

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Medical technology consultation document

# HeartFlow FFR<sub>CT</sub> for estimating fractional flow reserve from coronary CT angiography

The National Institute for Health and Care Excellence (NICE) is producing guidance on using HeartFlow FFR<sub>CT</sub> for the estimation of fractional flow reserve from coronary CT angiography in the NHS in England. The medical technologies advisory committee has considered the evidence submitted and the views of expert advisers.

This document has been prepared for public consultation. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the committee. NICE invites comments from the public. This document should be read along with the evidence base (see Sources of evidence considered by the committee).

The committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical effectiveness and resource savings reasonable interpretations of the evidence?
- Are the provisional recommendations sound, and a suitable basis for guidance to the NHS?
- Are there any equality issues that need special consideration and are not covered in the medical technology consultation document?

**Note that this document is not NICE's final guidance on HeartFlow FFR<sub>CT</sub> for the estimation of fractional flow reserve from coronary CT angiography. The recommendations in section 1 may change after consultation.** After consultation the committee will meet again to consider the evidence, this document and comments from public consultation. After considering these comments, the committee will prepare its final recommendations which will be the basis for NICE's guidance on the use of the technology in the NHS in England.

For further details, see the [Medical Technologies Evaluation Programme process guide](#) and [Medical Technologies Evaluation Programme methods guide](#).

Key dates:

- Closing time and date for comments: 09:00 26 September 2016
- Second medical technologies advisory committee meeting: 22 October 2015

- Update second medical technologies advisory committee meeting: 22 July 20

NICE medical technologies guidance addresses specific technologies notified to NICE by sponsors. The 'case for adoption' is based on the claimed advantages of introducing the specific technology compared with current management of the condition. This case is reviewed against the evidence submitted and expert advice. If the case for adopting the technology is supported, then the technology has been found to offer advantages to patients and the NHS. The specific recommendations on individual technologies are not intended to limit use of other relevant technologies which may offer similar advantages.

# 1 Provisional recommendations

- 1.1 The case for adopting HeartFlow FFR<sub>CT</sub> for estimating fractional flow reserve from coronary CT (CCT) angiography is supported by the evidence. The technology is non-invasive and safe, and has a high level of diagnostic accuracy.
- 1.2 HeartFlow FFR<sub>CT</sub> should be considered as an option for patients with stable, recent onset chest pain of suspected cardiac origin and a clinically determined intermediate (10% to 90%) risk of coronary artery disease. Using HeartFlow FFR<sub>CT</sub> may avoid the need for invasive coronary angiography and revascularisation. For correct use, HeartFlow FFR<sub>CT</sub> requires access to 64-slice (or above) coronary CT angiography facilities.
- 1.3 Based on the current evidence and assuming there is access to appropriate coronary CT angiography facilities, using HeartFlow FFR<sub>CT</sub> may lead to cost savings of £214 per patient. By adopting this technology, the NHS in England may save around £7.7 million. These estimated savings are achieved through the avoidance of invasive investigation and treatment.

## 2 The technology

### *Description of the technology*

- 2.1 HeartFlow FFR<sub>CT</sub> (developed by HeartFlow) is a post-processing image analysis software package that provides a non-invasive method of estimating fractional flow reserve (FFR) using standard coronary computed tomography angiography (CCTA) image data. FFR is the ratio between the maximum blood flow in a narrowed artery and the maximum blood flow in a normal artery. FFR is currently measured invasively using a pressure wire placed across a narrowed artery.

- 2.2 After a clinician decides to request a HeartFlow test, anonymised data from a CCTA scan (of at least 64 slices) are sent from the local imaging system, via secure data transfer to HeartFlow's central processing centre in the US. A case analyst employed by the company then uses the image data to create 3D computer models of the coronary arteries, incorporating coronary flow characteristics. The results are presented in a report which is sent, via secure data transfer, to the referring clinician within 48 hours. The report includes both 3D images of the coronary anatomy and calculated functional information, including the estimated FFR values (known as FFR<sub>CT</sub> values). Clinicians can then use the report to help guide the management of suspected coronary artery disease.
- 2.3 HeartFlow FFR<sub>CT</sub> is intended for use in patients with stable, recent onset chest pain and suspected angina. Because the safety and effectiveness of FFR<sub>CT</sub> analysis has not been evaluated in other patient subgroups, HeartFlow FFR<sub>CT</sub> is not recommended in patients who have an acute coronary syndrome or have had a coronary stent, coronary bypass surgery or myocardial infarction in the past month.
- 2.4 The company first received a CE mark in July 2011, covering all 1.X versions of the technology, including the current version, 1.7.
- 2.5 HeartFlow FFR<sub>CT</sub> costs £700 per test. A higher price of £888 is used in the company submission and assessment report. The cost was reduced in May 2015.
- 2.6 The claimed benefits of HeartFlow FFR<sub>CT</sub> in the case for adoption presented by the company were as follows:
- Analysis is done using standard CCTA scans, without the need for additional imaging, radiation or medication.
  - It provides the same accuracy in excluding coronary artery disease as CCTA, and characterizes the coronary arteries from

both functional and anatomical perspectives, differentiating between ischaemic and non-ischaemic vessels in a way that CCTA cannot.

- It allows physicians to evaluate anatomic coronary artery disease and accurately determine which coronary lesions are responsible for myocardial ischaemia, avoiding unnecessary invasive diagnostic or therapeutic procedures and related complications.
- It reduces the need for revascularisation in patients after identifying anatomic stenosis by invasive coronary angiography (ICA) alone, by more accurately identifying if those stenoses are ischaemic.
- It improves the diagnostic accuracy for coronary artery disease compared with CCTA alone against the gold standard of invasive FFR, and provides both functional and anatomic assessment of coronary arteries.
- It has better diagnostic performance than CCTA alone, or other non-invasive or invasive tests (such as nuclear myocardial perfusion, magnetic resonance perfusion, stress echocardiography, exercise treadmill testing, invasive angiography or intravascular ultrasound) for detecting and excluding coronary artery lesions that cause ischaemia.
- It reduces costs arising from inconclusive or inaccurate diagnostic tests.
- It avoids staff and procedure costs for unnecessary invasive coronary angiographies.
- It avoids staff and procedure costs for unnecessary interventions (such as angioplasty).
- It provides a more effective use of high-cost invasive procedure suites, providing the opportunity to reduce waiting times for these facilities and increase patient turnaround.

