NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Assessment report overview

HeartFlow FFR_{CT} for estimating fractional flow reserve from coronary CT angiography

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 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 sponsor's submission of evidence and with the EAC report (dated May 2015 and its addendum, dated May 2016). 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 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 (academic) or turquoise (commercial). This overview also contains:

- Appendix A: Sources of evidence
- Appendix B: Comments from professional bodies
- Appendix C: Comments from patient organisations
- Appendix D: Additional analyses carried out by external assessment centre

1 The technology

HeartFlow FFR_{CT} is a post-processing image analysis software package that provides a non-invasive method of estimating fractional flow reserve (FFR) using coronary CT angiography (CCTA) image data. FFR gives an indication of pressure differences in blood flow, from which the severity of any stenosis (narrowing of the blood vessels) can be assessed. It is usually measured invasively using a catheter.

Data from a CCTA scan (at least 64 slices) are sent securely from the local imaging system to HeartFlow's central processing centre in the USA. A case analyst 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 electronically to the referring clinician within 48 hours and includes both 3D images of the coronary anatomy and calculated functional information, including the estimated FFR values (known as FFR_{CT} values). Clinicians can use the report to help guide the treatment and management of suspected coronary artery disease.

HeartFlow FFR_{CT} is intended for use in patients with chest pain who need investigation for suspected stable coronary artery disease to guide treatment. Because the safety and effectiveness of FFR_{CT} analysis has not been evaluated in certain patient subgroups, it is not recommended for patients who have had a stent, bypass surgery or myocardial infarction in the past month. 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 Proposed use of the technology

2.1 Disease or condition

Coronary artery disease is a chronic condition and a major cause of morbidity and mortality in the UK. It is caused by a build-up of plaque in the coronary arteries which reduces the flow of blood to the heart. Symptoms vary but at their most extreme can lead to a heart attack or myocardial infarction. Around 1 in 5 men and 1 in 8 women die from the condition in the UK, although these figures have been falling over recent years. Many people live with coronary artery disease – around 2.3 million in the UK – but, depending on the severity of the illness, it can have a notable effect on their quality of life. People with the disease may be unable to take part in certain occupations and activities. A number of studies have also shown a link between coronary artery disease and depression.

2.2 Patient group

Figures for 2006 showed that 6.5% of all adult men (aged 16 years and over) and 4% of all adult women in England had coronary artery disease. It is a chronic condition that increases in prevalence with age; it is also most prevalent in men of Indian (6%) and Pakistani (8%) family origin.

2.3 Current management

The NICE guideline on chest pain of recent onset (currently being updated, see summary of changes below) recommends that in people presenting with stable chest pain without confirmed coronary artery disease, a diagnosis of stable angina should be based on clinical assessment either alone or combined with diagnostic testing.

The guideline recommends that patients should be stratified in terms of risk, using the Diamond Forrester criteria, to give an estimated likelihood of coronary artery disease (table 1 in the guideline). This assessment is based on a combination of the clinical characteristics of the patient, the nature of the

chest pain symptoms and the result of an ECG. After assessment, a patient is categorized into 1 of 5 groups, based on the percentage likelihood of their developing coronary artery disease:

- less than 10%
- 10–29%
- 30–60%
- 61–90%
- over 90%.

This classification is used to guide clinicians on the need for further investigations, if any, and to identify which investigations are appropriate.

The scope of this evaluation encompasses people with a pre-test likelihood of coronary artery disease ranging from 10% to 90%.

For these people, the NICE guideline on chest pain of recent onset recommends further investigation as follows:

- For patients with 61–90% likelihood of disease, for whom coronary revascularization is being considered and invasive coronary angiography (ICA) is clinically appropriate and acceptable, ICA should be offered as the first-line diagnostic investigation.
- For patients with 61–90% likelihood of disease and for whom coronary revascularization is not being considered, or ICA is not clinically appropriate or acceptable, non-invasive functional imaging for myocardial ischaemia should be considered.
- For patients with 30–60% likelihood of disease, non-invasive functional imaging for myocardial ischaemia should be offered.
- For patients with 10–29% likelihood of disease, CT coronary calcium scoring should be offered as the first-line diagnostic investigation. If the calcium score is:
  - 0, consider other causes of chest pain

- between 1 and 400, offer 64-slice or above coronary CT angiography (CCTA)
- over 400, offer ICA (if this is not clinically appropriate or acceptable and revascularization is not being considered, offer non-invasive functional imaging instead).

Additionally, the guideline recommends offering non-invasive functional imaging for myocardial ischaemia if the CCTA has shown coronary artery disease of uncertain functional significance.

When offering non-invasive functional imaging for myocardial ischaemia, the NICE guideline on chest pain of recent onset recommends the following, taking into account available technology, expertise and patient preferences:

- 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.

When the result of non-invasive functional imaging is inconclusive, the guideline recommends offering ICA. If after ICA the angiogram is inconclusive, non-invasive functional testing for imaging for myocardial ischaemia should be offered.

When ICA is used to determine the presence and severity of coronary stenosis, it may be necessary to combine it with the invasive measurement of FFR. This is usually the case when there is uncertainty about the functional significance of a coronary stenosis (40–70% severity) and involves inserting a fine pressure wire across the narrowing into the distal vessel. The pressure gradient across the stenosis is measured at baseline and again during maximal blood flow in the coronary vessel, which is induced by injecting adenosine. Although the NICE guideline on chest pain of recent onset does

not consider FFR, other guidelines (European Society of Cardiology, American College of Cardiology) state that lesions with an FFR of 0.80 or less (indicating blood flow of 80% or less) mean that functional significance is present and revascularization may be considered.

Expert advice suggests that current NHS practice is likely to vary depending on clinician preference and on local service infrastructure, in particular the availability of CCTA.

An updated version of the chest pain guideline is expected to be published in September 2016. The updated guideline will not include recommendations on HeartFlow FFR_{CT} because the available evidence did not meet the predefined threshold used for guideline development. However, changes to the standard care pathway and to the use of risk stratification tools will affect the proposed role of the device. The guideline currently recommends offering CCTA to patients who are at intermediate risk based on pre-test likelihood scoring, but the draft updated guideline recommends offering 64-slice (or above) CCTA to all patients with features of angina based on clinical assessment alone. This updated recommendation is based on an economic analysis which showed that CCTA had the lowest cost per correct diagnosis for all pre-test likelihood groups in the 10% to 90% range at both 50% and 70% stenosis thresholds. The current guideline also recommends the use of non-invasive functional imaging for myocardial ischaemia if 64-slice (or above) CCTA indicates coronary artery disease of uncertain functional significance or is non-diagnostic. The updated guideline adds a recommendation to offer invasive coronary angiography (ICA) as a second-line investigation when the results of non-invasive functional imaging are inconclusive.

2.4 Proposed management with new technology

The company has proposed that, with specific reference to the NICE guideline on chest pain of recent onset, HeartFlow FFR_{CT} would be used where:

- CCTA ('CT coronary angiography') appears in the pathway for 10–29% likelihood of disease
- 'appropriate functional imaging test' appears in the pathway for 30–60% likelihood of disease
- invasive coronary angiography appears in the pathway for 61–90% likelihood of disease.

The company has indicated that in these patients, clinicians would first examine the CCTA images locally for evidence of coronary artery disease with plaque, a sign of ischaemia. Where evidence of possible ischaemia was found, the CCTA image scan data would then be sent to HeartFlow. The EAC reviewed the place of HeartFlow FFR_{CT} in the care pathway in response to the draft changes to the chest pain guideline. It also made appropriate revisions to the company's cost consequences model. This work is described in full in the assessment report addendum (dated February 2016) which was fact checked by the company and is summarized below.

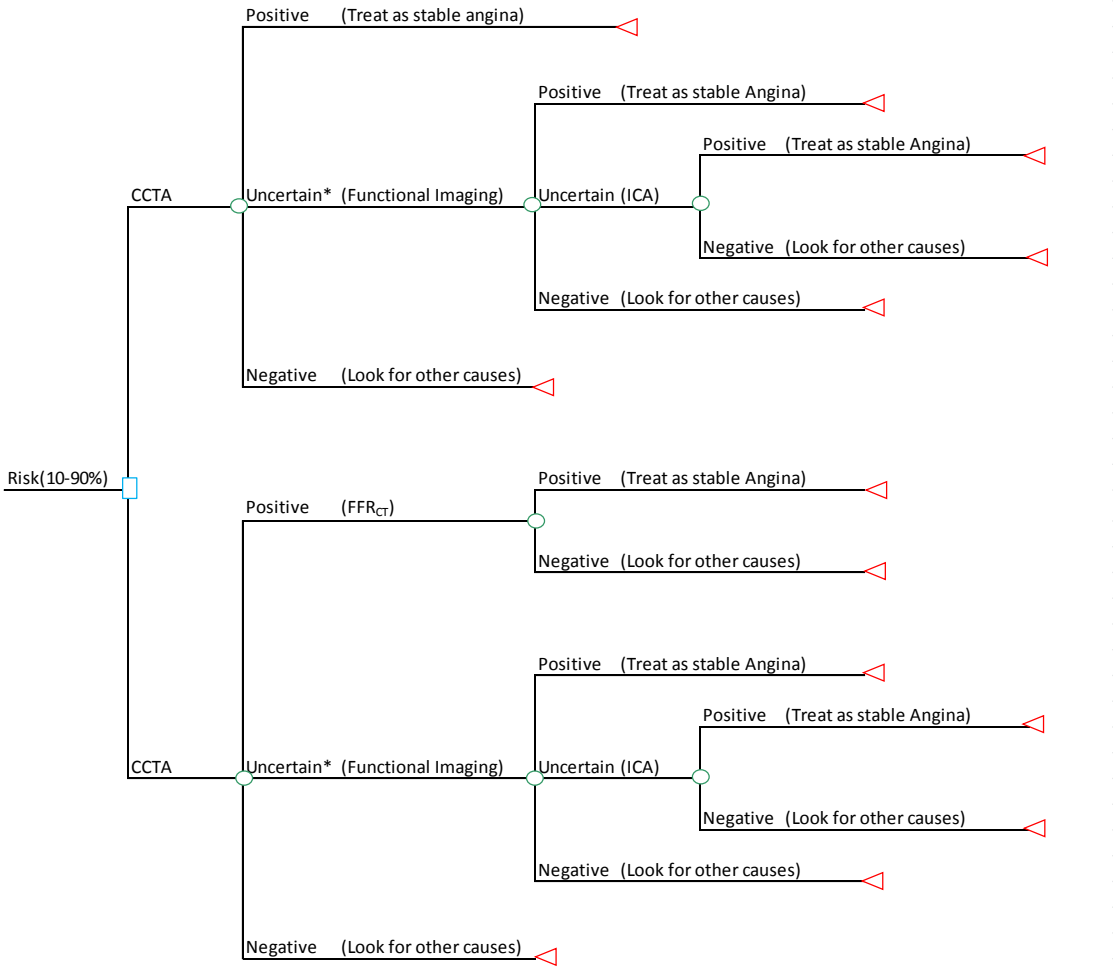
EAC pathway and economic model review

- The updated guideline combines 3 different pathways for the 3 likelihood groups into a single pathway (figure 1). Patients with a pre-test likelihood of 10–90% are now offered 64-slice (or above) CCTA as the first-line investigation. Functional imaging is offered following uncertain CCTA results, and ICA is offered if the results of functional imaging are also uncertain.
- The updated pathway is similar to the 10–29% pathway in the current guideline, except that calcium scoring is not included. CT calcium scoring has been excluded because topic experts who contributed to the chest pain economic model advised that this would rarely be done in isolation from a full CCTA in practice. The HeartFlow FFR_{CT} cost-consequences model also excludes isolated calcium scoring.
- In its revisions to the company's model, the EAC compared 2 strategies: using CCTA to inform treatment of stable angina, and using HeartFlow

FFR_{CT} after a positive CCTA result to inform treatment. In the pathway below, the square box e denotes a decision node, circles denote chance nodes and triangles denote terminal nodes, which indicate treatment for stable angina with either percutaneous coronary intervention (PCI) or optimal medical therapy. The time horizon for the model is 1 year to capture the impact of diagnosis on initial treatment.

