are not directly generalisable to NHS practice.

## Regulatory information

Impella 2.5 was CE marked as a class III medical device in February 2004.

A search of the Medicines and Healthcare Products Regulatory Agency website revealed that no manufacturer Field Safety Notices or Medical Device Alerts have been issued for this technology.

## Equality considerations

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. In producing guidance and advice, NICE aims to comply fully with all legal obligations to: promote race and disability equality and equality of opportunity between men and women, eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, marriage and civil partnership, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief (these are protected characteristics under the Equality Act 2010).

Coronary heart disease, for which PCI is indicated, is more common in people over the age of 65 and affects more men than women. Age and sex are protected characteristics under the Equality Act 2010.

## Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the published process and methods statement. This briefing includes the most relevant and best publicly available evidence relating to the clinical and cost effectiveness of the technology. The literature search strategy, evidence selection methods and detailed data extraction tables are available on request by contacting [mibs@nice.org.uk](mailto:mibs@nice.org.uk).

### Published evidence

This briefing summarises 5 studies: 1 meta-analysis ([Briasoulis et al. 2016](#)), 1 randomised controlled trial (PROTECT II, [O'Neill et al. 2012](#)), 2 registry studies (USpella, [Maini et al. 2012](#); Europella, [Sjauw et al. 2009](#)) and 1 retrospective, comparative, single-arm study using registry (USpella) and trial (PROTECT II) data ([Cohen et al. 2015](#)). These studies include a total of 1,586 patients excluding overlapping cohorts.

Table 2 summarises the clinical evidence as well as its strengths and limitations.

### Strengths and limitations of the evidence

The main limitation of the meta-analysis and observational studies is that they were descriptive and do not provide comparative data. One study from the meta-analysis that could not be identified ([Schreiber et al. 2016](#)) is likely to be unpublished data; however, the results are consistent with other studies.

The PROTECT II randomised controlled trial ([O'Neill et al. 2012](#)) was a high quality study that provides comparative data with clear, prospectively defined primary and secondary end points. However, after review of the interim data (n=327), the data safety monitoring board recommended early discontinuation of the study for futility. An extra 125 patients had been enrolled by the time the executive committee accepted the recommendation and study enrolment ceased, but the trial had not enrolled the number of patients for which it was powered. Therefore, definitive statements concerning the primary end point are speculative. However, the authors did report that they observed a notable learning curve in the trial, with marked improvement in safety for patients who had Impella in the last half of the trial.

The retrospective study by [Cohen et al. \(2015\)](#), which compared data from the PROTECT II



trial with registry data, suggests the results are generalisable to real-life clinical practice.

Two of the studies had funding from the manufacturer (O'Neill et al. 2012, Sjauw et al. 2009) and the authors of a third study had affiliations with and institutional research support from the manufacturer (Cohen et al. 2015).

## Table 2 Summary of the selected studies

Study	Details of intervention [and comparator]	Outcomes	Strengths and limitations
-------	--	----------	---------------------------

<p><u>Briasoulis et al. (2016)</u> n=1,346 Meta-analysis (11 cohort and registry studies, and the Impella arm of the PROTECT II trial)</p>	<p>Impella 2.5 assisted PCI (no control arm).</p>	<p>The pooled cohort analysis for 30-day mortality, 30-day MI, clinical major bleeding and vascular complication rates were 3.5%, 3.3%, 7.1% and 4.9% respectively. Significant heterogeneity between studies was observed for pooled 30-day MI rate, pooled clinical major bleeding rate and pooled vascular complication rate, but not for pooled clinical 30-day mortality rate. After exclusion of low quality studies, the rates of 30-day mortality, major bleeding, and MI did not change substantially. However, in the group of low risk of bias studies, the vascular complication rate was higher.</p>	<p>One study used in the meta-analysis for Impella was not referenced and could not be identified. The meta-analyses were based on single-armed data and were descriptive rather than analytic. There was heterogeneity between studies in terms of patient baseline characteristics and outcomes. Individual studies were critically appraised using appropriate methodology.</p>
--	---	---	--

<p><u>O'Neill et al. (2012)</u>  n=448 patients indicated for high-risk PCI  Randomised controlled trial – PROTECT II  Multinational – 112 sites  US, Canada and Europe</p>	<p>Impella 2.5 assisted PCI (intervention group; n=225) compared with IABP assisted PCI (control group; n=223).</p>	<p>There was no significant difference in the primary outcome (occurrence of MAEs at 30 days) between the Impella group compared with the IABP group.</p> <p>Fewer MAEs were reported at 90-day follow-up when using Impella 2.5. These were statistically significant using the per protocol analysis but not for the intention-to-treat analysis.</p> <p>After hospital discharge, there were significantly fewer irreversible MAEs involving death, stroke, MI or repeat vascularisation events in the Impella 2.5 group in comparison with the IABP group.</p> <p>Patient cardiac function and functional status improved significantly after revascularisation in the Impella 2.5 group.</p> <p>Impella 2.5 provided better haemodynamic</p>	<p>The study was terminated early after interim futility analysis indicated the primary outcome was unlikely to be achieved.</p> <p>Therefore insufficient patients were enrolled to adequately power the study to detect a treatment difference of 10% between Impella 2.5 and IABP (relative reduction in major adverse events of 33%).</p> <p>Blinding was not possible because of study nature and may have introduced potential changes leading to performance bias. Median rotational atherectomy time per lesion was significantly higher in the Impella arm.</p> <p>Patient characteristics at baseline were comparable.</p> <p>The authors also used an intention-to-treat analysis which allowed for a more pragmatic evaluation of the benefit of the</p>
---	---	---	--