## ***Current management***

- 2.7 The draft updated NICE guideline on [chest pain](#) recommends diagnostic testing for people in whom stable angina cannot be excluded by clinical assessment alone.
- 2.8 The draft updated guideline recommends offering 64-slice (or above) CCTA as the first-line diagnosis test when clinical assessment indicates typical or atypical angina; or non-anginal chest pain but 12-lead resting ECG has been done and indicates ST-T changes or Q waves.
- 2.9 Subsequent diagnostic tests can be requested dependent on the CCTA results. The guideline recommends offering non-invasive functional imaging for myocardial ischaemia if 64-slice (or above) CCTA has shown coronary artery disease of uncertain functional significance, or is non-diagnostic. Non-functional imaging includes:
- myocardial perfusion scintigraphy with single-photon emission computed tomography (MPS with SPECT)
  - stress echocardiography
  - first-pass contrast-enhanced MR perfusion
  - MR imaging for stress-induced wall motion abnormalities.
- ICA should be offered as a second-line investigation when the results of non-invasive functional imaging are inconclusive.
- 2.10 When ICA is used to determine the presence and severity of coronary stenosis, it may be combined with the invasive measurement of FFR using a pressure wire. Although the NICE draft updated guideline on [chest pain](#) does not consider FFR, other guidelines (such as those of the European Society of Cardiology and American College of Cardiology) state that lesions with an FFR of 0.80 or less are functionally significant and revascularisation may be considered.

### 3 Clinical evidence

3.1 The key clinical outcomes for HeartFlow FFR<sub>CT</sub> presented in the decision problem were:

- measures of diagnostic accuracy (sensitivity and specificity, positive and negative likelihood ratios, area-under curve) using invasive fractional flow reserve (FFR) as the reference standard
- rates of diagnostic coronary angiography, percutaneous coronary intervention and coronary artery bypass surgery
- adverse events (test-related, major adverse cardiac events, radiation exposure and so on)
- quality of life
- mortality.

#### ***Summary of diagnostic accuracy evidence***

3.2 The company conducted a literature search on the diagnostic accuracy of FFR<sub>CT</sub> and the existing tests in the current treatment pathway for patients with a 10% to 90% pre-test likelihood of coronary artery disease, against a reference standard of invasive FFR testing. This review identified 5 relevant meta-analysis studies and 23 individual studies, 1 of which was unpublished. Based on the 22 published studies, and using FFR as the reference standard, the company presented diagnostic accuracy per-patient results for HeartFlow FFR<sub>CT</sub> compared with:

- invasive coronary angiography (ICA)
- single-photon emission computed tomography (SPECT)
- stress echocardiogram (ECHO)
- magnetic resonance imaging (MRI)
- coronary computed tomography angiography (CCTA).

If there were multiple studies for a test, the company conducted a meta-analysis; for example, 3 studies were included in the meta-analysis for HeartFlow FFR<sub>CT</sub> (Koo et al. 2011, Min et al. 2012 and

Nørgaard et al. 2014). The methodology and results of the meta-analyses are reported as academic in confidence.

- 3.3 The external assessment centre (EAC) reviewed the company's selection of studies and considered that although they addressed the scope in terms of the comparators, reference test and outcomes, most included a mixture of patients with both high (over 90%) and intermediate (10% to 90%) pre-test likelihoods of disease. It also disagreed with the company's decision only to include studies that provided FFR measurements in more than 75% of blood vessels. The EAC considered this criterion not to be reflective of clinical practice, where visual assessment is sometimes used before proceeding with FFR measurements. The EAC also noted that this criterion did not reflect the company's proposed changes to the clinical pathway, where CCTA would be used to decide if HeartFlow FFR<sub>CT</sub> should be used.
- 3.4 To address these concerns, the EAC conducted a diagnostic literature search using extra keywords related to comparators and outcomes. It included only studies in which most patients had an intermediate pre-test likelihood of disease. The EAC identified 7 diagnostic studies, including 3 presented by the company (Bernhardt et al. 2012, Nørgaard et al. 2014 and Stuijzand et al. 2014) and 3 that the company had identified but excluded (Danad et al. 2013, Kajander et al. 2010 and Ponte et al. 2014.) Only 1 of these, Nørgaard et al. 2014, involved HeartFlow FFR<sub>CT</sub>.
- 3.5 Nørgaard et al. (2014) reported on a multicentre study (the NXT trial) involving 2 UK centres, which compared HeartFlow FFR<sub>CT</sub> (v1.4) with CCTA for diagnosing myocardial ischaemia in 254 patients with suspected stable coronary artery disease scheduled to have ICA. Most patients in the study (87%) were considered to have an intermediate likelihood of coronary artery disease. Invasive FFR was measured in all vessels (n=484). The study reported the



diagnostic performance of HeartFlow FFR<sub>CT</sub> and CCTA for diagnosing ischaemia compared with FFR measured during ICA as the reference standard. The diagnostic accuracy of each test was presented on a per-patient and a per-vessel basis compared with the reference standard, an FFR value of  $\leq 0.80$ . Per-vessel FFR<sub>CT</sub> was correlated to FFR (Pearson's correlation coefficient 0.82,  $p > 0.001$ ), with a slight underestimation of FFR<sub>CT</sub> compared with FFR. The authors concluded that HeartFlow FFR<sub>CT</sub> can identify functionally significant coronary artery disease with high sensitivity and specificity. Furthermore, adding FFR<sub>CT</sub> measurements to CCTA led to a marked increase in specificity.