- The diagnostic accuracy of CCTA, ICA and functional imaging are estimates from the EAC meta-analysis of per-patient-based diagnostic accuracy (see pages 108–112 of the assessment report). The EAC did not use the estimates from the clinical guideline because the EAC meta-analysis is based on studies more relevant to HeartFlow FFR_{CT}. However, the updated cost model has been subjected to a sensitivity analysis using diagnostic accuracy values taken from the economic model in the updated clinical guideline.
- In the chest pain economic model in the updated guideline, test costs are taken from the most recent NHS reference costs. The EAC included these costs in its revisions to the HeartFlow FFR_{CT} model. The cost of cardiac MRI is taken from the Payment by Results tariff rather than the reference cost, since the chest paint guideline committee determined that the reference cost for cardiac MRI was not representative of its true cost. The tariff is believed to better represent the cost of cardiac MRI.

Figure 1: Pathway incorporating draft recommendations for the updated chest pain guideline (CG95)



*Uncertain CCTA - image quality is not sufficient to clearly view degree of stenosis

2.5 Equality issues

No equality issues were identified in the submission or the assessment report.

3 Sponsor's claimed benefits

The benefits to patients claimed by the company are:

- Analysis is done using standard coronary CT angiography (CCTA) scans, without the need for additional imaging, radiation or medication.
- HeartFlow FFR_{CT} provides the same accuracy in excluding coronary artery disease as CCTA, while also characterizing the coronary arteries from both

functional and anatomical perspectives, differentiating between ischaemic and non-ischaemic vessels in a manner which CCTA cannot.

- It allows physicians to evaluate anatomic coronary artery disease and accurately determine which coronary lesions are responsible for myocardial ischemia, avoiding unnecessary invasive diagnostic or therapeutic procedures and related complications.
- It reduces the need for revascularization 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 to CCTA alone against the gold standard of invasive FFR, and provides both functional and anatomic assessment of coronary arteries.
- It has superior diagnostic performance to 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 the detection and exclusion of coronary artery lesions that cause ischaemia.

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

- Reduction of downstream costs arising from inconclusive or inaccurate diagnostic tests.
- Avoidance of staff and procedure costs for unnecessary invasive coronary angiographies
- Avoidance of staff and procedure costs for unnecessary interventions (such as angioplasty)
- A more effective utilisation of high-cost invasive procedure suites, providing the opportunity to reduce waiting times for these facilities and increase patient turnaround.
- Application of this non-invasive technology would significantly reduce costs while providing the same or better clinical outcomes as invasive FFR.

4 Decision problem

Table 1 Summary of the decision problem

Population	People with stable chest pain who require investigation for possible coronary artery disease and have a pre-test likelihood of coronary artery disease in the range 10–90%.
Intervention	HeartFlow FFR_{CT} applied to standard coronary CT angiography (CCTA) image data.
Comparator(s)	The comparator will vary depending on the pre-test likelihood of coronary artery disease and on whether coronary revascularization is being considered, in line with NICE guidance on chest pain of recent onset and depending on local treatment pathways and infrastructure. Comparators will include: • CCTA imaging without FFR_{CT} estimation • invasive coronary angiography combined with invasive measurement of FFR using pressure wire studies • myocardial perfusion scintigraphy with single photon emission computed tomography (MPS with SPECT) • other functional imaging (such as stress echocardiography or MR techniques) For diagnostic accuracy, the reference standard is invasive FFR measurement.
Outcomes	The outcome measures to consider will include: • sensitivity and specificity in determining functional significance of coronary artery disease • positive and negative likelihood ratios and area-under-curve for measurement of FFR_{CT} versus invasive FFR measurement • rates of undertaking diagnostic coronary angiography • rates of revascularization by percutaneous coronary intervention and coronary artery bypass graft • radiation exposure • mortality • invasive test related adverse events • major adverse cardiac events • use of non-invasive functional imaging • quality of life • device-related adverse events
Cost analysis	Costs will be considered from an NHS and personal social services perspective. Sensitivity analysis of costs will be considered for units with and without access to a CCTA system.

	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 tests are needed.
Special considerations, including issues related to equality	No special considerations

5 The evidence

5.1 Summary of evidence of clinical benefit

The evidence for the diagnostic accuracy and clinical outcomes associated with HeartFlow FFR_{CT} is described separately. Evidence searches were done for the assessment report and the addendum, and are described separately

Evidence assessment June 2015

The company conducted a literature search for evidence on the diagnostic accuracy of HeartFlow FFR_{CT} and existing tests in the current treatment pathway for patients with a 10–90% pre-test likelihood of coronary artery disease, against a reference standard of invasive fractional flow reserve (FFR) testing. This review identified 5 relevant meta-analysis studies and 23 individual studies, 1 of which was unpublished. The company undertook a meta-analysis of all 22 of the published individual studies identified, 3 of which involved HeartFlow FFR_{CT} (see pages 29–30 and 140–149 of the company's submission).

The external assessment centre (EAC) judged the company's search terms to be appropriate. However, it considered that additional keywords could have been used to increase its sensitivity and specificity. The EAC critiqued the company's selection of studies and considered that although they addressed the scope in terms of the comparators, reference test and outcomes, most of

the studies selected included a mixture of patients with both high (over 90%) and intermediate (20–90%) pre-test likelihoods of disease. It also disagreed with the company's decision to only include studies that provided FFR measurements in more than 75% of blood vessels (see page 141 of the company's submission). The EAC considered this criterion to not be reflective of clinical practice where a visual assessment is applied in some cases before proceeding with FFR measurements, or of the company's proposed changes to the clinical pathway, where the degree of stenosis in coronary CT angiography (CCTA) would be used to decide if HeartFlow FFR_{CT} should be done (see page 40 of the assessment report).

The EAC therefore conducted a diagnostic literature search using additional keywords related to comparators and outcomes (see pages 40–44 of the assessment report). 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 Stuijfzand et al. 2014) and 3 studies which the company identified but excluded (Danad et al. 2013, Kajander et al. 2010 and Ponte et al. 2014; see table 7, pages 50–58 of the assessment report).

HeartFlow FFR_{CT} studies

Nørgaard et al. (2014) reported on a multicentre study involving 2 UK centres which compared HeartFlow FFR_{CT} (v1.4) with CCTA for the diagnosis of myocardial ischaemia in 254 patients with suspected stable coronary artery disease scheduled to have invasive coronary angiography (ICA). Most patients in the study (87%) were considered to have an intermediate likelihood of developing disease. Invasive FFR was measured in all vessels (n=484). The study reported the diagnostic performance of FFR_{CT} and CCTA for diagnosing ischaemia compared with that of ICA as the reference standard. The diagnostic accuracy for each test was presented on a per-patient and a per-vessel basis compared against the reference standard (FFR≤0.80). The

per-patient diagnostic accuracy was 53% for CCTA, 81% for FFR_{CT} and 77% for ICA. The per-vessel diagnostic accuracy was 65% for CCTA, 86% for FFR_{CT} and 82% for ICA. Per-vessel FFR_{CT} was correlated to FFR (Pearson's correlation coefficient 0.82, p>0.001), with a slight underestimation of FFR_{CT} compared with FFR. The authors concluded that HeartFlow FFR_{CT} has high diagnostic performance and can identify functionally significant coronary artery disease with high sensitivity and specificity. Furthermore, adding FFR_{CT} measurements to CCTA leads to a marked increase in specificity.

The EAC considered that this study had a low risk of bias for flow and timing, index and reference test. It noted that an inclusion criterion was that patients had to have been referred for ICA, so there was a high risk of patient selection bias, but it noted no other risks of bias or applicability concerns. Confidence intervals and sample size calculations were reported.

Comparator studies

Bernhardt et al. (2012) compared the diagnostic performance of 1.5T and 3T 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). FFR measurements were taken in all patients in the left anterior descending, left circumflex and right coronary arteries during maximal hyperaemia (n=102 vessels). Analysis of 3T MRI data showed that the area under the curve (AUC) was 0.963 on a per-patient basis, yielding a sensitivity of 90.5% and specificity of 100%. Receiver operating characteristics analysis on a per-vessel basis for FFR≤0.80 yielded results of:

- left anterior descending artery: AUC 0.941, sensitivity=89.5%, specificity=100%
- left circumflex artery: AUC 0.808, sensitivity=75.0%, specificity=96.2%
- right coronary artery: AUC 0.941, sensitivity=90.9%, specificity=100%.

Ponte et al. (2014) compared the diagnostic accuracy of CCTA and MRI for detecting functionally significant coronary artery disease in patients referred with suspected disease, using ICA with FFR as the reference standard. The study included 95 patients with a 15–85% pre-test likelihood of coronary artery disease. Invasive FFR was measured in case of lesions with intermediate stenosis (40–90%). Confidence intervals were reported but sample size calculation was not. Compared with CCTA, MRI had lower sensitivity (100% compared with 88%) but higher specificity (59% compared with 89%). The authors concluded that although CCTA is an effective rule-out test for functionally significant coronary artery disease, stenosis of over 50% or inconclusive results may be better investigated using CCTA and subsequent non-invasive functional imaging.

Suijfzand et al. (2014) evaluated CCTA and transluminal attenuation gradient (TAG) 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. FFR was measured in all major coronary arteries except for occluded or subtotal lesions. Confidence intervals were reported but sample size calculation was not. Using a stenosis threshold of 50%, CCTA had a per-vessel and per-patient sensitivity of 95% and specificity of 75%. The results showed that TAG does not improve the diagnostic accuracy of CCTA alone in diagnosing functionally significant lesions.

Neglia et al. (2015) assessed the accuracy of several imaging techniques – CCTA, single photon emission computed tomography (SPECT) and stress echocardiogram (ECHO) – in 475 patients with intermediate likelihood of coronary artery disease. If at least 1 non-invasive imaging test was positive, patients also had ICA and FFR if their stenosis was 30–70%. Significant stenosis was defined as luminal narrowing of over 70%, and only stenoses between 30% and 70% were further investigated by FFR. As a result, FFR measurements were taken for only 45 of the 475 patients. Data were analysed

locally and in core laboratories dedicated to each technique. Diagnostic accuracy was 91% for CCTA, 70% for SPECT and 68% for ECHO. Revascularisation was done in 54% of patients with positive CCTA, 33% of patients with positive SPECT and 48% of patients with positive ECHO. No serious adverse events were reported during non-invasive imaging, but 4 patients had severe chest pain during CCTA. Mean radiation exposure was 11.2±8.1 mSv for CCTA, 10.0±2.7 mSv for SPECT, 1.7±1.5 mSv for cardiac positron emission topography (PET) and 12.8±14.8 mSv for ICA. The authors concluded that in a European population of patients with stable chest pain and low prevalence of disease, CCTA is the most accurate imaging technique for detecting functionally significant coronary artery disease as defined by ICA.