		<p>support than IABP during the high-risk procedures based on maximal drop in cardiac power output from baseline.</p> <p>Patients with STS morbidity risk scores of &lt;10 had better 90-day outcomes with Impella 2.5 than with IABP.</p>	<p>treatment change.</p>
--	--	--	--------------------------

<p><u>Maini et al. (2012)</u> n=175 patients indicated for elective or urgent PCI</p> <p>Retrospective single-arm cohort study – based on prospectively collected registry data (USpella)</p> <p>Multicentre – 18 centres North America</p>	<p>Impella 2.5 assisted high-risk PCI (single-arm study).</p>	<p>Overall, angiographic revascularisation was successful in 99% of patients and in 90% of those with multi-vessel revascularisation.</p> <p>Systolic and diastolic blood pressures improved significantly while on support.</p> <p>Overall, there was a significant reduction of the mean SYNTAX score (grade for severity of coronary artery disease).</p> <p>There was an improvement of the functional status by one or more NYHA classes at discharge.</p> <p>Major vascular complications, haematomas (&gt;4 cm), renal failure and bleeding requiring transfusion were reported in 4.0, 8.6, 2.8 and 9.7% of patients respectively.</p> <p>All deaths were considered cardiac and not directly related to the Impella 2.5 device.</p>	<p>Provides real-world data on the safety profile and clinical outcomes of the Impella 2.5.</p> <p>The single-armed design of the registry did not provide comparative data for Impella 2.5 with standard care or a no-device approach.</p> <p>Main outcomes were related to the effectiveness of PCI rather than Impella.</p> <p>This was the only study to investigate follow-up at 12 months.</p> <p>Consecutive patients were analysed reducing the likelihood of selection bias.</p>
---	---	--	---

<p><u>Sjauw et al. (2009)</u> n=144 consecutive patients having elective high-risk PCI Retrospective single-arm cohort study – based on prospectively collected registry data (Europella Registry) Multicentre – 10 tertiary PCI centres across Europe</p>	<p>Cardiac support with Impella 2.5 (single-arm study).</p>	<p>Successful passage through the femoral artery and implantation of the Impella 2.5 into the LV was achieved in all 144 patients. Both implantation and removal of the Impella were considered easy or suitable in &gt;99% of the cases. Mortality at 30 days was 5.5%. Rates of MI, stroke, bleeding requiring transfusion/surgery, and vascular complications at 30 days were 0%, 0.7%, 6.2% and 4.0% respectively.</p>	<p>All adverse events were based on clinical diagnoses by the patient's physician. However, events were entered in a prospectively developed case report form and centrally adjudicated by an independent clinician. Consecutive patients were analysed reducing the likelihood of selection bias.</p>
--	---	--	--

<p><u>Cohen et al. (2015)</u>  n=637 patients having high-risk PCI (USpella registry)  n=216 (PROTECT II trial)  Retrospective comparative single-arm study – using registry (USpella) and trial (PROTECT II) data  USpella – multicentre (49 centres: US and Canada)  PROTECT II – multinational (112 centres, US, Canada and Europe)</p>	<p>Cardiac support with Impella 2.5 – comparison of real-world registry data with clinical trial data.  A subset of patients (n=339) included in the USpella registry were identified that would have met eligibility for the PROTECT II trial and defined as PROTECT II-like patients.</p>	<p>The baseline risk of the PROTECT II-'like' patients was comparable to the clinical trial data. However, they were considered at higher risk of mortality in terms of age, renal insufficiency, coronary heart failure and LVEF.  At hospital discharge, registry patients experienced a similar reduction in NYHA class III to IV symptoms compared to trial patients.  There was a significantly lower rate of post-procedural MI and repeat revascularisation in USpella PROTECT II-'like' patients compared with the PROTECT II Impella arm patients.  Registry patients had a trend toward lower in-hospital mortality.  Despite the higher risk profile of registry patients, clinical outcomes appeared</p>	<p>No propensity matching was performed. As data were collected retrospectively, only the major exclusion criteria from the PROTECT II trial could be assessed, which makes the interpretation of the results somewhat limited.  Results within the abstract do not correspond with those within the table of the study.</p>
--	---	--	--

		to be favourable and consistent compared with those in the randomised trial.	
Abbreviations: IABP, intra-aortic balloon pump; LV, left ventricle; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MAE, major adverse event; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; STS, Society for Thoracic Surgery.			