- 3.6 The EAC identified 6 studies which both used the comparator tests and included patients with an intermediate likelihood of coronary artery disease. Bernhardt et al. (2012) compared the diagnostic performance of 1.5 T and 3 T MRI scanners using FFR as a reference standard in 34 patients with stable angina and suspected or known coronary artery disease. The authors studied an intermediate-risk population with a mean PROCAM score of 42.7 (a risk assessment metric which estimates the 10-year risk of developing a coronary event). Ponte et al. (2014) compared the diagnostic accuracy of CCTA and MRI for detecting functionally significant coronary artery disease in patients referred with suspected coronary artery disease, using ICA with FFR as the reference standard. The study included 95 patients with a 15% to 85% pre-test likelihood of coronary artery disease. Suijzand et al. (2014) evaluated CCTA and transluminal attenuation gradient compared with CCTA alone for diagnosing functionally significant lesions, using invasive FFR as the reference standard. The study included 85 patients (253 vessels) with an intermediate likelihood of coronary artery disease. Neglia et al. (2015) assessed the accuracy of several imaging techniques – CCTA, SPECT and ECHO – in 475 patients with an intermediate likelihood of coronary artery disease. Danard et al. (2013) evaluated the diagnostic accuracy of CCTA in

120 patients with suspected coronary artery disease who had cardiac positron emission topography (PET), CCTA and ICA. CCTA was done using a hybrid PET/CT scanner. Kajander et al. (2010) evaluated the diagnostic accuracy of PET and CCTA in 107 patients with a history of stable chest pain and a 30% to 70% pre-test likelihood of coronary artery disease. All patients had ICA independently of the non-invasive imaging results, and treatment decisions were based on both ICA and FFR.

3.7 Table 1 summarises the EAC’s analysis of diagnostic accuracy for HeartFlow FFR<sub>CT</sub> and its comparators at both per-vessel and per-patient levels, as shown in table 1. When there was more than 1 diagnostic accuracy study available, the EAC conducted a meta-analysis.

**Table 1: Diagnostic accuracy: HeartFlow FFR<sub>CT</sub> and comparator tests**

Index test	N	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
<b>Patient-based analysis</b>					
<b>HeartFlow FFR<sub>CT</sub></b> <i>(Nørgaard, 2014: NXT trial)</i>	254	0.86 0.77–0.93	0.79 0.72–0.85	4.07 3.02–5.49	0.18 0.10–0.31
<b>CCTA</b> <i>(6 studies)</i>	1136	0.95 0.92–0.97	0.68 0.65–0.71	3.18 1.56–6.47	0.09 0.05–0.16
<b>ECHO</b> <i>(Neglia, 2015)</i>	261	0.45 0.33–0.57	0.90 0.85–0.94	4.52 2.74–7.45	0.61 0.49–0.76
<b>ICA</b> <i>(Nørgaard, 2014)</i>	254	0.64 0.52–0.74	0.83 0.76–0.88	3.70 2.57–5.33	0.44 0.33–0.59
<b>MRI</b> <i>(2 studies)</i>	129	0.89 0.78–0.95	0.91 0.82–0.97	8.59 4.12–17.9	0.13 0.07–0.26
<b>SPECT</b> <i>(Neglia, 2015)</i>	293	0.73 0.63–0.81	0.67 0.60–0.74	2.20 1.74–2.79	0.41 0.29–0.57
<b>Vessel-based analysis</b>					
<b>HeartFlow FFR<sub>CT</sub></b> <i>(Nørgaard, 2014)</i>	484	0.84 0.76–0.91	0.86 0.82–0.89	5.97 4.60–7.75	0.18 0.12–0.29

Index test	N	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
<b>CCTA</b> (4 studies)	1645	0.85 0.81–0.89	0.75 0.73–0.77	4.15 2.38–7.23	0.19 0.12–0.32
<b>ICA</b> (Nørgaard, 2014)	484	0.55 0.45–0.65	0.90 0.87–0.93	5.56 3.92–7.89	0.50 0.40–0.62
<b>MRI</b> (Bernhardt, 2012)	102	0.87 0.72–0.96	0.98 0.92–1.00	55.6 7.92–390	0.13 0.06–0.30

Abbreviations: CCTA, cardiac coronary CT angiography; ECHO, stress echocardiogram; FFR<sub>CT</sub>, fractional flow reserve computed tomography; ICA, invasive coronary angiography; MRI, magnetic resonance imaging; SPECT, photon emission computed tomography.

3.8 The EAC considered that despite the limitations associated with patients having a different reference test in some studies, all contributed to the decision problem and provided data for synthesis. It judged that the Nørgaard (2014) study had a low risk of bias for flow and timing, index and reference test. It noted that there was a risk of patient selection bias because an inclusion criterion was that patients had to have been referred for ICA, but it noted no other risks of bias or applicability concerns. Although it acknowledged that there were no studies directly comparing all the tests, it concluded that HeartFlow FFR<sub>CT</sub> has:

- similar sensitivity but higher specificity compared with CCTA
- higher sensitivity but lower specificity compared with ECHO
- similar sensitivity but lower specificity compared with MRI
- higher sensitivity and specificity compared with SPECT.

### **Summary of clinical-effectiveness evidence**

3.9 The company conducted a literature search for evidence on the clinical outcomes specified in the decision problem for HeartFlow FFR<sub>CT</sub>, and the existing treatments, against any comparator. It identified 16 studies of which 5 included HeartFlow FFR<sub>CT</sub>, 1

published (Guar et al. 2014) and 4 unpublished (PLATFORM, Radiation FFR<sub>CT</sub>, Real World Usage FFR<sub>CT</sub> and FFR<sub>CT</sub> RIPCORDER) which included HeartFlow FFR<sub>CT</sub>.

3.10 The EAC included extra intervention and comparator keywords and identified 11 studies, 4 of which had already been identified by the company: 2 published studies (Hachamovitch et al. 2012 and Douglas et al. 2015) and 2 unpublished studies. The EAC noted that only the 2 unpublished studies fully matched the population, intervention, comparators and outcomes defined in the scope; the other 9 included various comparators but not HeartFlow FFR<sub>CT</sub>. The 2 unpublished studies including HeartFlow FFR<sub>CT</sub> were PLATFORM (see section 3.18) and Radiation FFR<sub>CT</sub>; the company provided both in the form of interim results for the former and an abstract for the latter. Two studies (Real World Usage FFR<sub>CT</sub> and FFR<sub>CT</sub> RIPCORDER) included HeartFlow FFR<sub>CT</sub> but were excluded because they did not provide information on patients' pre-test likelihood of coronary artery disease.

