

# HeartFlow FFRct for the computation of fractional flow reserve from coronary CT angiography

**Produced by:** King's Technology Evaluation Centre (KiTEC)

**Authors:** Anastasia Chalkidou, Senior Health Technology Assessor, KiTEC  
Muralikrishnan Radhakrishnan Kartha, Senior Health Economist, KiTEC  
Fiona Reid, Research Fellow in Medical Statistics, KiTEC  
Naomi Herz, Health Technology Assessor and Health Economist, KiTEC  
Kate Goddard, Health Technology Assessor, KiTEC  
Viktoria McMillan, Centre Manager, KiTEC  
Stephen Keevil, Co-director, KiTEC  
Cornelius Lewis, Co-director, KiTEC

**Correspondence to:** Viktoria McMillan – [viktoria.mcmillan@kcl.ac.uk](mailto:viktoria.mcmillan@kcl.ac.uk)

**Date completed:** 20/05/2015

## Declared interests of the authors

None

## Acknowledgements

Names, titles and organisational affiliations (for example, main employer) of individuals who provided advice.

## Rider on responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

# Contents

The table of contents can be updated using the Reference tab in Microsoft Word

1	Summary .....	5
1.1	Scope of the sponsor's submission .....	5
1.2	Summary of clinical evidence submitted by the sponsor .....	5
1.3	Summary critique of clinical evidence submitted by the sponsor .....	6
1.4	Summary of economic evidence submitted by the sponsor .....	6
1.5	Summary critique of economic evidence submitted by the sponsor ...	7
1.6	External Assessment Centre commentary on the robustness of evidence submitted by the sponsor .....	7
1.7	Summary of any additional work carried out by the External Assessment Centre .....	8
2	Background.....	9
2.1	Overview and critique of sponsor's description of clinical context.....	9
2.1.1.	Critique of sponsor's description of background condition.....	9
2.1.2.	EAC's overview of the condition and technology .....	9
2.1.3.	Overview of relevant clinical guidelines .....	14
2.1.4.	Critique of the sponsor's description of the clinical context .....	16
2.1.5.	Issues relating to current practice.....	17
2.1.6.	Potential changes to the pathway introduced by FFR <sub>CT</sub> .....	18
2.2	Overview of sponsor's description of ongoing studies .....	20
2.3	Critique of sponsor's definition of the decision problem .....	21
3	Clinical evidence.....	26
3.1	Critique of the sponsor's search strategy.....	26
3.2	Critique of the sponsor's study selection .....	27
3.3	Included and excluded studies.....	30
3.4	Overview of methodologies of all included studies .....	32
3.5	Overview and critique of the sponsor's critical appraisal .....	34
3.6	Results.....	36
3.7	Description of the adverse events reported by the sponsor .....	37
3.8	Description and critique of evidence synthesis and meta-analysis carried out by the sponsor.....	37
3.9	Additional work carried out by the External Assessment Centre in relation to clinical evidence .....	39
3.10	Conclusions on the clinical evidence .....	112
4	Economic evidence.....	115
4.1	Published economic evidence .....	115
4.2	De novo cost analysis .....	119
4.3	Results of de novo cost analysis.....	131
4.4	Interpretation of economic evidence .....	132
4.5	Additional work undertaken by the External Assessment Centre in relation to economic evidence.....	132
4.6	Conclusions on the economic evidence.....	163
5	Conclusions .....	163
6	Implications for research.....	165
	References .....	166
	Appendix.....	174