Danard et al. (2013) evaluated the diagnostic accuracy of CCTA in 120 patients with suspected coronary artery disease who had PET, CCTA and ICA. CCTA was done using a hybrid PET/CT scanner. FFR measurements were not routinely done in patients with an intermediate coronary stenosis, and neither confidence intervals nor sample size calculation were not reported. On a per-patient basis, the sensitivity and specificity of CCTA were 100% and 34% respectively. The authors concluded that adding PET to CCTA improves the diagnostic accuracy of the latter for detecting functionally significant coronary artery disease, mainly by improving the specificity.

Kajander et al. (2010) evaluated the diagnostic accuracy of PET and CCTA in 107 patients with a history of stable chest pain and a 30–70% 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. FFR measurements were taken for most stenoses over 30%. CCTA was done using a hybrid PET/CT scanner. Confidence intervals and sample size calculation were not reported. CCTA had per-patient sensitivity of 95% and specificity of 87%, and per-vessel sensitivity of 75% and specificity of 95%. The authors concluded that adding PET to CCTA improves the

diagnostic accuracy of the latter for detecting functionally significant coronary artery disease, by improving the sensitivity and specificity.

Diagnostic accuracy evidence synthesis

The company conducted a meta-analysis of 22 primary diagnostic outcome studies, the methodology and results of which are reported as academic in confidence on pages 142 to 148 of the submission. Results were reported on a per-patient level. The EAC did per-patient and per-vessel level meta-analyses of the 7 diagnostic studies it had selected from its literature search. The results of these are presented in tables 10 and 11 on pages 109–115 of the assessment report, and summarised in table 2 below. The EAC noted that the results of the meta-analyses should be interpreted with caution, because no adjustment was made for confounding variables such as patient characteristics. A comparison of the company's and the EAC's meta-analyses is possible for the patient-level results. In most cases, the 2 meta-analyses agree in that the 95% confidence intervals overlap. However, for FFR_{CT} the company's specificity value is lower: 0.71 (0.65 to 0.75) and the sensitivity and specificity for CCTA are also lower: sensitivity 0.90 (0.85 to 0.93), specificity 0.39 (0.34 to 0.44). There are also differences in the ECHO sensitivity and specificity (sensitivity 0.77 (0.61 to 0.88), specificity 0.75 (0.63 to 0.85) and in the ICA specificity 0.67 (0.63 to 0.71).

Table 2: Results from the EAC's meta-analysis (adapted from table 10 of the assessment report)

Index test	N	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
Patient-based analysis					
FFR_{CT} *(Nørgaard, 2014: NXT trial)*	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
CCTA *(6 studies)*	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
ECHO *(Neglia, 2015)*	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
ICA *(Nørgaard, 2014)*	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
MRI *(2 studies)*	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
SPECT *(Neglia, 2015)*	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
Vessel-based analysis					
FFR_{CT} *(Nørgaard, 2014)*	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
CCTA *(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
ICA *(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
MRI *(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

Clinical outcomes

The company conducted a literature search for evidence on the clinical outcomes specified in the decision problem for HeartFlow FFR_{CT} and the existing treatments, against any comparator. It identified 16 studies, 5 of which included HeartFlow FFR_{CT} (see pages 31 and 33 of the submission).

The EAC included additional intervention and comparator keywords and identified 11 studies, 4 of which had already been included 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 the specified intervention (that is, HeartFlow FFR_{CT}).

The 2 unpublished studies including HeartFlow FFR_{CT} were PLATFORM and Radiation FFR_{CT}, both provided by the company in the form of interim results for the former and an abstract for the latter.

The PLATFORM study is a multicentre, multinational, post-market, prospective, controlled study comparing clinical outcomes, resource utilization and quality of life of CCTA/FFR_{CT}-guided evaluation (cohort 2) versus standard care (cohort 1) in patients with suspected coronary artery disease. Patients were further delineated, with those presenting for initial non-invasive testing designated as cohorts 1A and 2A, and those already referred for ICA designated as cohorts 1B and 2B. The study recruitment started in September 2013 and was completed in November 2014. In total, 584 patients with an intermediate pre-test likelihood of coronary artery disease were enrolled, 287 in cohort 1 and 297 in cohort 2. The company has provided preliminary data from 90 days of follow-up for this study. The study enrolled the 2 cohorts sequentially with each site completing enrolment objectives for cohort 1 before commencing cohort 2. Among patients referred originally for ICA, 65% fewer had ICA in the group having CCTA/FFR_{CT}-guided evaluation compared to those having standard care (cohort 1B: 75%, 95% confidence interval [CI] 69% to 81%; cohort 2B: 11%, 95% CI 7% to 16%, $p<0.0001$). The rate of unnecessary ICA done (that is, it was done but no obstructive coronary artery disease was found) fell from 75% in the standard care group (consistent with the literature) to 11% in the CCTA/FFR_{CT} group. Major adverse cardiac event rates at 90 days were less than 1% and were similar between the 2 groups

(cohort 1: 0.4%, 95% CI 0.01% to 2.0%; cohort 2: 0.7%, 95% CI 0.08% to 2.0%, p value not specified). Percutaneous coronary intervention (PCI) rates were similar between the groups, indicating that in a pathway using CCTA and FFR_{CT}, patients with functionally important coronary artery disease were not being under-diagnosed despite the lower rate of invasive angiography (cohort 1B: 23% (42/180); cohort 2B: 24% (44/184), p value not specified). Quality of life, assessed using EQ-5DL and SAQ, showed greater improvement in the CCTA/FFR_{CT} group than in the standard care group (SAQ, cohort 1: 14.0±18.9; cohort 2: 18.3±17.5, p=0.009. EQ5DL, cohort 1: 0.04±0.13; cohort 2: 0.07±0.13, p=0.017)

In its appraisal of PLATFORM, the EAC noted that it is powered for both primary outcome and secondary outcome measures. Confidence intervals and p values are presented for all outcomes. However, expert opinion provided to the EAC indicated that 90 days is not long enough to assess clinical outcomes such as major adverse cardiac events. As a result, the EAC considered that the evidence submitted so far by the company can support its claims regarding resource utilisation, rates of ICA and PCI, and quality of life, but not major adverse cardiac events.

The Radiation FFR_{CT} study is a single-centre modelling study based in Canada investigating the potential effect of HeartFlow FFR_{CT} on radiation dose exposure and downstream clinical event rate. In the modelling, a clinical pathway in which CCTA plus FFR_{CT} 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. There was no clinical follow up for this study. 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_{CT} 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. The EAC considered this evidence to be of limited usefulness due to the lack of detail on the methodology in the abstract supplied by the company.

The 9 published studies identified by the EAC on comparator diagnostic technologies were:

- Douglas et al. (2015a) compared health outcomes in 10,003 patients randomly assigned to CCTA or functional imaging (including stress ECHO) as a first-line diagnostic test. The composite primary end point was death, myocardial infarction, and hospitalisation for unstable angina or major procedural complication. Secondary end points included invasive cardiac catheterisation that did not show obstructive coronary artery disease and radiation exposure. Over a median follow-up of 25 months, a primary end-point event occurred in 3.3% patients in the CCTA group and in 3.0% in the functional imaging group (adjusted hazard ratio 1.04; 95% CI 0.83 to 1.29; p=0.75). CCTA was associated with fewer catheterisations showing no obstructive coronary artery disease than functional imaging (3.4% compared with 4.3%, p=0.02), although more patients in the CCTA group had catheterisation within 90 days of randomisation (12.2% compared with 8.1%). The study concluded that in symptomatic patients with suspected coronary artery disease who needed non-invasive testing, an initial strategy of CCTA was not associated with better clinical outcomes than functional imaging over a median follow-up of 2 years.
- Hachamovitch et al. (2012) examined short-term cardiac catheterisation rates and medication changes after cardiac imaging in 1,703 patients who had no history of coronary artery disease, an intermediate to high likelihood of coronary artery disease and who were having cardiac SPECT, PET, or

64-slice CCTA. Risk-adjusted analyses revealed that, compared with stress SPECT-CT or PET, changes in aspirin and lipid-lowering agent use was greater after CCTA, as was the 90-day catheterisation referral rate in the setting of normal/non-obstructive and mildly abnormal test results. The authors concluded that compared with stress SPECT, catheterisation referral rates and subsequent need for revascularisation were greater after CCTA, but the rates of medication use were similar.

- Cheezum et al. (2011) compared the clinical and cost outcomes of SPECT with those of CCTA in 241 patients without known coronary artery disease. The mean follow-up was 30±7 months. Sample size calculation and CIs were not reported. No significant difference was found in the rates of major adverse cardiac events between CCTA and SPECT (0.4% versus 0.9%, p=0.54). Of the 8 patients found to have obstructive disease with CCTA, subsequently confirmed by cardiac catheterisation, 2 had revascularisation. Of the 6 patients found to have ischaemia or infarction with SPECT and who had obstructive disease confirmed by cardiac catheterisation, 2 had revascularisation. No patients in either group were found to have confirmed cardiac death.
- Min et al. (2008) examined healthcare expenditures and clinical outcomes of patients without known coronary artery disease who had CCTA (n=3,331) or SPECT (n=138,043) for diagnostic coronary evaluation. Sample size calculation was not reported for this study. No statistically significant differences in rates of percutaneous transluminal coronary angioplasty, intracoronary stent placement, percutaneous interventions, coronary artery bypass surgery, or coronary artery revascularisation were found between the 2 groups. There were also no significant differences at 9-month follow-up in rates of coronary artery disease-related hospitalisation, coronary artery disease-related outpatient visits, post-test myocardial infarction, or new-onset angina between patients who had CCTA compared with those who had SPECT.

- Min et al. (2012) determined the near-term clinical effect and resource utilisation after CCTA compared with SPECT. Of the patients enrolled, 180 had a low risk, 117 had an intermediate risk, and 51 had a high risk of coronary artery disease. Patients were randomly assigned to initial diagnostic evaluation by CCTA (n=91) or SPECT (n=89). No patients experienced myocardial infarction or death with 98.3% follow-up at 55 days. Patients who had CCTA had increased aspirin (22% compared with 8%, p=0.04) and statin (7% compared with −3.5%, p=0.03) use, as well as increased revascularisation (8% compared with 1%, p=0.03). Similar rates of coronary artery disease-related hospitalisation, ICA, and non-invasive cardiac imaging tests were reported for both CCTA and SPECT groups.
- Mouden et al. (2014) assessed the impact and resulting clinical and prognostic implications of myocardial perfusion imaging using SPECT in 282 patients with suspected coronary artery disease, low-to-intermediate risk of a coronary event and high calcium score (≥1,000). Sample size calculation and CIs were not reported. On follow-up at 18 months invasive angiography, coronary revascularisation, non-fatal myocardial infarction and death were recorded. One patient died from a cardiac cause, 1 patient had myocardial infarction and 92 patients (33%) had revascularisation.
- Ovrehus et al. (2013) evaluated the influence of CCTA as a first-line diagnostic test on treatment and prognosis in 1,055 patients with a low-to-intermediate risk of coronary artery disease. Patients were followed for a median of 18 months. Sample size calculation and CIs were not reported. patients with non-obstructive coronary artery disease and 1.9% of patients with obstructive coronary artery disease met the primary end point (cardiovascular death and myocardial infarction, p=0.008); 1.5% of patients with non-obstructive coronary artery disease and 30% patients with obstructive coronary artery disease met the secondary end point (cardiovascular death, myocardial infarction, and coronary revascularisation, p<0.0001).