3.11 Radiation FFR<sub>CT</sub> is a single-centre modelling study, based in Canada, investigating the potential effect of HeartFlow FFR<sub>CT</sub> on radiation dose exposure and downstream clinical event rate. In the modelling, a clinical pathway in which CCTA plus FFR<sub>CT</sub> was the initial diagnostic test was compared with 3 clinical pathways instead utilising SPECT, ECHO or CCTA as initial diagnostic tests. The model included 100 patients with suspected coronary artery disease, 34% of whom had intermediate disease. Patients were stratified into 3 categories of likelihood of disease: 50% low, 40% moderate and 10% high. No clinical outcomes were measured in this modelled population. The primary outcome was the estimated radiation dose and the secondary outcome was death or myocardial infarction estimates at one year after the test. Of the 4 diagnostic pathways studied, ECHO had the lowest radiation dose (5.3 mSv) but had a higher clinical event rate related to both false-

positive and false-negative findings. The FFR<sub>CT</sub> pathway had lower cumulative radiation exposure (9.4 mSv) than SPECT (26.4 mSv) or CCTA (13.9 mSv) and also had the lowest clinical adverse event rate for low and intermediate-risk patients. For high-risk patients, the lowest clinical event rate was with ICA.

- 3.12 The EAC identified 9 published studies containing information on clinical outcomes in comparator diagnostic technologies. Further information about these studies can be found in the assessment report.

### **Chest pain guideline update: second literature search**

- 3.13 During the period of this assessment of HeartFlow FFR<sub>CT</sub>, NICE updated the chest pain guideline. This resulted, in the draft updated guideline, in changes to the recommendations for investigating chest pain. It therefore became necessary to update the evidence and cost modelling for the HeartFlow FFR<sub>CT</sub> assessment. The EAC repeated the evidence searches up to February 2016 and asked the company to identify any recent and ongoing studies. In total, the EAC assessed 7 new studies, 6 of which included FFR<sub>CT</sub>.
- 3.14 Tanaka et al. (2016) is a technical study on a subgroup of the NXT study investigating the association between FFR<sub>CT</sub> and invasive FFR in coronary arteries with serial lesions. The authors investigated patients (n=18 patients and 18 vessels) with stable angina and clinically suspected coronary artery disease. There was no clinical follow-up. The primary outcome was the per-segment correlation between FFR<sub>CT</sub> and invasive FFR values, expressed as translesional delta (the difference between the proximal and distal FFR measurement of all sequential lesions). Values of translesional delta for FFR and FFR<sub>CT</sub> were  $0.10 \pm 0.09$  and  $0.09 \pm 0.10$  in distal segments, and  $0.17 \pm 0.10$  and  $0.22 \pm 0.13$  in proximal segments respectively. The coefficient of correlation between translesional delta FFR and FFR<sub>CT</sub> in each segment was 0.92 ( $p < 0.001$ ). The

authors concluded that translesional delta FFR is highly correlated with FFR<sub>CT</sub>.

3.15 Thompson et al. (2015) investigated the diagnostic performance of FFR<sub>CT</sub> in relation to patients' sex and age, using invasive FFR measurements as the reference standard for a subgroup of the DeFACTO study. Previous evidence from DeFACTO was not considered eligible because it included patients with a high pre-test likelihood of coronary artery disease (Min et al. 2012). Thompson et al. (2015) was included because it reports results based on subgroup analyses for age and sex. The baseline pre-test likelihood did not differ in statistical significance within these subgroups, so it is not expected to bias the results. The authors investigated 252 patients (407 vessels) with stable angina, clinically suspected coronary artery disease and at least 1 coronary stenosis of 30% to 90%. For their analysis, the authors used a clinical rule that included all vessels of diameter  $\geq 2$  mm and assigned an FFR value of 0.90 for vessels with stenoses  $< 30\%$  and an FFR value of 0.50 for vessels with stenoses  $> 90\%$ . There was no clinical follow-up. The primary outcome was per-patient and vessel diagnostic performance of FFR<sub>CT</sub>. Using this clinical rule, diagnostic performance improved in both sexes with no statistically significant differences between them. There were no differences in the discrimination of FFR<sub>CT</sub> after application of the clinical use rule when stratified by age  $\geq 65$  or  $< 65$  years. The authors concluded that FFR<sub>CT</sub> had similar diagnostic accuracy and discriminatory power to FFR for ischaemia detection in men and women irrespective of age using a cut-off point of 65 years.

3.16 The other 4 studies on HeartFlow FFR<sub>CT</sub> looked at clinical outcomes. The PLATFORM study (Douglas et al. 2015b and 2016) was presented to the committee as academic in confidence in June 2015 (Douglas et al. 2015a). The study included 584 patients recruited at 11 international centres. They were prospectively

assigned to have either functional imaging (n=287) or CCTA/FFR<sub>CT</sub> (n=297). Each cohort was subdivided into 2 groups based on the evaluation plan decided before enrolment in the study: non-invasive testing (any form of stress testing or CCTA without FFR<sub>CT</sub>) or ICA (invasive testing).

- 3.17 Douglas et al. (2015b) report the study results at 3-month follow-up. The primary end point was the percentage of patients with planned ICA in whom no significant obstructive coronary artery disease (no stenosis  $\geq 50\%$  by core laboratory quantitative analysis or invasive FFR $<0.80$ ) was found at ICA within 90 days. Secondary end points included a composite measure of MACE consisting of death, myocardial infarction and unplanned revascularisation, all of which were independently and blindly assessed. Among patients with intended ICA (CCTA/FFR<sub>CT</sub> =193; functional imaging=187), no obstructive coronary artery disease was found with ICA in 24 patients (12%) in the CCTA/FFR<sub>CT</sub> arm and 137 patients (73%) in the functional imaging arm (risk difference 61%, 95% CI 53 to 69,  $p<0.0001$ ). Among patients intended for non-invasive testing, the rates of finding no obstructive coronary artery disease with ICA were 13% in the CCTA/FFR<sub>CT</sub> arm and 6% in the functional imaging arm ( $p=0.95$ ). ICA was cancelled in 61% of patients after reviewing the CCTA/FFR<sub>CT</sub> results. There were low numbers of MACE and vascular complications in all groups.
- 3.18 Douglas et al. (2016) report outcomes from the same study at 1 year. The clinical end points measured were MACE and MACE plus vascular events within 14 days of procedure. Quality of life and resource use outcomes were also collected. There were 2 MACE events in each arm of the planned invasive group (risk difference  $-0.03$  [CI  $-8.6$  to  $8.5$ ]) and 1 in the planned non-invasive group (risk difference  $-1.00$  [CI  $-12.7$  to  $10.7$ ]). Cumulative 1-year radiation exposure in patients with an intended invasive evaluation was similar in the functional imaging (mean:  $10.4\pm 6.7$  mSv) and