## Recent and ongoing studies

One in-development trial on Impella 2.5 was identified in the preparation of this briefing:

- [NCT02468778](#): Coronary Interventions in High-Risk Patients Using a Novel Percutaneous Left Ventricular Support Device (SHIELD II) – currently recruiting patients to evaluate the use of HeartMate PHP with Impella 2.5 as the active comparator for both the elective and urgent indications.

## Specialist commentator comments

Comments on this technology were invited from clinical experts working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

Four of the 5 specialist commentators have used this technology.

## Level of innovation

Two specialist commentators indicated that, when it was introduced, the Impella 2.5 was a marked improvement on existing technology with greater cardiac output than intra-aortic balloon pumps (IABPs) and the ability to provide a stable output independent of the underlying heart rhythm or function. However, the Impella pump has been available for a number of years and is now not considered to be novel. They considered that the Impella 2.5 has been superseded by the Impella CP (Cardiac Power), which increases cardiac output by up to 3.5 litres per minute, requires slightly larger-bore vascular access and is likely to be of greater benefit to patients. Two specialists noted that several similar



devices are currently available but did not think that the Impella 2.5 had been superseded.

## Potential patient impact

The specialist commentators each identified subgroups of patients who may benefit from Impella 2.5. Five specialist commentators considered Impella 2.5 to be of more benefit in patients who are in extreme haemodynamic states, for example cardiogenic shock following myocardial infarction. One added that Impella 2.5 could be used as a 'bridge' to more invasive methods in these patients.

Other subgroups identified by specialist commentators as potentially benefitting from Impella 2.5 included:

- Patients with multiple comorbidities such as those who have had bypass surgery, who are often older and need more complex percutaneous coronary intervention (PCI) procedures.
- During high-risk PCI when left main stem angioplasty needs rotablation in the context of severe left ventricular dysfunction and a chronically occluded right coronary artery.
- Patients at early stages of heart failure after myocardial infarction.

## Potential system impact

Four specialist commentators noted that the use of Impella 2.5 would have cost implications because of the high device cost. One added that the device would also add complexity to treatment.

One commentator suggested that although Impella 2.5 may have a dramatic and potentially life-saving impact for selected patients for whom it is suitable, this is unlikely to translate to system-wide cost savings.

However, 2 specialist commentators suggested that it may reduce costs in the long term if it prevents patients from progressing to more complex forms of haemodynamic support.

Another specialist considered that, for particular high-risk cohorts (such as patients who need rotational atherectomy or complex chronic total occlusion angioplasty), using Impella 2.5 may allow PCI procedures that would otherwise not be possible. This would

have a positive system impact because Impella would allow for revascularisation procedures in these patients, and so would lead to fewer future hospital admissions.

One specialist highlighted the fact that using Impella 2.5 allowed cardiogenic shock patients to be managed in a coronary care unit (CCU) rather than cardiac ICU (cICU). This was likely to have a major system impact because of the significant reduction in terms of cost and bed management. However, the specialist noted that these cost savings would not be seen in centres that do not use surgical LVADs; these centres would see an increase in costs, because patients having Impella 2.5 are more likely to be managed medically in the early period following PCI. Similarly, extracorporeal membrane oxygenation (ECMO) can lead to cancellation of elective cardiac surgical cases because so many cICU staff are needed; 2 commentators felt that reducing the need for ECMO would avoid these implications.

Three specialist commentators noted the need for training to use Impella 2.5. One considered there to be a clear learning curve associated with using Impella 2.5, not only for interventional cardiologists but for the intensive care and coronary care units and staff managing the patients once they leave the cardiac catheter laboratory.

## General comments

Two specialist commentators suggested that the broad patient inclusion criteria in the PROTECT II trial may account for the lack of mortality benefit or differences in outcomes observed. One noted that it may not be feasible to carry out a randomised controlled trial for patients having high-risk PCI as this is a select group and the risks may be too high.

Two commentators noted the lack of definitive clinical evidence and saw this, along with the cost of the technology, as a barrier to the adoption of Impella 2.5 across the NHS.

## Specialist commentators

The following clinicians contributed to this briefing:

- Dr Alan Bagnall, Consultant Cardiologist, Newcastle-upon-Tyne Hospitals NHS Foundation Trust (no conflicts of interest reported).

- Dr Farzin Fath-Ordoubadi, Consultant Cardiologist, Central Manchester University Hospitals NHS Foundation Trust (received reimbursement for attending a symposium).
- Professor Keith Oldroyd, Consultant Cardiologist, Western Infirmary, Glasgow (no conflicts of interest reported).
- Dr Divaka Perera, Consultant Cardiologist and Reader in Interventional Cardiology, Guy's and St Thomas' NHS Foundation Trust (received speaker fees from the manufacturer for a lecture at the Circulatory Support Meeting in Bournemouth. He has received hospitality subsistence for a training visit at the Abiomed headquarters in the USA).
- Professor Azfar Zaman, Consultant Cardiologist, Newcastle-upon-Tyne Hospitals NHS Foundation Trust (no conflicts of interest reported).

## Development of this briefing

This briefing was developed for NICE by Newcastle and York external assessment centre. The [interim process and methods statement](#) sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

ISBN: 978-1-4731-2180-5