- Sahinarslan et al. (2013) compared the radiation exposure between CCTA and ICA in 72 patients with stable angina with no history of CCTA or ICA. Patients were evenly divided into 2 groups, 1 of which was investigated with CCTA and the other with ICA. Sample size calculation and confidence intervals were not reported. The effective radiation dose was found to be higher for CCTA than for ICA (14.2±2.7 compared with 6.4±31.1, p<0.001).

Adverse events

The company undertook a literature search for adverse events as a result of using HeartFlow FFR_{CT}. It identified 1 relevant study, PLATFORM, from which the company reported 16 adverse events (see pages 134 and 135 of the submission). The EAC considered the company's search to be appropriate and that none of the adverse events raised concerns about the safety of HeartFlow FFR_{CT} (see page 38 of the assessment report).

The company undertook a search of the FDA Manufacturer and User Facility Device Experience (MAUDE) database that revealed no reports of adverse events. One vigilance report was filed but this related to a formatting issue on a PDF report which had no effect on patient care (see page 136 of the submission).

EAC conclusions on clinical evidence

The EAC considered all of the included diagnostic accuracy literature to have a low risk of bias for the conduct and reporting of the index and reference test. However, it noted that in 4 comparator studies (Kajander et al. 2010, Danad et al. 2013, Ponte et al. 2014 and Neglia et al. 2015), not all patients had the same reference test. Instead, some patients were considered to have functionally significant coronary artery disease based on ICA findings and not invasive FFR. The EAC sought expert advice on the assignment of functionally significant status to a stenosis based on the ICA findings alone and concluded that it is well accepted that there is discordance between diameter stenosis and physiological significance as evaluated by invasive

FFR. It is, however, more unusual to have a positive FFR for a lesion with mild stenosis (<50%) in ICA.

Two of the diagnostic studies (Bernhardt et al. 2012 and Nørgaard et al. 2014) were considered to be at risk of bias for patient selection, because they included patients who had already been referred for ICA. However, most patients included in these studies had an intermediate pre-test likelihood of coronary artery disease, supporting the generalisability of their findings. The EAC concluded that despite these limitations all studies contributed to the decision problem and, therefore, provided data for synthesis in its meta-analysis.

The EAC considered only 1 of the identified studies, the unpublished PLATFORM study, to be useful in assessing HeartFlow FFR_{CT}'s effect on resource use. The EAC considered the Radiation FFR_{CT} study to be of limited usefulness because of the lack of detail regarding methodology in the available abstract.

The EAC considered the other clinical outcomes studies that did not include HeartFlow FFR_{CT} to be of limited relevance to the decision problem because of limitations to their generalisability and limited follow-up (see pages 72 and 73 of the assessment report).

Updated evidence assessment February 2016

The EAC repeated its searches for new evidence in February 2016 and the company was asked to identify recent and ongoing studies. In total, the EAC assessed 7 new studies.

Technical studies

Tanaka et al. (2016) is a technical study, the first to investigate the association between FFR_{CT} and invasive FFR in coronary arteries with serial lesions, in a subgroup population of the NXT study. 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_{CT} 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_{CT} were 0.10±0.09 and 0.09±0.10 in distal segments, and 0.17±0.10 and 0.22±0.13 in proximal segments respectively. The coefficient of correlation between translesional delta FFR and FFR_{CT} in each segment was 0.92 ($p<0.001$). The authors concluded that translesional delta FFR is highly correlated with FFR_{CT}.

Diagnostic accuracy

Thompson et al. (2015) investigated the diagnostic performance of FFR_{CT} in relation to patients' sex and age, using invasive FFR measurements as the reference standard for a subgroup population 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. was included because it reports results based on subgroup analyses for age and gender. 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 30–90%. For their analysis, the authors used a clinical rule that included all vessels of diameter ≥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_{CT}. Using the clinical rule, the diagnostic performance improved in both sexes with no significant differences between them (AUC: 0.93 vs. 0.90, p=0.43). There were no differences in the discrimination of FFR_{CT} after application of the clinical use rule when stratified by age ≥65 or <65 years (AUC: 0.95 vs. 0.90, p=0.10). The authors concluded that FFR_{CT} had similar diagnostic accuracy and discriminatory power to FFR for ischemia detection in men and women

irrespective of age using a cutoff point of 65 years.

Clinical outcomes

The SCOT-HEART randomised controlled trial (2015) investigated the effect of adding CCTA to standard care on the diagnosis, management and outcome of patients with suspected angina due to coronary artery disease. Secondary outcomes investigated were the radiation dose and adverse reactions to the CT scanning procedure (such as contrast reaction, renal impairment or vasovagal response). The trial recruited 1,778 patients at 12 cardiology centres across Scotland. At 6 weeks, CCTA reclassified the diagnosis of coronary artery disease in 27% of patients and the diagnosis of angina due to coronary artery disease in 23% of patients (standard care=1% and 1%, respectively, p<0.0001). This changed planned investigations (15% vs. 1%, p<0.0001) and treatments (23% vs. 5%, p<0.0001), but did not affect 6-week symptom severity or subsequent admittances to the hospital for chest pain. CCTA was associated with a 38% reduction in fatal and non-fatal myocardial infarction after 1.7 years (26 vs. 42, HR=0.62, 95% CI 0.38 to 1.01; p=0.0527). There was a higher rate of revascularisation with CCTA, but again the difference was not significant (11.2 vs. 9.7%; p=0.0611). The authors concluded that the addition of CCTA to standard clinical care clarifies the diagnosis, reduces the need for further stress testing, increases the use of ICA, and results in more focused treatment regimens that are associated with an apparent reduction in fatal and non-fatal myocardial infarction. The EAC concluded that the study supports the findings of PROMISE (Douglas et al. 2015) which were included in the original assessment report, that demonstrate that there is no statistically significant difference in the rates of major adverse cardiac events (MACE) when using CCTA compared with functional imaging alone.

The PLATFORM study (Douglas et al. 2015b and 2016) was presented to the committee in limited form, as academic-in-confidence data, in June 2015. The study included 584 patients recruited at 11 international centres. They were

prospectively assigned to have either functional imaging (n=287) or CCTA/FFR_{CT} (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_{CT}) or ICA.

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 ≥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 revascularization, all of which were independently and blindly assessed. Among patients with intended ICA (CCTA/FFR_{CT} =193; functional imaging=187), no obstructive coronary artery disease was found with ICA in 24 patients (12%) in the CCTA/FFR_{CT} 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_{CT} arm and 6% in the functional imaging arm (p=0.95). ICA was cancelled in 61% of patients after reviewing the CCTA/FFR_{CT} results. There were low numbers of MACE and vascular complications in all groups.

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±6.7 mSv) and CCTA/FFR_{CT} arms (mean: 10.7 ± 9.6 mSv; p=0.21), but higher in the functional imaging arm in patients with an FFR_{CT}-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_{CT} compared with patients having functional imaging (mean change: 0.12 for CCTA/FFR_{CT} vs. 0.07 for functional imaging, p=0.02)

Lu et al. (2015) used a subgroup analysis of the PROMISE trial (n=181) to investigate the added value of FFR_{CT} 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_{CT} 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_{CT} >0.80 had an adverse event which ICA would have prevented

Norgaard (2016) reports on the first real-world experience of using CCTA with FFR_{CT} 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_{CT} on further downstream diagnostic testing. Other end points were the agreement between FFR_{CT} and invasive FFR, and the short-term clinical outcome after FFR_{CT} 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_{CT} testing is feasible in real-world patients with intermediate-range coronary stenosis determined by CCTA, that implementation of FFR_{CT} for clinical decision-making may influence the downstream diagnostic workflow, and that patients with an FFR_{CT} >0.80 who are not referred for ICA have a favourable short-term prognosis. The authors also 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.

Additional work by the EAC: technical evaluation

Based on the committee's selection and routing considerations, NICE asked the EAC to complete a technical evaluation as a supplementary piece of work to the Assessment Report, to assess the following:

- The reproducibility of HeartFlow FFR_{CT} analysis and the robustness of quality assurance procedures to maintain reproducibility in the face of increasing workload.
- The adequacy of information governance arrangements for remote data processing.

Reproducibility

Having reviewed information from the company, the EAC also reviewed publically available and commercial-in-confidence information related to analyst training and workload, risk analysis and security protocols. Its main findings were as follows:

- The company has a quality assurance process in place that fulfils data quality requirements. This includes checks by different team members, and the separation of tasks to ensure that no single analyst is responsible for a case diagnosis. Once the process has been completed, 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 analysis process is largely automated, an analyst can manually edit any part of the process, which can affect FFR_{CT} estimation. However, the available evidence (Gaur et al. 2014) suggests that reproducibility is within the 95% confidence interval limits of agreement.
- Lumen extraction reproducibility, one step in the process of FFR_{CT} computation, decreases in the distal portion of the vessel (Gage R&R = 29.4%). This could be a result of multiple variables including lower contrast perfusion/CT quality at the distal end of the vessel, lower CT resolution,

smaller vessel diameter, and disease burden. FFR_{CT} reproducibility was found to be equivalent to invasive FFR reproducibility

- 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 internationally recognised standards for data confidentiality and integrity protection requirements for remote processing. It offers NHS customers the option to upload fully anonymised DICOM data to comply with UK data protection law.