CCTA/FFR<sub>CT</sub> arms (mean: 10.7 ± 9.6 mSv; p=0.21), but higher in the functional imaging arm in patients with an FFR<sub>CT</sub>-guided evaluation (mean: 9.6±10.6 mSv vs. 6.4±7.6 mSv, p<0.001). Functional status and quality of life improved from baseline to 1-year follow-up in the planned non-invasive group (p<0.001 for all measures), with greater improvements on the EQ-5D in patients having CCTA/FFR<sub>CT</sub> compared with patients having functional imaging (mean change: 0.12 for CCTA/FFR<sub>CT</sub> vs. 0.07 for functional imaging, p=0.02).

- 3.19 Lu et al. (2015) used a subgroup analysis of the PROMISE trial (n=181) to investigate the added value of FFR<sub>CT</sub> compared with CCTA in improving efficiency of referral to ICA. End points for the subgroup analysis were rate of revascularisation and ICA that did not show obstructive coronary artery disease and MACE. Over a median follow-up of 25 months, the addition of FFR<sub>CT</sub> increased the rate of ICA with revascularisation from 49% to 61%. The rate of angiography without obstructive disease decreased from 27% to 11%. No patient with FFR<sub>CT</sub> >0.80 had an adverse event which ICA would have prevented.
- 3.20 Nørgaard (2016) reports on the real-world experience of using CCTA with FFR<sub>CT</sub> as gatekeeper to ICA in patients with stable coronary artery disease and intermediate-range coronary lesions (n=189). Patients were followed-up for a median of 12 months. The primary end point was the impact of FFR<sub>CT</sub> on further downstream diagnostic testing. Other end points were the agreement between FFR<sub>CT</sub> and invasive FFR, and the short-term clinical outcome after FFR<sub>CT</sub> testing defined as the occurrence of MACE (death and acute myocardial infarction) or an angina episode leading to hospital admission or visit in the outpatient clinic. The authors concluded that FFR<sub>CT</sub> testing is feasible in real-world scenarios involving patients with intermediate-range coronary stenosis determined by CCTA. They also concluded that implementing FFR<sub>CT</sub> for clinical



decision-making may influence the downstream diagnostic workflow, and patients with an  $FFR_{CT} > 0.80$  who are not referred for ICA have a favourable short-term prognosis. The authors highlight that in patients with  $FFR_{CT}$  ranging between 0.76 and 0.80, a non-negligible number of false-positive results may be expected.

- 3.21 The EAC considered that the 1-year follow-up data from the PLATFORM study supported the company's claims regarding resource use, rates of ICA and percutaneous coronary intervention, and quality of life with HeartFlow  $FFR_{CT}$ . Additionally, the 1-year follow-up evidence from the PLATFORM and PROMISE studies supports the company's claim that MACE are equivalent between the current pathway and a pathway that includes the use of  $FFR_{CT}$ . The EAC also considered that the evidence from the PLATFORM study showed higher 1-year radiation exposure in the HeartFlow  $FFR_{CT}$  group in patients intended for non-invasive evaluation. However, this is to be expected because many patients in the non-invasive evaluation had a non-invasive test which did not require the use of radiation. The EAC concluded that the submitted evidence on clinical outcomes supports the value proposition of an  $FFR_{CT}$ -guided strategy compared with standard of care, mainly in patients with planned invasive investigation, with equivalent results between  $FFR_{CT}$  and functional imaging in the non-invasive group.

### **Committee considerations**

- 3.22 The committee considered that the evidence showed high diagnostic accuracy and increased specificity with HeartFlow  $FFR_{CT}$  compared with CCTA alone. It also noted promising results from the PLATFORM study, in a population which closely matches that in the scope. The evidence was sufficient to conclude that HeartFlow  $FFR_{CT}$  has a high diagnostic accuracy for coronary artery disease, and that its use has the potential to reduce the need for invasive coronary investigations.

- 3.23 The committee considered the technology to be innovative and understood that its adoption may serve to simplify a complex patient pathway. The committee heard from clinical experts that they had confidence in the diagnostic accuracy of HeartFlow FFR<sub>CT</sub>, and that it could provide an effective early rule-out test for coronary artery disease. This would reduce the need for ICA and invasive FFR measurement, and potentially reduce radiation exposure.
- 3.24 The committee understood that there are differences in the local implementation of the patient pathway for diagnosing coronary artery disease. It was advised by clinical experts that the choice of functional imaging test depends on local access, available expertise and clinician preference. It heard that although HeartFlow FFR<sub>CT</sub> has the potential to reduce the number of tests that are done, the other non-invasive functional imaging tests that are part of the current patient pathway offer different functionality and in some cases provide additional information. Overall, the committee concluded that HeartFlow FFR<sub>CT</sub> should be considered for use as a non-invasive investigation for diagnosing angina in patients with stable, recent onset chest pain of suspected cardiac origin, and that it provides the clinician with additional functional information to determine which coronary lesions are responsible for myocardial ischaemia.
- 3.25 The committee considered the evidence from the PLATFORM study to be most relevant to the decision problem. It considered that the results demonstrate the potential of FFR<sub>CT</sub> to avoid ICA and improve quality of life.
- 3.26 The committee discussed the relative importance of a per-patient or a per-vessel diagnosis. It heard from experts that per-patient diagnostic accuracy was more important for initial diagnosis, and that a per-vessel assessment provides additional information to inform patient management. The committee concluded that per-

patient level figures were the most reliable and relevant to the diagnosis of coronary artery disease.