## Abbreviations

Term	Definition
AUC	Area under the curve of receiver operating characteristic
BMI	Body Mass Index
CAD	Coronary artery disease
CABG	Coronary Artery Bypass Grafting
CCTA	Coronary CT angiography
CT	Computed tomography
CI	Confidence interval
DA	Diagnostic accuracy
DOR	Diagnostic odds ratio
DTU	Downstream Test Utilization
ECHO	Stress echocardiography
FFR	Fractional flow reserve
FFR <sub>CT</sub>	Fractional flow reserve derived from CT
FN	False Negatives
FP	False Positives
ICA	Invasive Coronary Angiography
IV	Intravenous
LAD	Left Anterior Descending Artery
LCX	Left Circumflex Artery
MACE	Major Adverse Cardiovascular Events
MI	Myocardial infarction
MRI	Magnetic resonance imaging
mSv	milliSievert
NIT	Noninvasive Testing
NLR	Negative likelihood ratio
NPV	Negative predictive value
NS	Non-significant
OMT	Optimal Medical Therapy
PCI	Percutaneous Coronary Intervention
PLR	Positive likelihood ratio
PPV	Positive predictive value
QOL	Quality of Life
RCA	Right Coronary Artery
RCT	Randomised controlled trial
SD	Standard deviation
SN	Sensitivity
SP	Specificity

SPECT	Myocardial perfusion scintigraphy
T	Tesla
TN	True Negatives
TP	True Positives
QCA	Quantitative Coronary Angiography
QOL	Quality of life
QUADAS 2	Revised Quality Assessment of Diagnostic Accuracy Studies
UDF	Updated Diamond Forrester Score

# 1 Summary

## 1.1 *Scope of the sponsor's submission*

This report assesses the submission to NICE by the manufacturer (HeartFlow) supporting the use of HeartFlow FFR<sub>CT</sub> for the diagnosis of people with an intermediate pre-test likelihood of CAD.

The sponsor submitted clinical and economic evidence related to FFR<sub>CT</sub> and all the comparators listed in the scope. The sponsor submitted some of the available evidence relating to FFR<sub>CT</sub> and its comparators. However, the sponsor mainly included studies with a mixed population of patients with both intermediate and high pre-test likelihood of CAD, which fell outside the scope. The EAC identified several additional papers from their systematic review, which had, in the majority, been identified and excluded by the sponsor. The reason cited for excluding these studies was the requirement to provide measurements of more than 75% of vessels included in the analysis, independent of the degree of stenosis. However, in clinical practice not all vessels are measured with FFR and a pre-specified cut-off for the degree of stenosis based on visual CCTA or ICA is often applied before proceeding with FFR measurements. As a result the EAC did not consider this criterion to be representative of clinical practice and decided to include these papers.

The cost analysis submitted by the sponsor assessed the impact of the FFR<sub>CT</sub> and its comparators in the patient population as specified by the scope, however, the EAC identified issues related to the model structure and specific assumptions used in the model.

## 1.2 *Summary of clinical evidence submitted by the sponsor*

The EAC reviewed all of the sponsor-submitted evidence, including the sponsor-excluded studies. Clinical evidence was provided on the intended intervention and all scope-specified comparators. The sponsor provided diagnostic accuracy evidence drawn from 5 meta-analyses and 23 primary studies. All the meta-analyses were excluded by the EAC as they included mixed patient cohorts. Of the 23 sponsor-included primary studies, 20 were excluded by the EAC as their patient cohorts did not meet the scope and/or they included overlapping patient populations.

The sponsor provided clinical outcome evidence based on 20 publications, 2 meta-analyses and 18 primary studies (the majority published in full text). The 2 meta-analyses were excluded by the EAC as they included mixed patient cohorts. Of the 18 sponsor-included primary studies, 14 were excluded by the EAC as their patient cohorts fell outside the scope outlined by NICE. Two

unpublished and 2 published studies met the scope and were accepted by the EAC.

### **1.3 Summary critique of clinical evidence submitted by the sponsor**

The sponsor included some of the relevant evidence on FFR<sub>CT</sub> and its comparators. Their interpretation of the available clinical evidence was reasonable and provided a fair assessment of the studies submitted. Of the 48 (diagnostic accuracy and clinical outcomes) studies provided by the sponsor, all fitted the required scope in terms of comparators and outcome measures. The majority of these publications (mainly full text) provided sufficient study details, such as baseline characteristics of patients and study design. However, many of these studies included mixed patient populations (intermediate and high pre-test likelihood of CAD); as a result the EAC subsequently rejected many of the sponsor-included studies.