Table 3 Diagnostic literature included by the EAC

Study	Study design (country)	Population (n)	Intervention versus comparator	Outcomes considered	EAC comments on study
Full, peer-reviewed articles					
Nørgaard, 2014 (NXT trial)	Prospective cohort International multicentre study (10 participating centres including 2 in the UK)	Patients with intermediate pretest likelihood of CAD (n=254, 220 had an intermediate pre-test likelihood of CAD)	FFR_{CT} FFR was measured in 97% of the vessels.	Diagnostic accuracy	This was a large prospective study providing evidence on the diagnostic accuracy of FFRCT in comparison with ICA and CCTA. However, it did not include non-invasive functional imaging comparators. FFR was measured in 97% of the vessels. In comparison with the other included diagnostic accuracy studies this would be less affected by bias associated with the reference test.
Bernhardt et al (2012)	Prospective cohort study (Germany)	Patients with stable angina and suspected or known CAD (n=34)	MRI perfusion at 1.5 and 3 Tesla (only results for 3T included in meta-analysis.)	Diagnostic accuracy	The PROCAM score uses different variables from the NICE proposed algorithm for assigning a pre-test likelihood of CAD.
Danad et al (2013)	Prospective cohort (Holland)	Patients being evaluated for CAD, predominantly with an	CCTA	Per patient and per vessel level analysis: Sensitivity, specificity, NPV, PPV, Diagnostic	Although 49 patients had significant coronary artery stenosis (>50%) at ICA only 17 had undergone an FFR measurement. FFR

Study	Study design (country)	Population (n)	Intervention versus comparator	Outcomes considered	EAC comments on study
		intermediate pre-test likelihood (n=120)		accuracy	measurements were not routinely performed in all patients with an intermediate coronary stenosis. This could introduce bias associated with the reference test.
Kajander et al. (2010)	Prospective cohort (Finland)	Patients with an intermediate (30% to 70%) pre-test likelihood of CAD (n=107)	CCTA All patients underwent ICA independently of the non-invasive imaging results. FFR measurements were performed for stenoses >30%.	Diagnostic accuracy	Some stenoses were not subjected to FFR because of logistics or the operator's clinical and visual assessments of complicated lesions. This could introduce bias associated with the reference test.
Neglia 2015	Prospective cohort (participants were recruited from 14 European centres.)	Patients with an intermediate probability of CAD (20% to 90%) based on age, sex, symptoms, and exercise ECG when available (n=475)	CCTA, SPECT, and ECHO. Only stenoses with luminal narrowing between 30% and 70% were further investigated by FFR. As a result only 10% (45/475) of the patients had FFR measured	Diagnostic accuracy	A significant stenosis was defined as luminal narrowing >70%, and only stenoses between 30% and 70% were further investigated by FFR. As a result only 10% (45/475) of the patients had FFR measured. This could introduce bias associated with the reference test.
Ponte, 2014	Prospective cohort (Portugal)	Patients with intermediate pre-test probability of	CCTA MRI	Diagnostic accuracy	The aim of the study was to compare the diagnostic accuracy of non-invasive anatomical and functional

Study	Study design (country)	Population (n)	Intervention versus comparator	Outcomes considered	EAC comments on study
		CAD (n=95)			imaging. CCTA scans were obtained as part of a stress-rest protocol. Therefore, CCTA results could be improved if a different scan protocol (including the use of oral instead of intravenous pre-test beta-blockage) had been used.
Stuijfzand, 2014	Prospective cohort (Netherlands)	Patients with an intermediate probability of CAD, determined using the Diamond and Forrester criteria (n=85)	CCTA	Diagnostic accuracy	The main aim of the study was to explore the diagnostic potential of TAG in comparison with CCTA. Therefore the diagnostic accuracy of CCTA was a secondary endpoint.
Thompson, 2015	Retrospective analysis of DeFACTO trial sub-cohort (20 US, Canadian, European and Aisan centres)	Patients with stable angina and clinically suspected CAD (n=252)	CCTA v FFR	Diagnostic accuracy	This study provides evidence that age and sex do not impact on the diagnostic accuracy of FFR_{CT}.
Diagnostic accuracy refers to measures of the test sensitivity and specificity, and its positive and negative predictive value.					

Study	Study design (country)	Population (n)	Intervention versus comparator	Outcomes considered	EAC comments on study
Note that the reference standard is invasive FFR.					
Abbreviations: CAD, coronary artery disease; CCTA, coronary computed tomography angiography; ECHO, stress echocardiography; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value; SPECT, single photon emission computed tomography.					

Table 4: Clinical outcomes literature included by the EAC

Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
Abstracts: FFR_{CT}					
PLATFORM	Prospective, controlled, sequential cohort,	Patients at intermediate likelihood of obstructive CAD (20% - 80%) (n=584)	FFR_{CT} vs standard of care	Primary: 90-day rate of coronary angiogram showing no obstructive disease	The sponsor has provided preliminary data from 90 days of follow-up for this study. The study is powered for the primary outcome
Radiation FFRCT	Modelling study (Canada)	Symptomatic patients with stable angina and suspected CAD with intermediate disease burden (n=200)	Intervention: clinical pathway utilizing CCTA+ FFR_{CT} as initial diagnostic study Comparator(s): 3 clinical pathways utilizing SPECT, ECHO and CCTA	Radiation dose Death/MI estimates at 1 year	This is a simulation/modelling study submitted as an abstract. Given the lack of detail regarding the investigators methodology, robust conclusions cannot be extracted.

Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
			as initial diagnostic study		
Lu (2015)	Retrospective observational cohort study (International)	(n=181)	CCTA FFR_{CT}	Efficiency of FFR_{CT} as gatekeeper to ICA (%ICA leading to revascularisation)	Demonstrates that FFR_{CT} ≤0.80 could improve treatment efficiency by increasing the rate of ICA resulting in revascularisation from 49% to 61%. Rate of ICA without obstructive disease decreased from 27% to 11%. No patient with FFR_{CT} > 0.80 had an adverse event which ICA would have prevented.
Full peer-reviewed articles: FFR_{CT}					
The SCOT-HEART investigators (2015)	Prospective RCT, multi-centre (Scotland)	Symptomatic patients with suspected, but undiagnosed CAD (n=4146)	CCTA ECHO SPECT MRI	Primary: proportion of patients diagnosed with angina pectoris secondary to CAD at 6 weeks Secondary: Resource utilisation Survival MACE Radiation dose	The study confirms the results of the US-based PROMISE study with no significant differences noted in MACE events between CCTA and functional imaging, while CCTA was associated with reduced ICA normalcy rates (fewer "false-positive" studies), and

Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
					greater diagnostic certainty. CCTA was also associated with an increase in coronary revascularization rates (particularly of CABG), with a trend toward reduced death and myocardial infarction at 1 year.
Douglas (2015b)	Prospective controlled comparative effectiveness observational study (USA and Europe)	Symptomatic patients with suspected, but undiagnosed CAD (n=584)	CCTA/FFR_{CT} SPECT ECHO CCTA	Primary: 90-day rate of coronary angiogram showing no obstructive disease Secondary: (MACE) and MACE + vascular complications, all-cause death, non-fatal MI, resource utilization, quality of life (QOL) assessment (90 days, 180 days, 365 days), and cumulative radiation exposure at 365 days.	The study is of high relevance to the decision problem. It showed that in patients with planned ICA, a diagnostic strategy based on CCTA/FFR_{CT} yielded a significantly lower rate of ICA showing no obstructive CAD. In patients with planned non-invasive testing, there was no difference between the use of CCTA/FFRCT and usual care. Clinical events through 90 days were rare with either strategy. This study adds further evidence to the PROMISE and SCOT-HEART trials.
Douglas (2016)	As per Douglas (2015b)	As per Douglas (2015b)	As per Douglas (2015b)	MACE events at 1 year Cost savings at 1 year QOL at 1 year	The study is of high relevance to the decision problem. The study showed that in patients with planned ICA, patient care guided by CCTA/FFR_{CT} resulted

Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
					in equivalent clinical outcomes, a greater increase in the EQ5D-assessed quality of life and lower costs. In patients with planned ICA mean costs were 33% lower with a strategy incorporating CCTA and selective FFR_{CT}.

Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
Nørgaard (2016)	Single-centre, observational study	n=185	CCTA/FFR_{CT}	Impact on downstream diagnostic testing Agreement between FFR_{CT} and invasive FFR Short-term clinical outcomea after FFR_{CT}	Of some use to the decision problems. Demonstrates that FFR_{CT} testing is feasible in real-world symptomatic patients.
Tanaka (2016)	Retrospective analysis of NXT trial sub-cohort Technical study	18 patients with a total of 18 vessels	FFR_{CT} FFR	Per-segment correlation between FFR_{CT} and invasive FFR values	Of low usefulness to the decision problem. Serial coronary stenoses impact upon the hemodynamic significance of each other. This study addresses the issue of assessing sequential stenoses with FFR_{CT} that was raised in the technical evaluation report.
Full peer-reviewed articles: comparators					
Cheezum (2011)	Retrospective (USA)	Patients without known CAD who underwent CCTA for possible angina. (n=241)	CCTA vs MPS	Utilisation of ICA Cardiac testing	The results of this study can provide further evidence on the post-test resource utilisation of functional vs. anatomical imaging. However, for this study ICA and coronary revascularisation were not considered a repeat downstream test if it was correctly indicated by the index testing strategy.
Douglas (2015)	Prospective	Patients with	Functional testing,	Resource utilization	By showing that there is no

Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
PROMISE study	cohort (with registry) (USA)	intermediate pre-test likelihood of obstructive CAD (n=10,003)	including SPECT v CCTA	MACE Radiation dose	statistically significant difference between the rates of MACE events occurring in a diagnostic pathway that utilises CCTA vs. one that uses functional imaging, it provides further evidence on the diagnostic pathway proposed by the sponsor
Hachamovitch (2012)	Prospective cohort (with registry) (USA)	Patients without previous CAD with an intermediate to high CAD likelihood (n=1,717)	CCTA v SPECT	Referral for ICA within 90 days of the index study Referral to revascularization within 90 days after non-invasive procedures	The primary aim of the study was to assess the impact of functional imaging (SPECT, PET) and CCTA on post-test ICA referrals within 90 days. The results of this study can be compared with those reported in the sponsor's PLATFORM study. Bonferroni adjustment for multiple comparison was performed
Min (2008)	Observational (registry) (USA)	Patients, without known CAD, who underwent CCTA (n=1,938) matched to those who underwent SPECT (n=7,752)	CCTA v SPECT	Resource utilisation MACE Revascularisation rates	This was a large private administrative American claims database of >10 million members. The results might not be applicable to the NHS setting.
Min (2012)	Prospective	Patients	CCTA v SPECT	Radiation dose	This study did not fulfil the

Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
	RCT (USA)	presenting with stable chest pain and suspected CAD (n=180)			population requirements for pre-test intermediate likelihood. As a result only the results related to radiation dose were included.
Mouden (2014)	Prospective cohort (Netherlands)	Patients without a history of CAD with suspected stable angina referred for MPI (n=282)	SPECT	Revascularisation rates	The study included only one comparator (SPECT). Therefore, the results should be interpreted with caution
Neglia (2015)	Prospective cohort (14 centres from across Europe)	Patients with an intermediate probability of CAD (20% to 90%) based on age, sex, symptoms, and exercise ECG when available (n=475)	CCTA, SPECT, ECHO	Adverse events Revascularisation rates Radiation dose	Sample size calculation reported, however, the study was powered for the primary outcome of diagnostic accuracy.
Ovrehus (2011)	Observational (registry) (Denmark)	patients with suspected stable angina pectoris and a low to intermediate pretest likelihood	CCTA	Resource utilisation MACE Radiation dose	The study included only one comparator (CCTA). Therefore, the results should be interpreted with caution.

Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
		of CAD (n=1055)			
Sahinarslan (2013)	Prospective cohort (Turkey)	Patients presenting with stable angina pectoris, who had not previously undergone ICA or CCTA (n=72)	CCTA v ICA	Radiation dose	Although a biological measure of radiation dose damage was analysed this was done immediately after the procedure not allowing the assessment of more relevant outcomes of radiation exposure.
Abbreviations: CAD, coronary artery disease; CCTA, coronary computed tomography angiography; ECHO, stress echocardiography; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value; SPECT, single photon emission computed tomography.					

5.2 Summary of economic evidence

The company conducted a search of the health economics literature on HeartFlow FFR_{CT} and the comparators specified in the decision problem. This identified a total of 174 studies, 24 of which the company included in its analysis (see pages 156–159 of submission).

The EAC critiqued this search, and considered that most of the presented economic studies did not include an appropriate patient population or treatment pathway. Only 1 published study, Rajani et al. (2015), was considered by the EAC to be relevant to the decision problem. The EAC conducted its own review of the literature and did not identify any additional relevant published studies, although it also considered the ongoing PLATFORM study to be relevant to the economic analysis.