## 4 NHS considerations

### *System impact*

- 4.1 The company's claimed system benefits included reduced costs from fewer inconclusive or inaccurate diagnostic tests and avoidance of unnecessary staff and procedure costs. It claimed that this would lead to more effective use of invasive procedure suites.
- 4.2 The company confirmed that, with specific reference to the draft updated guideline on [chest pain](#), the proposed place in the diagnostic pathway for HeartFlow FFR<sub>CT</sub> (to inform management following a positive coronary computed tomography angiography (CCTA) result) was unchanged.
- 4.3 The number of patients who would be eligible for HeartFlow FFR<sub>CT</sub> is estimated to be around 36,000. This estimate is based on 2010/11 Department of Health data on patient attendance at rapid-access chest-pain clinics in England, pre-test probability splits reported in Rajani et al. (2015), and estimates of the numbers of CCTA scans that would be eligible for FFR<sub>CT</sub> as described in the cost-consequences modelling.
- 4.4 During selection and routing, the committee asked for additional information on compliance with data protection legislation, and the reproducibility of HeartFlow FFR<sub>CT</sub> analysis, especially in the face of an increasing workload which might be expected to arise from adoption of the technology in the NHS. The EAC produced a technical report that concluded:
- The company has a quality assurance process in place that fulfils data quality needs. This includes checks by different team members, and the separation of tasks to ensure that no single

analyst is fully responsible for a diagnosis. After the procedure, a more experienced analyst reviews the process, focusing mainly on areas of stenosis. Expert clinician advice is also available should it be needed.

- Although the analytical process is largely automated, any part of it can be manually changed by the analyst. This may affect the  $FFR_{CT}$  estimate. Manual editing is part of the quality assurance process, negating the risk of spurious results generated from the automated analysis. Gaur et al. (2014) suggest that reproducibility is within acceptable 95% confidence interval limits of agreement.  $FFR_{CT}$  reproducibility was found to be equivalent to invasive FFR reproducibility.
- The reproducibility of outlining the coronary artery lumen, part of the  $FFR_{CT}$  computation analysis, decreases in the distal portion of the vessel (Gage repeatability and reproducibility=29.4%). This could be a result of different factors including lower CT quality, lower CT resolution, smaller vessel diameter at the distal end and higher disease burden.
- The company monitors  $FFR_{CT}$  reproducibility by re-processing 5% of its case volume on a weekly basis. The company has confirmed that this has shown a reproducibility rate consistent with the literature (Gaur et al. 2014).
- The company fulfils regulatory approval standards for data confidentiality and integrity protection for remote processing. It offers NHS customers the option to upload fully anonymised DICOM data to comply with UK data protection law.

### **Committee considerations**

- 4.5 The committee was satisfied with the EAC's conclusions on reproducibility (see section 4.4). It accepted that the company has protocols in place to manage an increased demand for HeartFlow  $FFR_{CT}$ .

- 4.6 The committee considered the protection and oversight of data transferred during the administration of HeartFlow FFR<sub>CT</sub> to be an important factor in its adoption, and was satisfied on the basis of the information available, that the company's data transfer protocols meet regulatory requirements. The committee noted that patients should be informed when sending personal data outside the EEA with HeartFlow FFR<sub>CT</sub>, and that it may be necessary to obtain written consent.
- 4.7 The committee considered the availability of CCTA facilities. It understood that the cost model assumed access to CCTA facilities, but heard from experts that access to CCTA varies across the NHS despite recommendations in NICE's guideline, CG95 on [chest pain](#). Furthermore, because CT scanners are used for many purposes, a constraint currently exists with regard to both the availability of scanners and scanning time. The committee heard from experts that a sizable investment would be needed for the wider implementation of HeartFlow FFR<sub>CT</sub> but acknowledged that this consideration was beyond the scope of the current assessment. It understood that adopting 64-slice CCTA was ongoing in the NHS, in line with the recommendations in the NICE guideline, CG95 on [chest pain](#).

## 5 Cost considerations

### *Cost evidence*

- 5.1 The company conducted a search of the health economics literature on HeartFlow FFR<sub>CT</sub> and the comparators specified in the decision problem. They identified a total of 174 studies, 24 of which it considered relevant to the decision problem.
- 5.2 The EAC reviewed this search, and considered that most of the studies included neither an appropriate patient population nor a treatment pathway. Only 1 published study, Rajani et al. (2015), was considered by the EAC to be relevant to the decision problem.

It conducted a further review of the literature up to February 2016 and identified an additional relevant published study, Hlatky et al. (2015).

- 5.3 Rajani et al. (2015) was a single-centre retrospective cost analysis of 410 patients referred to a rapid-access chest-pain clinic in Guy's and St Thomas' Hospital, London, from April 2012 to March 2013. Patients were grouped into pre-test likelihood categories and diagnostic imaging was done based on standardised protocols as recommended in the NICE guideline, CG95, on [chest pain](#). A standardised unit cost for each test and procedure was taken from the NHS National Tariff 2013/14. A decision-tree economic model was used to evaluate the cost of 1,000 patients passing through the current treatment pathway compared with the same 1,000 patients after incorporating HeartFlow FFR<sub>CT</sub>. The authors found that introducing HeartFlow FFR<sub>CT</sub> to the pathway resulted in cost savings of £200 per patient. The EAC noted that although the derivation of costs in the study is explicit, details of the decision model structure are unclear.
- 5.4 Hlatky et al. (2015) investigated the quality-of-life and economic outcomes of FFR<sub>CT</sub> in the PLATFORM study (see section 3.18). Cumulative medical costs were measured over 90 days for each patient by multiplying a standardised cost weight for each medical resource by the number of resources used by the patient. Medicare reimbursement rates (the national average of technical and professional fees in the US) from 2015 were applied because cost weights and online pharmacy costs were used for drugs. Patients were prospectively assigned to either functional imaging (n=287) or coronary computed tomography angiography (CCTA)/HeartFlow FFR<sub>CT</sub> (n=297). Mean costs were \$7,343 (£4,993) among the CCTA/FFR<sub>CT</sub> patients and \$10,734 (£7,299) among functional imaging patients (p<0.0001). In the non-invasive group of the PLATFORM study, mean costs were not significantly different

( $p=0.26$ ) between the CCTA/FFR<sub>CT</sub> patients (\$2,679; £1,822) and the functional imaging patients (\$2,137; £1,453). Overall, each quality-of-life (EQ-5D) score improved at 90 days compared with baseline in the study population ( $p<0.0001$ ), and scores improved more in CCTA/FFR<sub>CT</sub> patients than in functional imaging patients. In the invasive group in the PLATFORM study, quality-of-life improvements were similar in both arms