The EAC conducted its own systematic review to ensure that all available evidence had been considered. In doing so, 4 additional studies on diagnostic accuracy and 6 on clinical outcomes were identified as including only intermediate pre-test likelihood patient populations and, consequently, as fitting the scope. The EAC also performed its own meta-analysis to provide pooled estimates for sensitivity and specificity of FFR<sub>CT</sub> and its comparators. The results of the meta-analysis also contributed to the revised economic model.

### **1.4 Summary of economic evidence submitted by the sponsor**

The sponsor submitted the results of a search strategy combining terms related to the population (obstructive, stable, or suspected CAD), the intervention (non-invasive FFR) or the comparator (CCTA, ICA, myocardial perfusion scintigraphy, magnetic resonance perfusion imaging, MPS, SPECT, stress perfusion, stress myocardial perfusion, or ECHO) with economics terms. The sponsor included 24 studies in their final review.

The sponsor submitted a decision tree model based on the NICE guideline on the stable chest pain pathway (CG95). It is proposed that HeartFlow's non-invasive FFR<sub>CT</sub> technology be used in conjunction with CCTA in place of the following: "CT coronary angiography" in the pathway for Likelihood of Disease 10% to 29%; "Appropriate functional imaging test" in the pathway for Likelihood of Disease 30% to 60%; and "Invasive coronary angiography" in the pathway for Likelihood of Disease 61% to 90%. A cost saving of £159 per patient for the adapted NICE guideline using FFR<sub>CT</sub> (£2,080) compared to the current NICE guideline (£2,239) is reported.

### **1.5 Summary critique of economic evidence submitted by the sponsor**

Out of the 24 studies included by the sponsor, only one published study (Rajani et al. 2015) incorporated the appropriate patient population, with pre-test likelihood categories as indicated by NICE guidelines. One unpublished study, the PLATFORM study, did not include patients with a pre-test likelihood ratio of 10-20% or 80-90%, and the model structure used was unclear. Revising the search strategy, the EAC did not find any studies in addition to Rajani et al. (2015) which included economic evidence related to the technology and relevant to the population.

The EAC concluded that the de novo cost model structure captured the guideline in an appropriate manner for this evaluation. However, the submitted model also included the population with pre-test likelihood of <10% and >90%, which need to be excluded to estimate the cost-savings. In the cost model, the sponsor has used SPECT as the preferred method of functional imaging. Other functional imaging techniques (such as stress echocardiography or MR techniques) are also used in the UK and their cost impact also needs to be estimated.

Most of the clinical parameters (patient based) used in the model are based on individual studies, instead of estimates from the meta-analysis submitted by the sponsor. Further, the EAC felt that vessel-based estimates are preferred over per-patient estimates for this technology and comparators. Cost estimates were derived from payment by results tariffs and are considered reasonable by the EAC. However, an appropriate cost for optimal medical therapy has not been included in the model. Given these issues, the EAC considered it necessary to revise the cost model by excluding the <10% and >90% populations, using vessel based estimates from the EAC's meta-analysis separately for SPECT and other functional imaging techniques and including a cost for optimal medical therapy, before any cost saving conclusion could be drawn.

### **1.6 External Assessment Centre commentary on the robustness of evidence submitted by the sponsor**

All of the clinical evidence provided on the diagnostic accuracy of FFR<sub>CT</sub> and its comparators was based on published full text evidence. The submitted evidence included a mixture of study designs: retrospective/prospective, cross-sectional, observational and meta-analysis. In addition, many of the studies contained mixed patient cohorts, therefore, the results could not be synthesised for the majority of the submitted evidence. All the submitted

evidence compared the intervention to at least one of the comparators outlined in the scope, however, none of the studies compared the intervention to all the listed comparators.

With the exception of 2 unpublished studies (provided by the sponsor) and 2 studies published as abstracts, the majority of the clinical evidence provided on the clinical outcomes of FFR<sub>CT</sub> and its comparators was based on published full text evidence. The submitted evidence included a mixture of study designs: retrospective/prospective, cross-sectional, observational, RCTs and meta-analysis. All the submitted evidence used at least one of the comparators, however, none of the studies compared the intervention and all the comparators. As a result, the evidence submitted by the sponsor was not robust enough to assess comparative effectiveness and efficacy between the intervention and the comparators.