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 over 12 months 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 on chest pain of recent onset. A standardised unit cost for each test and procedure was taken from the NHS National Tariff 2013/2014. A decision-tree economic model was used to evaluate the cost of 1000 patients passing through the current treatment pathway compared with the same 1000 patients after incorporating HeartFlow FFR_{CT}. The authors found that introducing FFR_{CT} resulted in cost savings of £200 per patient. The EAC noted that although how the costs were derived in the study is explicit, details of the decision model structure applied are unclear.

The PLATFORM study is an ongoing trial looking at, among other factors, resource use in patients having various diagnostic tests and surgical procedures (see Clinical outcomes in section 5 for details). Preliminary results showed notable savings in average cost per-patient using FFR_{CT}: cohorts 1

and 2 (£3,916 versus £2,584); cohorts 1A and 2A (£1,101 and £1,176); and cohorts 1B and 2B (£5,429 and £3,351).

The EAC conducted a further search for published economic studies in April 2016, which identified 1 new study.

Hlatky et al. (2015) investigated the quality of life and economic outcomes of FFR_{CT} in the PLATFORM study. 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 individual patient. Medicare reimbursement rates (the national average of technical and professional fees in the US) from 2015 were applied as cost weights and online pharmacy costs were used for drugs. Patients were prospectively assigned to either functional imaging (n=287) or CCTA/FFR_{CT} (n=297). Mean costs were $7,343 (£4,993) among the CCTA/FFR_{CT} patients and $10,734 (£7,299) among functional imaging patients ($p<0.0001$). In the non-invasive group, mean costs were not significantly different ($p=0.26$) between the CCTA/FFR_{CT} 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_{CT} patients than in functional imaging patients. In the invasive group, quality of life improvements were similar in both arms.

De novo analysis

The company presented a decision tree model based on integrating HeartFlow FFR_{CT} into the existing diagnostic pathway (see sections 2.3 and 2.4 and pages 237–241 of the submission).

A theoretical population of 1,000 individuals with suspected coronary artery disease were allocated to either the current treatment pathway or the company's revised pathway (including HeartFlow FFR_{CT}). 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.

Model parameters

The patient population was stratified by pre-test likelihood using the cut-offs in the current treatment pathway (see section 2.3). The proportion of patients placed into each category 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 ICA, have an inconclusive CCTA result and have an uncertain SPECT result.

Figures for the sensitivity and specificity of the diagnostic tests were taken from selected papers, and costs were based on hospital resource group tariffs (see table C7, pages 249 and 250 of the submission). These are summarised below.

Table 5 Clinical parameters used in the company's model and EAC revisions

Variable	Base-case value (source)	EAC value if different^ (source)
Sensitivity FFR_{CT}	86% (Nørgaard 2014)	86% **84%** (EAC meta-analysis)
Specificity FFR_{CT}	79% (Nørgaard 2014)	79% **86%** (EAC meta-analysis)
Sensitivity SPECT	76% (Melikian 2010)	73% **59%**+ (EAC meta-analysis) **(+Company meta-analysis)**
Specificity SPECT	38% (Melikian 2010)	67% **76%**+ (EAC meta-analysis) **(+Company meta-analysis)**
Sensitivity CCTA	94% (Meijboom 2008)	95% **85%** (EAC meta-analysis)
Specificity CCTA	48% (Meijboom 2008)	68% **75%** (EAC meta-analysis)
Sensitivity ICA	69% (Meijboom 2008)	64% **55%** (EAC meta-analysis)
Specificity ICA	67% (Meijboom 2008)	83% **90%** (EAC meta-analysis)

Sensitivity MRI		89% **87%** (EAC meta-analysis)
Specificity MRI		91% **98%** (EAC meta-analysis)
Sensitivity ECHO		45% **50%**+ (EAC meta-analysis) **(+Company meta-analysis)**
Specificity ECHO		90% **90%**+ (EAC meta-analysis) **(+Company meta-analysis)**
Disease burden		
10–29% likelihood of disease	18.6% (Rajani 2015)	–
30–60% likelihood of disease	28.4% (Rajani 2015)	–
61–90% likelihood of disease	27.7% (Rajani 2015)	–
Assumed proportions where procedure is inappropriate or test results inconclusive		
Angiography	10%	–
FFR_{CT}	10%	–
CCTA	10%	–
Per vessel figures, and source where different, are shown in **bold** ^ No new diagnostic accuracy data was identified in the recent literature searches to change these parameters		

Costs and resource use

Sources from which the model costs were taken are provided in table C5.2 of the submission (pages 242 and 243). Payment by results 2014/15 hospital resource group codes were used for the comparator diagnostic prices used in their model. The list price of £888 was used for HeartFlow FFR_{CT}.

Table 6 Cost parameters used in company's model and EAC revisions

Variable	Company base-case value (source)	EAC value if different (source)
SPECT	£220 (HRG: RA37Z)	**£367* (RN21Z, myocardial perfusion scan, stress only)**
CCTA	£136 (HRG: RA14Z)	**£122* (RD28Z, complex computerised tomography)**

Calcium Score	£77 (HRG RA08Z)	
FFR_{CT}	£888 (List price)	£700[1]
Angiography	£1,241 (HRG: EA36A)	**£1,685* (EY43A to EY43F, standard cardiac catheterisation, weighted average)**
PCI, weighted estimate based on 25% of patients requiring more than 2 stents	£2,832 - PCI≤ 2 stents = £2,704 (HRG: EA31Z), PCI > 2 stents = £3,216 (HRG: EA49Z)	£2,865, following addition of £33 drug costs for aspirin and clopidogrel (BNF,2015)
ECHO		£74 (HRG: RA60Z) **£271* (EY50Z, Complex echocardiogram)**
MRI		£188 (HRG: RA03Z) **£515* (RA67Z, Cardiac magnetic resonance imaging scan, pre and post)**
*NHS Reference costs 2014-15 [1] This figure was revised before the committee meeting in July 2015 but not used in the company's submission or initial EAC report **Figures in bold and underlined shows figures used in revised model for CG95 update**		

Company's results

The company reported a base-case per-patient cost of £2,239 using the current NICE pathway and £2,080 using the adapted pathway with FFR_{CT}, representing an average saving of £159 per patient.

The company conducted 1-way sensitivity analyses on the sensitivity and specificity of FFR_{CT} and the comparator tests, as well as the costs of FFR_{CT}. The analyses showed that HeartFlow FFR_{CT} continued to be cost saving until its price reached £1,126. With regard to changes in the sensitivity and

specificity of HeartFlow FFR_{CT} and the other diagnostic tests, FFR_{CT} remained cost saving for nearly all the values tested when considered in the context of the entire patient population. However, there were large differences between pre-test likelihood groupings. Whereas FFR_{CT} was cost saving on all sensitivity and specificity values in the 61–90% likelihood of disease group, it incurred costs when the specificity of SPECT and ICA improved from the base case in both the 10–29% and 30–60% pre-test likelihood groups. For certain sensitivity and specificity values within the ranges examined for CCTA, FFR_{CT} was also found to incur costs (see pages 265–268 of the submission).

The company also conducted multiway scenario sensitivity analyses, varying the sensitivity and specificity parameters of SPECT and FFR_{CT}. These provided cost figures for combinations of the base case, and specified best and worse diagnostic accuracy figures for the 2 tests. HeartFlow FFR_{CT} was found to be cost saving in 7 of the 9 scenarios, the exception being when SPECT's diagnostic sensitivity and specificity figures were at their best (sensitivity 91%, specificity 87%) and when HeartFlow FFR_{CT} figures were at their base and their best (see table C12.10 on page 268 of the submission).

EAC's critique of the company's analysis

The EAC considered the company's model to appropriately capture the current pathway, but identified 5 areas of concern. Firstly, it included patients who did not have an intermediate risk of coronary artery disease (those with pre-test likelihoods of disease of less than 10% and over 90%). Secondly, the model only included SPECT when non-invasive functional imaging was indicated in the pathway, and did not consider other non-invasive functional imaging tests also in the current pathway (such as ECHO and MRI). Thirdly, the company did not include any costs for optimal medical therapy. Fourthly, the company did not include drug costs for patients who had PCI. Finally, the company only did a patient-based analysis, when for completeness a per-vessel analysis should also have been done. The EAC also noted a number of

inputted errors in the company's electronic model (see page 134 of the assessment report).

EAC revisions to the company's model June 2015

Clinical parameters

The EAC reviewed the company's clinical parameters and made a number of changes (see tables 13.1 and 13.2 on pages 135 and 136 of the assessment report) These changes are summarised above in table 5.

Costs

The EAC reviewed the costs used in the company's model. Based on hospital resource group codes, it introduced revised costs of £74 for ECHO and £188 for MRI. Expert opinion was consulted to derive an annual cost for optical medical therapy of £84. This figure was based on the annual cost of administering aspirin, simvastatin, glyceryl trinitrate and propranolol hydrochloride using 2015 British national formulary prices. The EAC noted that patients having PCI need medication, and that this cost should have been included with the PCI tariff. It added £33 to the PCI tariff to reflect the annual cost of aspirin and clopidogrel (BNF, 2015), increasing the cost of PCI in the EAC's revised model to £2,865.

Results from the EAC's revisions to the model

The EAC's base-case analysis found a standard pathway cost of £2,211 per patient (£1,868 per vessel) and an adapted pathway cost (that is, with HeartFlow FFR_{CT}) of £2,044 per patient (£1,717 per vessel). This represents a cost saving of £167 per patient and £151 per vessel.

These figures were based on the company's scenario in which SPECT was used wherever functional imaging was indicated in the clinical pathway. The EAC explored 2 other scenarios in which MRI and ECHO were used where functional imaging was indicated in the clinical pathway. For MRI, the standard pathway cost was £2,174 per patient (£1,946 per vessel) and the

adapted pathway cost was £2,034 per patient (£1,717 per vessel), representing a cost saving of £140 per patient and £229 per vessel. For ECHO, the standard pathway cost was £1,708 per patient (£1,623 per vessel) and the adapted pathway cost was £1,993 per patient (£1,690 per vessel), representing a cost increase of £285 per patient and £67 per vessel.

The EAC ran sensitivity analyses on a number of parameters and found that with the exception of the price of FFR_{CT}, none of the parameters altered the cost conclusion. These are presented in a series of tables in the assessment report on pages 138 and 139 for per-vessel results and pages 152–163 for per-patient results. The EAC's patient-based sensitivity analysis found that HeartFlow FFT_{CT} was cost neutral at £1,193 in the SPECT model, £1,144 in the MRI model and £367 in the ECHO model. On a per-vessel basis, HeartFlow FFT_{CT} was cost neutral at £1,203 in the SPECT model, £1,365 in the MRI model and £748 in the ECHO model. Above these per-patient values, FFR_{CT} is cost incurring; below them, cost saving. These results relate to average savings when considered in the context of the whole treatment pathway for all patients. When analysed by likelihood of disease, in all scenarios HeartFlow FFR_{CT} is cost saving in patients with a 61–90% pre-test likelihood but cost incurring in patients with 10–29% and 30–60% pre-test likelihoods.

Additional results including price reduction

Following the completion of the assessment report, the company submitted a lower list price for HeartFlow FFR_{CT} of £700. The EAC re-ran its base-case analysis with this new figure. The full results are reported in appendix D, and show that FFR_{CT} is cost incurring on a per-patient basis, but is cost saving compared with ECHO on a per-vessel basis.