## Economic model

- 5.5 The company presented a decision-tree model based on integrating HeartFlow FFR<sub>CT</sub> into the existing diagnostic pathway. A theoretical population of 1,000 patients with suspected coronary artery disease was allocated to either the current treatment pathway (based on the NICE guideline, CG95, on [chest pain](#)) or the company's revised pathway, which included HeartFlow FFR<sub>CT</sub> (as described in section 4.2). The cost consequences of the treatment pathways were compared based on the mix of diagnostic technologies used in each. The model had a 1-year time horizon after testing, but included no clinical outcomes.
- 5.6 The proportion of patients eligible for CCTA as a first-line test and their probability of having coronary artery disease were taken from Rajani et al. (2015). In the model, 10% of patients were assumed to be ineligible for invasive coronary angiography (ICA), have an inconclusive CCTA result and have an uncertain single-photon emission computed tomography (SPECT) result.
- 5.7 The diagnostic accuracy of HeartFlow FFR<sub>CT</sub> and its comparators in the company's model were based on per-patient level results reported in selected papers, as follows:
- HeartFlow FFR<sub>CT</sub>: sensitivity 86%, specificity 79% (Nørgaard et al. 2014)
  - SPECT: sensitivity 76%, specificity 38% (Melikian et al. 2010)
  - CCTA: sensitivity 94%, specificity 48% (Meijboom et al. 2008)

- ICA: sensitivity 69%, specificity 67% (Meijboom et al. 2008).

The cost of HeartFlow FFR<sub>CT</sub> (£888) was based on the company's original list price. Costs for comparator tests were based on 2014/15 hospital resource group (HRG) tariffs, as follows:

- SPECT: £220 (HRG code RA37Z, nuclear medicine category 3)
- CCTA: £136 (HRG code RA14Z, computerised tomography scan, more than 3 areas)
- Calcium scoring: £77 (HRG code RA08Z, computerised tomography scan, 1 area, no contrast)
- ICA: £1241 (HRG code EA36A, catheter 19 years and over)
- Percutaneous coronary intervention (PCI): £2,832 (weighted average of 2 tariffs, assuming that 25% of patients needing PCI will need more than 2 stents. HRG codes EA31Z [£2,704] and EA49Z [£3,216]).

5.8 The company's base-case results reported an average per-patient cost of £2,239 using the current pathway and £2,080 using the adapted pathway with HeartFlow FFR<sub>CT</sub>, representing an average saving of £159 per patient.

5.9 The company conducted 1-way sensitivity analyses on the sensitivity and specificity of HeartFlow FFR<sub>CT</sub> and the comparator tests, as well as the costs of HeartFlow FFR<sub>CT</sub>. The analyses showed that HeartFlow FFR<sub>CT</sub> continued to be cost saving until its price reached £1,126. With regard to changes in the sensitivity and specificity, HeartFlow FFR<sub>CT</sub> remained cost saving for nearly all the values tested when considered in the context of the entire patient population.

### **Parameter revisions by the external assessment centre**

5.10 The EAC reviewed the parameters and costs used in the company's model. It revised the company's sensitivity and



specificity parameters for the comparator diagnostic tests, based on its own analyses of diagnostic accuracy (see table 1).

5.11 The EAC used the company's revised list price of £700 for HeartFlow FFR<sub>CT</sub>, instead of £888 as used in the company's model.

5.12 The EAC used the NICE draft updated guideline on [chest pain](#) to determine the costs of all comparator tests except MRI, to ensure that they were consistent with 2014/15 reference costs. The cost of MRI was taken from the Payment by Results tariff, because the chest pain guideline committee determined this to be more representative of the true cost. These costs were as follows:

- SPECT: £367 (RN21Z, Myocardial perfusion scan, stress only )
- CCTA: £122 (RD28Z, Complex computerised tomography scan)
- ECHO: £271 (EY50Z, Complex echocardiogram)
- ICA: £1,685 (EY43A to EY43F, Standard cardiac catheterisation)
- MRI: £515 (RA67Z, Cardiac magnetic resonance imaging scan, pre and post contrast)
- PCI: £2,865 (weighted average of 2 tariffs, assuming that 25% of patients needing PCI will need more than 2 stents. HRG codes EA31Z [£2,704] and EA49Z [£3,216]). Includes an estimated annual cost of £33 for medication following a PCI [aspirin and clopidogrel, BNF (2015)].

5.13 The EAC noted that the company's model did not include costs of drug therapy for patients having PCI. It consulted the NICE guideline on [stable angina](#) and estimated an annual drug treatment cost for these patients of £33 based on British national formulary (2015) prescription costs for aspirin and clopidogrel, and used a cost of £2,865 (PCI tariff with drug costs) in its revised model.

5.14 The EAC included a cost for optimal medical therapy. It obtained expert advice that optimal medical therapy usually consists of aspirin, statins, nitrates and beta blockers. Based on this

information it estimated an annual cost of £84 (aspirin, simvastatin, glyceryl trinitrate and propranolol hydrochloride) from the British national formulary (2015) and used it in the revised model.

- 5.15 Using these updated assumptions, the EAC found a base-case cost saving of £214 per patient for HeartFlow FFR<sub>CT</sub> compared with the current treatment pathway for all functional imaging tests (SPECT, MRI and ECHO)
- 5.16 The EAC ran a number of sensitivity analyses, varying: the price of HeartFlow FFR<sub>CT</sub>; the diagnostic accuracy of the functional imaging tests, HeartFlow FFR<sub>CT</sub>, ICA and CCTA; and the proportion of uncertain CCTA and functional imaging tests. It also used estimates of diagnostic accuracy for CCTA and ICA from the NICE draft updated guideline on [chest pain](#). In all instances, HeartFlow FFR<sub>CT</sub> remained cost saving.

### **Committee considerations**

- 5.17 The committee considered the cost modelling done by the EAC to be both appropriate and plausible. The committee heard from experts that percutaneous or surgical revascularisation is only offered to patients following ICA, and sometimes a confirmatory invasive FFR. The availability of data from HeartFlow FFR<sub>CT</sub> may help to plan treatment in individual vessels and patients.