### ***1.7 Summary of any additional work carried out by the External Assessment Centre***

The EAC conducted a systematic review of the clinical evidence, identifying 1113 publications for the diagnostic accuracy and 3073 publications for the clinical outcomes. The review included key words relevant to the population, intervention, comparators and outcomes as specified in the scope. In addition, the EAC reviewed all the studies excluded by the sponsor and all the studies included in the meta-analyses submitted by the sponsor.

The diagnostic accuracy search resulted in the selection of 7 studies (Kajander et al. 2010, Bernhardt et al. 2012, Danad et al. 2013, Mouden et al. 2014, Norgaard et al. 2014, Ponte et al. 2014, Stuijtzand et al. 2014, Neglia et al. 2015) of which 3 were included in the sponsor's submission (Bernhardt et al. 2012, Norgaard et al. 2014, Stuijtzand et al. 2014), and 2 had been excluded by the sponsor (Mouden et al. 2014, Ponte et al. 2014). Diagnostic accuracy estimates from these studies were incorporated into a meta-analysis to provide pooled estimates for sensitivity, specificity, PLR, NLR, DOR.

The clinical outcomes search resulted in the selection of 9 studies (Min et al. 2008, Cheezum et al. 2011, Ovrehus et al. 2011, Hachamovitch et al. 2012, Min et al. 2012a, Sahinarslan et al. 2013, Mouden et al. 2014, Neglia et al. 2015) of which 2 (Hachamovitch et al. 2012, Douglas et al. 2015) were included in the sponsor's submission. Data on 2 additional unpublished studies were provided by the sponsor.

To address issues related to the model submitted by the sponsor, the EAC re-estimated the cost impact of the technology (FFR<sub>CT</sub>) and its comparators based on the NICE guideline on the stable chest pain pathway. The EAC excluded the pre-test likelihood populations of <10% and >90% and used

vessel-based diagnostic accuracy estimates. The EAC also assigned a cost for optimal medical therapy. The cost impact of using other functional imaging (MRI and ECHO) instead of SPECT was also considered.

Results show that the technology is cost-saving if SPECT and MRI are the functional imaging tests used in the recommended pathway. The technology is cost-incurring if ECHO is used as the functional imaging test.

## **2 Background**

### **2.1 Overview and critique of sponsor's description of clinical context**

#### **2.1.1. Critique of sponsor's description of background condition**

The sponsor provided a brief overview of the condition and its prevalence in the UK. Since the sponsor used statistics from 2006, the EAC has provided a more comprehensive and up to date description of the condition in the sections below.

#### **2.1.2. EAC's overview of the condition and technology**

### **Coronary artery disease**

In the UK, approximately 2.3 million people currently live with coronary artery disease (CAD), 1.4 million men and 850,000 women. If left untreated, CAD can lead to myocardial infarction and death. CAD is the most common cause of death in the UK and is responsible for around 73,000 deaths every year, 23,000 of which are in people under the age of 75. This equates to an average of 200 deaths each day, or one every 7 minutes. Most deaths from CAD are caused by acute myocardial infarctions (MI). There are up to 175,000 MIs in the UK each year, 65,000 in women and 110,000 in men. Death rates from CAD are highest in Scotland and the north of England and lowest in the south of England. The main risk factors for developing CAD are as follows<sup>1</sup>.

1. Diabetes
2. Smoking
3. Obesity
4. Sedentary lifestyle
5. High blood pressure

---

<sup>1</sup> <https://www.bhf.org.uk/research/heart-statistics>

6. High blood cholesterol levels (5mmol/l or above)
7. Low consumption of fruit and vegetables
8. Increased alcohol intake

### Pathogenesis of CAD

CAD occurs when the lumen of coronary arteries narrows as a result of atherosclerosis; an accumulation of atherosclerotic plaque. The atherosclerotic plaque, or atheroma, consists mainly of cholesterol, fat and calcium. Traditionally, the lumen of coronary arteries was thought to be fixed in size and, therefore, any accumulation of atherosclerotic plaque was believed to automatically lead to luminal narrowing. However, it has since been established that this is not always the case, as artery external elastic membranes (EEM) are able to change over time and, consequently, alter the width of the arterial lumen. This process is referred to as 'arterial remodelling' and can be classified as positive or negative.