Error in the June 2015 EAC revisions to the company model

An error was identified in the EAC revisions to the company's model which meant that some patients who did not have an intermediate pre-test likelihood of coronary artery disease were wrongly included in the model. This meant

that the costs of the NICE treatment pathway were overestimated. As a result, the cost savings presented to the committee were inaccurate. These were corrected for the per-patient analyses as shown in table 7 (see table 10 for the original, uncorrected figures).

Table 7: Per-patient cost savings following correction of EAC error

	Average total cost per patient (patient based)		
	SPECT model	**MRI model**	**ECHO model**
NICE pathway	£1,989	£1,934	£1,521
Adapted pathway (using HeartFlow FFR_{CT})	£1,941	£1,931	£1,890
Difference	£48	£3	−£369

EAC revisions in response to updated draft recommendations

The EAC re-ran its analyses after making revisions in response to the draft recommendations for updated clinical guideline on chest pain (CG95). No changes were made to the clinical parameters, so these remained as in table 5, but only per-patient figures were examined. The EAC updated its costs in line with those used in the draft updated guideline, which uses the most recent NHS reference costs as shown in table 6. The only exception was the cost of cardiac MRI, which was taken from the Payment by Results tariff, because the chest pain guideline committee judged this to be more representative of its true cost. The company's revised cost of the technology, £700, was also used in the EAC's updated model.

Having made the changes to the model, the EAC found a base-case cost saving of £214 per patient for HeartFlow FFR_{CT} compared with all functional imaging tests (table 8).

Table 8: Per patient level comparison with EAC's revisions

	Average total cost per patient (patient-based)

	SPECT model	MRI model	ECHO model
NICE pathway based on CG95 update	£1,321	£1,301	£1,259
Adapted pathway based on CG95 update including use of HeartFlow FFR_{CT}	£1,107	£1,087	£1,045
Difference	−£214	−£214	−£214

The EAC ran a number of sensitivity analyses, varying the price of the technology, the diagnostic accuracy of the functional imaging tests, HeartFlow FFR_{CT}, ICA and CCTA, as well as on the proportion of uncertain CCTA and functional imaging tests. It used estimates of diagnostic accuracy for CCTA and ICA as used in the revised chest pain guideline. In all instances, HeartFlow FFR_{CT} remained cost saving.

6 Ongoing research

The company identified 1 ongoing study, PLATFORM (Clinicaltrials.gov identifier: NCT01943903). This trial has reported 90-day end points for both clinical and economic outcomes, which are reported in the company's submission, external assessment centre (EAC) report and this document as academic-in-confidence information. The company will provide further information from the trial as it becomes available, again on an academic-in-confidence basis. It expects initial results to be submitted for presentation at the European Society of Cardiology Scientific Sessions in August 2015. The results of this trial are now published and are presented in the additional evidence section.

The EAC identified another ongoing study, the EMERALD trial (Clinicaltrials.gov identifier: NCT02374775). This is an international, multicentre study aiming to explore plaque rupture in patients with acute myocardial infarction using coronary computed tomography angiography

(CCTA) and computational fluid dynamics. The population includes patients who presented with acute myocardial infarction and definite evidence of plaque rupture and who had CCTA between 1 month and 2 years before the event (retrospectively searched). The estimated study completion date is September 2015. Although the study involves HeartFlow FFR_{CT}, it is a secondary measure and one of many fluid dynamic parameters investigated. Furthermore, the study is retrospective and explorative in nature. For these reasons the EAC considered that it is unlikely to have an effect on the decision problem.

The EAC identified further ongoing studies during their evidence searches in May 2016, the details of which are presented in the table below.

Trial name	NCT number	Number of patients	Study Objectives
CREDENCE	NCT02173275	618	Direct head-to-head comparison of coronary CTA plus FFR_{CT} versus myocardial perfusion imaging by SPECT or PET
DECIDE-Gold	NCT02178904	156	Comparison of FFR_{CT} versus dual-energy CT rest/stress perfusion imaging
CONSERVE	NCT01810198	1500	Evaluation of FFR_{CT} as a 'gatekeeper' to invasive coronary angiography (secondary aim)
ADVANCE	NCT02499679	ND	Prospective longitudinal registry to evaluate prognostic implications of FFR_{CT}

7 Issues for consideration by the committee

7.1 Clinical evidence

Limited published evidence in an intermediate pre-test likelihood population

The external assessment centre (EAC) considered that only 1 study provided relevant information on the diagnostic accuracy of HeartFlow $FFR_{CT,}$ a peer-reviewed publication by Nørgaard et al. (2014). For clinical outcomes the EAC

was only able to identify 2 unpublished studies, PLATFORM and Radiation FFRCT. The EAC considered that Radiation FFRCT was of limited relevance to the decision problem given the lack of detail on methodology, so ultimately found only 2 studies that provided usable information on the accuracy and efficacy of HeartFlow FFR_{CT}.

Complexity of the treatment pathway

HeartFlow FFR_{CT} was considered in all patients with an intermediate pre-test likelihood (10–90%) of coronary artery disease, and in the context of its potentially disruptive role in the current treatment pathway (specified in the NICE guideline on chest pain of early onset). However, both expert opinion and the scope recognise that there is local variation in the treatment pathway. For this reason, the modelled pathway may not be representative of all local treatment pathways and so adopting HeartFlow FFR_{CT} may incur additional costs (such as having to purchase a 64-slice CT scanner).

Meta-analysis results

The EAC noted that caution should be used when interpreting the results of its meta-analyses, mainly because no adjustments for made for confounding variables. It also noted that some of the included studies did not measure invasive FFR in all the vessels, irrespective of degree of coronary stenosis, and as a result it is possible that the sensitivity and specificity values reported in the primary studies, especially at the vessel level, could have been affected. With respect to vessel-based meta-analyses, the EAC highlighted an additional area of concern regarding the inclusion of several vessels per patient. This contravenes the principle of statistical independence of observations, meaning the confidence intervals for the pooled estimates are likely to be too conservative.

7.2 Cost evidence

Per-patient or per-vessel results

The company evaluated the cost case for HeartFlow FFR_{CT} based on per-patient only diagnostic results for FFR_{CT} and comparator diagnostic tests. The EAC conducted its own evaluation based on both per-patient and per-vessel diagnostic accuracy. The choice of patient- or vessel-level analysis has a direct effect on the cost case for HeartFlow FFR_{CT}

Economic case by pre-test likelihood grouping

Although HeartFlow FFR_{CT} was found to be cost saving in patients with an intermediate likelihood of disease, these results are driven by large savings in patients with a 61–90% pre-test likelihood (for which HeartFlow FFR_{CT} is cost saving throughout). In the other 2 pre-test likelihood groupings (10–29% and 30–60%), HeartFlow FFR_{CT} was found to be cost incurring in the base-case and sensitivity analyses.

Choice of functional imaging test

In its economic model, the company included diagnostic accuracy and cost parameters for SPECT where functional imaging was indicated in the treatment pathway. This resulted in cost savings with HeartFlow FFR_{CT} but neglected other functional imaging tests. The EAC conducted additional economic modelling with MRI and ECHO in the treatment pathway where functional imaging was indicated. Although HeartFlow FFR_{CT} remained cost saving when MRI was used, it was cost incurring when ECHO was substituted in place of SPECT. Following a revision of its list price (see appendix D), HeartFlow FFR_{CT} became cost saving based on a per-vessel basis but remained cost incurring on a per-patient basis.

Update to the economic model and results

The model has been updated to incorporate the draft changes to the recommendations of the chest pain guideline. These result in greater cost saving for HeartFlow FFR_{CT}, and the same cost savings regardless of which

functional imaging test is used. This has eliminated the previous uncertainty concerning the cost case for HeartFlow $FFR_{CT.}$

8 Authors

Neil Hewitt, technical analyst

Bernice Dillon, technical adviser

Paul Dimmock, technical analyst (evaluations)

NICE medical technologies evaluation programme

June 2016

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

A Details of assessment report:

- Chalikidou A, Kartha M, Reed F et al. HeartFlow FFRct for the computation of fractional flow reserve from coronary CT angiography (May 2015)
- Chalikidou A, Herz N, Kartha M et al. HeartFlow FFRct 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)

B Submissions from the following sponsors:

- HeartFlow

C Related NICE guidance

- Bioresorbable stent implantation for treating coronary artery disease. NICE interventional procedures guidance 492, May 2014
- Services for the prevention of cardiovascular disease. NICE commissioning guide 45, May 2012
- New generation cardiac CT scanners (Aquilion ONE, Brilliance iCT, Discovery CT750 HD and Somatom Definition Flash) for cardiac imaging in people with suspected or known coronary artery disease in whom imaging is difficult with earlier generation CT scanners. NICE diagnostics guidance 3, January 2012
- Management of stable angina. NICE clinical guideline 126, July 2011
- Percutaneous laser coronary angioplasty. NICE interventional procedures guidance IPG378, January 2011. Available from: http://www.nice.org.uk/guidance/IPG378
- Off-pump coronary artery bypass grafting. NICE interventional procedures guidance, IPG377, January 2011. Available from: http://www.nice.org.uk/guidance/IPG377

- SeQuent Please balloon catheter for in-stent coronary restenosis. NICE medical technologies guidance, MTG1, December 2010. Available from: http://www.nice.org.uk/guidance/MTG1
- Prevention of cardiovascular disease. NICE guidelines, PH25, June 2010. Available from: http://www.nice.org.uk/guidance/PH25
- Chest pain of recent onset: Assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. NICE guidelines, CG95, March 2010. Available from: http://www.nice.org.uk/guidance/CG95
- Drug-eluting stents for the treatment of coronary artery disease. NICE technology appraisals, TA152, July 2008. Available from: http://www.nice.org.uk/guidance/TA152
- Totally endoscopic robotically assisted coronary artery bypass grafting. NICE interventional procedures guidance, IPG128, June 2005. Available from: http://www.nice.org.uk/guidance/IPG128
- Myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction. NICE technology appraisals, TA73, November 2003. Available from: http://www.nice.org.uk/guidance/TA73
- Guidance on the use of coronary artery stents. NICE technology appraisals, TA71, October 2003. Available from: http://www.nice.org.uk/guidance/TA71

D References

Bernhardt, P., T. Walcher, W. Rottbauer, et al. (2012). "Quantification of myocardial perfusion reserve at 1.5 and 3.0 tesla: A comparison to fractional flow reserve." International Journal of Cardiovascular Imaging 28(8): 2049-56.

BNF (2015). British National Forumulary, NICE: evidence services.

Cheezum, M. K., E. A. Hulten, A. J. Taylor, et al. (2011). "Cardiac CT angiography compared with myocardial perfusion stress testing on downstream resource utilization." Journal of Cardiovascular Computed Tomography 5(2): 101-09.

Chen, L., X. Wang, J. Bao, et al. (2014). "Direct comparison of cardiovascular magnetic resonance and single-photon emission computed tomography for detection of coronary artery disease: a meta-analysis." PLoS One 9(2): e88402.

Danad, I., P. G. Raijmakers, Y. E. Appelman, et al. (2013). "Hybrid imaging using quantitative H215O PET and CT-based coronary angiography for the detection of coronary artery disease." Journal of Nuclear Medicine 54(1): 55-63.

Diamond, G. A. and J. S. Forrester (1979). "Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease." New England Journal of Medicine 300(24): 1350-58.