## **6 Conclusions**

- 6.1 The committee concluded that the evidence suggests that HeartFlow FFR<sub>CT</sub> is safe, has high diagnostic accuracy, and that its use may avoid the need for invasive investigations.
- 6.2 The committee concluded that cost savings of £214 per patient are plausible and likely to be realized in practice, providing that sites adopting HeartFlow FFR<sub>CT</sub> have access to 64-slice (or above) coronary CT angiography.

Peter Groves  
Chair, medical technologies advisory committee  
August 2016

## **7 Committee members and NICE lead team**

### ***Medical technologies advisory committee members***

The medical technologies advisory committee is a standing advisory committee of NICE. A list of the committee members who took part in the discussions for this guidance appears below.

Committee members are asked to declare any interests in the technology to be evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each medical technologies advisory committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

#### **Dr Peter Groves (Chair)**

Consultant cardiologist, Cardiff and Vale University Health Board

#### **Dr Fiona Denison (Vice-chair)**

Reader/honorary consultant in maternal and fetal Health, University of Edinburgh

#### **Ms Susan Bennett**

Lay member

#### **Mr Matthew Campbell-Hill**

Lay member

#### **Professor Daniel Clark**

Head of clinical engineering, Nottingham University Hospitals NHS Trust

#### **Professor Tony Freemont**

Professor of osteoarticular pathology, University of Manchester

#### **Professor Shaheen Hamdy**

Professor of neurogastroenterology, University of Manchester

**Dr Cynthia Iglesias**

Health economist, University of York

**Professor Mohammad Ilyas**

Professor of pathology, University of Nottingham

**Dr Greg Irving**

GP and clinical lecturer, University of Cambridge

**Professor Eva Kaltenthaler**

Professor of health technology assessment, School of Health and Related Research (SchARR), University of Sheffield

**Dr Paul Knox**

Reader in vision science, University of Liverpool

**Professor Rory O'Connor**

Charterhouse professor of rehabilitation medicine, University of Leeds

**Dr Jai V Patel**

Consultant vascular radiologist, Leeds Teaching Hospitals NHS Trust

**Mr Brian Selman**

Managing director, Selman and Company Limited

**Professor Wendy Tindale**

Scientific director, Sheffield Teaching Hospitals NHS Foundation Trust

**Professor Allan Wailoo**

Professor of health economics, School of Health and Related Research (SchARR), University of Sheffield

**Mr John Wilkinson**

Director of devices, Medicines and Healthcare Products Regulatory Agency

**Mr Alun Williams**

Consultant paediatric urologist & transplant surgeon

Nottingham University Hospitals

**Professor Janelle Yorke**

Lecturer and researcher in nursing, University of Manchester

**Dr Amber Young**

Consultant paediatric anaesthetist, Bristol Royal Hospital for Children

## ***NICE lead team***

Each medical technology assessment is assigned a lead team of a NICE technical analyst and technical adviser, an expert adviser, a technical expert, a patient expert, a non-expert member of the medical technologies advisory committee and a representative of the external assessment centre.

### **Neil Hewitt**

Technical analyst

### **Bernice Dillon**

Technical adviser

### **Dr Ronak Rajani**

Lead expert adviser

### **Professor Nick Curzen**

Lead expert adviser

### **Dr Rob Henderson**

Lead expert adviser

### **Professor Wendy Tindale**

Non-expert committee member

### **Anastasia Chalikidou**

External assessment centre representative

### **Murali Kartha**

External assessment centre representative

## 8 Sources of evidence considered by the Committee

The external assessment centre report for this assessment was prepared by KiTEC:

- Chalikidou A, Kartha M, Reed F et al. HeartFlow FFR<sub>CT</sub> for the computation of fractional flow reserve from coronary CT angiography (May 2015)
- Chalikidou A, Herz N, Kartha M et al. HeartFlow FFR<sub>CT</sub> for the computation of fractional flow reserve from coronary CT angiography — Chest pain of recent onset: assessment and diagnosis NICE guidelines [CG95]: Guidance update (May 2016)

Submissions from the following sponsor:

- HeartFlow

The following individuals gave their expert personal view on HeartFlow FFR<sub>CT</sub> by providing their expert comments on the draft scope and assessment report.

- Professor Keith Oldroyd, ratified by British Cardiovascular Intervention Society – clinical expert
- Professor Andreas Baumbach, ratified by British Cardiovascular Intervention Society – clinical expert
- Dr Ian Purcell, ratified by British Cardiovascular Intervention Society – clinical expert
- Professor Nick Curzen, ratified by British Cardiovascular Intervention Society – clinical expert
- Dr Rob Henderson, ratified by British Cardiovascular Society – clinical expert
- Dr Ronak Rajani, ratified by British Cardiovascular Society – clinical expert
- Dr Francesca Pugliese, ratified by British Cardiovascular Society – clinical expert



The following individuals gave their expert personal view on HeartFlow FFR<sub>CT</sub> in writing by completing a patient questionnaire or expert adviser questionnaire provided to the committee.

- Professor Keith Oldroyd, ratified by British Cardiovascular Intervention Society – clinical expert
- Professor Andreas Baumbach, ratified by British Cardiovascular Intervention Society – clinical expert
- Dr Ian Purcell, ratified by British Cardiovascular Intervention Society - clinical expert
- Professor Nick Curzen, ratified by British Cardiovascular Intervention Society – clinical expert
- Dr Rob Henderson, ratified by British Cardiovascular Society – clinical expert
- Dr Ronak Rajani, ratified by British Cardiovascular Society – clinical expert
- Dr Francesca Pugliese, ratified by British Cardiovascular Society – clinical expert

## About this guidance [NICE to complete on publication]

This guidance was developed using the NICE [medical technologies guidance process](#).

It updates and replaces NICE medical technology guidance XXX (published [month year]). [Amend as necessary. Delete if not relevant.]

It has been incorporated into the NICE pathway on XXX, along with other related guidance and products. [Amend as necessary. Hyperlink to pathway from pathway name. Delete if not relevant.]

We have produced a summary of this guidance for the public [add hyperlink to the UNG page]. Tools [add hyperlink to the guidance summary page] to help you put the guidance into practice and information about the evidence it is based on are also available. [delete any wording that isn't relevant]

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