Negative remodelling refers to a shrinkage of the EEM area around an atheroma, which compounds the narrowing of the lumen, or stenosis, and, subsequently, the restriction of blood flow to the myocardium (Schoenhagen et al. 2001). In contrast, positive remodelling refers to a compensatory expansion of the EEM area during atheroma development. This expansion means that the degree of stenosis is limited and that the blood flow to the myocardium is largely unaffected by the atheroma. In other words, atherosclerosis can exist without producing stenosis.

Atheromas that cause stenosis tend to have small lipid cores, fibrosis, calcification, thick fibrous caps and less compensatory enlargement (positive remodelling) (Libby and Theroux 2005). Non-stenotic atheromas, which outnumber stenotic atheromas, tend to have undergone substantial positive remodelling and have large lipid cores and thin, fibrous caps susceptible to rupture and thrombosis. Consequently, their size is often underestimated by angiography. Non-stenotic atheromas may cause no symptoms for many years but when disrupted can provoke an episode of unstable angina or a MI.

### CAD symptoms

The most common symptoms of CAD are shortness of breath and chest pain. The chest pain caused by CAD is called angina, and occurs when atherosclerosis narrows one of the coronary arteries to the extent that blood, and consequently oxygen, supply to the myocardium becomes restricted. Angina is broadly divided into 2 categories.

- Stable angina; when the pain is caused by anticipated factors (triggers), such as physical exercise.

- Unstable angina; when the pain occurs unpredictably, without triggers. This should be managed as a form of acute coronary syndrome.

Chest pain is a very common symptom and 20% to 40% of the population will experience chest pain at least once in their lives. Chest pain caused by CAD can be life-threatening unless treated, highlighting the need for early and accurate diagnosis.

## Diagnosis

Different diagnostic pathways exist depending on whether a patient presents with symptoms of stable or unstable angina. When a patient presents with features of stable angina the diagnosis is established by taking a clinical history and examination, with or without diagnostic tests, such as the following<sup>2</sup>.

1. Exercise stress test.
2. Anatomical and functional imaging tests.
3. Invasive coronary angiography (ICA) with or without invasive fractional flow reserve (FFR) measurement.

The decision of which diagnostic test to use is dependent on the patient's prior probability of having CAD based on the recommendations of the [Chest pain of recent onset: Assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin](#) (NICE guidelines, CG95, March 2010). The prior probability, which can take values between 0% and 100%, is calculated on the basis of symptoms, age, sex and risk factors (

Table 1).

- If people have features of typical angina based on clinical assessment and their estimated likelihood of CAD is greater than 90%, then the patient is diagnosed with angina and managed accordingly.
- In people without confirmed CAD, in whom stable angina cannot be diagnosed or excluded based on clinical assessment alone, the following diagnostic tests are recommended.
  - ICA if the estimated likelihood of CAD is 60-90%.

---

<sup>2</sup> <http://www.nice.org.uk/guidance/cg95/evidence/cg95-chest-pain-of-recent-onset-full-guideline2>

- Functional imaging if the estimated likelihood of CAD is 30-60%.
- CT calcium scoring if the estimated likelihood of CAD is 10-29%.

**Table 1: Percentage of people estimated to have coronary artery disease according to typicality of symptoms, age, sex and risk factors**

Age (years)	Non-anginal chest pain				Atypical angina				Typical angina			
	Men		Women		Men		Women		Men		Women	
	Lo	Hi	Lo	Hi	Lo	Hi	Lo	Hi	Lo	Hi	Lo	Hi
35	3	35	1	19	8	59	2	39	30	88	10	78
45	9	47	2	22	21	70	5	43	51	92	20	79
55	23	59	4	25	45	79	10	47	80	95	38	82
65	49	69	9	29	71	86	20	51	93	97	56	84

For men older than 70 with atypical or typical symptoms, assume an estimate > 90%.  
For women older than 70, assume an estimate of 61–90% EXCEPT women at high risk AND with typical symptoms where a risk of > 90% should be assumed.