Douglas, P. S., U. Hoffmann, M. R. Patel, et al. (2015a). "Outcomes of Anatomical versus Functional Testing for Coronary Artery Disease." New England Journal of Medicine 372(14): 1291-300.

Douglas, P. S., G. Pontone, M. A. Hlatky, et al. (2015b). "Clinical outcomes of fractional flow reserve by computed tomographic angiography-guided diagnostic strategies vs. usual care in patients with suspected coronary artery disease: the prospective longitudinal trial of FFR(CT): outcome and resource impacts study." Eur Heart J 36(47): 3359–67.

Douglas, P.S, De Bruyne B., Pontone G, et al. (2016). "One-Year Outcomes of FFRCT-Guided Care in Patients With Suspected Coronary Disease: PLATFORM Study." JACC (In Press).

Gaur, S., H. G. Bezerra, J. F. Lassen, et al. (2014). "Fractional flow reserve derived from coronary CT angiography: Variation of repeated analyses." Journal of Cardiovascular Computed Tomography 8(4): 307-14.

Hachamovitch, R., B. Nutter, M. A. Hlatky, et al. (2012). "Patient management after noninvasive cardiac imaging results from SPARC (Study of myocardial

perfusion and coronary anatomy imaging roles in coronary artery disease)." J Am Coll Cardiol 59(5): 462-74.

Hlatky, M. A., B. De Bruyne, G. Pontone, et al. (2015). "Quality-of-Life and Economic Outcomes of Assessing Fractional Flow Reserve With Computed Tomography Angiography: PLATFORM." J Am Coll Cardiol 66(21): 2315-23.

Kajander, S., E. Joutsiniemi, M. Saraste, et al. (2010). "Cardiac positron emission tomography/computed tomography imaging accurately detects anatomically and functionally significant coronary artery disease." Circulation 122(6): 603-13.

Koo, B. K., A. Erglis, J. H. Doh, et al. (2011). "Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms: Results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study." Journal of the American College of Cardiology 58(19): 1989-97.

Lu M, F. M., Roberts R, Ivanov A, Adami E, et al (2015). Noninvasive Fractional Flow Reserve Derived from Coronary CT Angiography (FFRCT) in the PROMISE Trial: Revascularization, Events and Efficiency of Referral to Invasive Coronary Angiography. Conference: Unknown, Conference location: Unknown.

Meijboom, W. B., C. A. Van Mieghem, N. van Pelt, et al. (2008). "Comprehensive assessment of coronary artery stenoses: computed tomography coronary angiography versus conventional coronary angiography and correlation with fractional flow reserve in patients with stable angina." Journal of the American College of Cardiology 52(8): 636-43.

Melikian, N., P. De Bondt, P. Tonino, et al. (2010). "Fractional flow reserve and myocardial perfusion imaging in patients with angiographic multivessel coronary artery disease." JACC: Cardiovascular Interventions 3(3): 307-14.

Mouden, M., J. P. Ottervanger, S. Knollema, et al. (2014). "Myocardial perfusion imaging with a cadmium zinc telluride-based gamma camera versus invasive fractional flow reserve." Eur J Nucl Med Mol Imaging 41(5): 956-62.

Mouden, M., J. P. Ottervanger, J. R. Timmer, et al. (2014). "Myocardial perfusion imaging in stable symptomatic patients with extensive coronary atherosclerosis." European Journal of Nuclear Medicine & Molecular Imaging 41(1): 136-43.

Neglia, D., D. Rovai, C. Caselli, et al. (2015). "Detection of significant coronary artery disease by noninvasive anatomical and functional imaging." Circulation. Cardiovascular imaging 8(3).

Norgaard, B. L., J. Leipsic, S. Gaur, et al. (2014). "Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps)." Journal of the American College of Cardiology 63(12): 1145-55.

Norgaard, B. L., J. Hjort, S. Gaur, et al. (2016). "Clinical Use of Coronary CTA-Derived FFR for Decision-Making in Stable CAD." Jacc: Cardiovascular Imaging. doi: 10.1016/j.jcmg.2015.11.025. [Epub ahead of print]

Ovrehus, K. A., H. E. Botker, J. M. Jensen, et al. (2011). "Influence of coronary computed tomographic angiography on patient treatment and prognosis in patients with suspected stable angina pectoris." American Journal of Cardiology 107(10): 1473-79.

Ponte, M., N. Bettencourt, E. Pereira, et al. (2014). "Anatomical versus functional assessment of coronary artery disease: direct comparison of computed tomography coronary angiography and magnetic resonance myocardial perfusion imaging in patients with intermediate pre-test probability." The International Journal of Cardiovascular Imaging 30(8): 1589-97.

Rajani, R., J. Webb, A. Marciniak, et al. (2015). "Comparative efficacy testing - Fractional flow reserve by coronary computed tomography for the evaluation of patients with stable chest pain." Int J Cardiol 183: 173-7.

Sahinarslan, A., G. Erbas, S. A. Kocaman, et al. (2013). "Comparison of radiation-induced damage between CT angiography and conventional coronary angiography." Acta Cardiologica 68(3): 291-7.

The SCOT-HEART investigators. (2015). CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. [Erratum appears in Lancet. 2015 Jun 13;385(9985):2354; PMID: 26088642]." Lancet 385(9985): 2383-91.

Stuijfzand, W. J., I. Danad, P. G. Raijmakers, et al. (2014). "Additional value of transluminal attenuation gradient in CT angiography to predict hemodynamic significance of coronary artery stenosis." JACC: Cardiovascular Imaging 7(4): 374-86.

Tanaka, K., H. G. Bezerra, S. Gaur, et al. (2016). "Comparison Between Non-invasive (Coronary Computed Tomography Angiography Derived) and Invasive-Fractional Flow Reserve in Patients with Serial Stenoses Within One Coronary Artery: A NXT Trial substudy." Ann Biomed Eng 44(2): 580-9.

Thompson, A. G., R. Raju, P. Blanke, et al. (2015). "Diagnostic accuracy and discrimination of ischemia by fractional flow reserve CT using a clinical use rule: Results from the Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography study." Journal of cardiovascular computed tomography 9(2): 120-28.

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.

Professor Keith Oldroyd
Consultant Interventional Cardiologist and Director of Research, British Cardiovascular Intervention Society

Professor Andreas Baumbach
Expert Cardiology Consultant and interventional cardiology specialist, British Cardiovascular Intervention Society

Dr Ian Purcell
Consultant cardiologist, British Cardiovascular Intervention Society

Professor Nick Curzen
Consultant cardiologist, British Cardiovascular Intervention Society

Dr Rob Henderson
Consultant cardiologist, British Cardiovascular Society

Dr Ronak Rojani
Consultant cardiologist, British Cardiovascular Society

Dr Francesca Pugliese
Consultant radiologist, British Cardiovascular Society

- Four of the expert advisers have had direct involvement with the technology. One in particular managed patients for whom it was used in another part of their care pathway.
- All 3 experts who had not had direct experience with the technology indicated that they would like to use the technology. One of these

suggested that this should be in a research setting because the current evidence does not support its routine use.

- Five experts considered HeartFlow FFR_{CT} to be a significant modification of an existing technology, and 2 thoughts it to be a thoroughly novel technology.
- Six of the experts felt that the appropriate use of the technology was in the diagnosis or rule out of coronary artery disease in those with chest pain, coronary artery disease risk factors, or to determine the significance of their condition in those with existing disease. One was of the opinion that it had the potential to identify patients who might benefit from invasive coronary angiography but was unclear how it could be incorporated more widely to investigate chest pain of suspected cardiac origin.
- A number of comparators from across the treatment pathway were suggested.
- Four of the experts felt that there were no competing products. One mentioned that there are a number of technologies being developed to derive fractionated flow rate (FFR) from invasive coronary angiography, including one by MEDIS which is ready to launch. One referred to invasive FFR in this section. The remaining expert was aware that simplified algorithms are in development with some CT scanner companies.
- Fewer invasive procedures and a more comprehensive, accurate and quicker diagnosis were mentioned as possible benefits for patients. Access to facilities that perform high quality coronary computed tomography angiograph (CCTA) was identified as a likely obstacle to the realisation of these benefits by 3 experts. One expert identified a number of conditions which currently exclude patients from CCTA and would therefore exclude them from this technology (such as BMI>35 or atrial fibrillation).
- There were a range of responses on the possible benefits to the healthcare system, which were similar in theme to the responses for possible patient benefits (namely reductions in invasive procedures, lower waiting times, and a more rapid diagnosis).

- Five experts were of the opinion that CCTA or high quality CT imaging would be needed, suggesting that the CCTA facilities, or facilities of sufficient quality, are missing from a number of locations in the county. One expert was of the opinion that no additional facilities or infrastructure would be needed in centres currently with cardiac CT scanner facilities.
- In terms of general advice, 1 expert felt that clinicians may be unwilling to accept that it is possible to measure FFR from mathematical modelling of a static CT image. Another raised concerns about funding and potential financial issues resulting from trusts not carrying out ICAs. Validation of results was also a concern raised specifically for patients with high calcium scores. Four of the experts felt that NICE guidance would be useful. Two expressed concerns around it possibly being too early for guidance, specifically since the evidence is limited to a few manufacturer-funded trials.

Appendix C: Comments from patient organisations

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

- Action Heart
- British Cardiac Patients Association (BCPA)
- British Heart Foundation (BHF)
- Cardiovascular Care Partnership (UK)
- Pumping Marvellous
- South Asian Health Foundation
- The Coronary Artery Disease research Association
- UK Health Forum (formerly National Heart Forum)

Appendix D: Additional analyses carried out by the external assessment centre

The company approached NICE following the submission of the assessment report and indicated that it wished to lower the list price of the technology to £700. NICE asked the external assessment centre (EAC) to re-run its analyses to determine the effect this may have.

Results: base case (vessel-based)

The EAC estimated 3 separate models, considering SPECT, MRI and ECHO as first-line interventions in the current pathway. On a per-vessel basis, the results show that HeartFlow FFR_{CT} is cost saving when SPECT (£241), MRI (£319) or ECHO (£23) is the functional imaging test used.

Table 9: Base-case results (vessel-based)

	Average total cost per patient		
	SPECT model	**MRI model**	**ECHO model**
NICE pathway	£1,868	£1,946	£1,623
Adapted pathway (using HeartFlow FFR_{CT})	£1,627	£1,627	£1,600
Difference	−£241	−£319	−£23

Results: base case (patient-based)

As with the vessel-based approach, the EAC estimated 3 separate models, considering SPECT, MRI and ECHO as first-line interventions in the current pathway. On a per-patient basis, the results show that HeartFlow FFR_{CT} is cost saving when SPECT (£270) or MRI (£243) is the functional imaging test used. Unlike the vessel-based results, the cost saving is not higher for MRI compared with SPECT. However, HeartFlow FFR_{CT} is not cost saving if ECHO is used as the functional imaging test.

Table 10: Base-case results (patient based)

	Average total cost per patient		
	SPECT model	**MRI model**	**ECHO model**
NICE pathway	£2,211	£2,174	£1,708
Adapted pathway (using HeartFlow FFR_{CT})	£1,941	£1,931	£1,890
Difference	−£270	−£243	+£182
Note that these figures do not correct for the error identified in the EAC's initial revisions to the model (see table 7)			