Values are per cent of people at each mid-decade age with significant coronary artery disease (CAD)<sup>[a]</sup>.  
Hi = High risk = diabetes, smoking and hyperlipidaemia (total cholesterol > 6.47 mmol/litre).  
Lo = Low risk = none of these three.  
The 'non-anginal chest pain' columns represent people with symptoms of non-anginal chest pain, who would not be investigated for stable angina routinely.  
Note:  
These results are likely to overestimate CAD in primary care populations.  
If there are resting ECG ST-T changes or Q waves, the likelihood of CAD is higher in each cell of the table.

### Fractional Flow Reserve

FFR is an invasive technique used to measure pressure differences across a coronary artery stenosis. This measurement can be used to determine whether the stenosis obstructs oxygen delivery and, therefore, causes myocardial ischemia. To measure FFR, an FFR-specific guide wire intended to record the coronary arterial pressure proximal and distal to the stenosis is needed. FFR provides a functional evaluation, by measuring the pressure decline caused by vessel narrowing.

It has been shown that invasive FFR measurements correlate more closely with relative flow reserve derived from positron emission tomography (a functional imaging technique) than angiographic parameters (De Bruyne et al. 1994). It has also been shown that an FFR value of 0.80 or less identifies ischemia-causing coronary stenoses with an accuracy of more than 90% (Pijls et al. 1995, Pijls et al. 1996, De Bruyne et al. 2001).

FFR is now considered to be the standard of care for the functional assessment of lesion stenosis severity (Pijls et al. 1996), and for guiding percutaneous coronary revascularisation with class IA European Society of

Cardiology and class IIA American Heart Association practice guideline recommendations (Levine et al. 2011, Windecker et al. 2014). There is, therefore, sufficient evidence to support a close relationship between pressure differences and clinically significant vessel disease which causes ischemia.

### The technology

HeartFlow  $FFR_{CT}$  is a post-processing image analysis software package that non-invasively estimates FFR using previously acquired coronary CT angiography (CCTA) studies.  $FFR_{CT}$  is derived from simulated pressure, velocity and blood flow information obtained from a 3-dimensional (3D) computer model. The CCTA imaging data for HeartFlow analysis must be acquired by scanners designed for coronary imaging applications ( $\geq 64$  slices). Scanners from all major vendors including GE, Siemens, Phillips and Toshiba, have been successfully used for HeartFlow analysis. HeartFlow's scanning protocol follows the SCCT guideline (Abbara et al. 2009).

The process starts with the clinician uploading the image data to HeartFlow servers using HeartFlow Connect, a cloud-based network application that enables the CCTA data to be transmitted via a secure connection to the HeartFlow core laboratory for analysis. Data can be uploaded from any device capable of sending DICOM data including PACS, workstations or directly from CT scanners.

Subsequently, these data are used to construct the anatomy (step B) and physiology (step C) of a patient-specific model (Figure 1). For each patient, a quantitative 3-dimensional anatomic model of the aortic root and epicardial coronary arteries is generated from CCTA images.

HeartFlow uses a coronary segmentation algorithm that models the arterial lumen boundaries to a resolution of approximately 1 mm. According to (Serruys et al. 2012), in order to provide smooth luminal surfaces of the coronary arteries for  $FFR_{CT}$  analysis the process involves the segmentation of the major vessels and plaque detection and removal. The analyst interacts with the software in step B to make necessary edits to the patient specific anatomical model. A detailed overview of these steps is provided in the technical evaluation of HeartFlow.

Coronary blood flow and pressure are computed under conditions simulating maximal hyperaemia.  $FFR_{CT}$  is estimated throughout the coronary arterial tree although vessels with  $< 2$  mm diameter are excluded. The  $FFR_{CT}$  analysis can take up to 8 hours per examination depending on the CT image quality and atherosclerotic disease burden (Nørgaard et al. 2014).

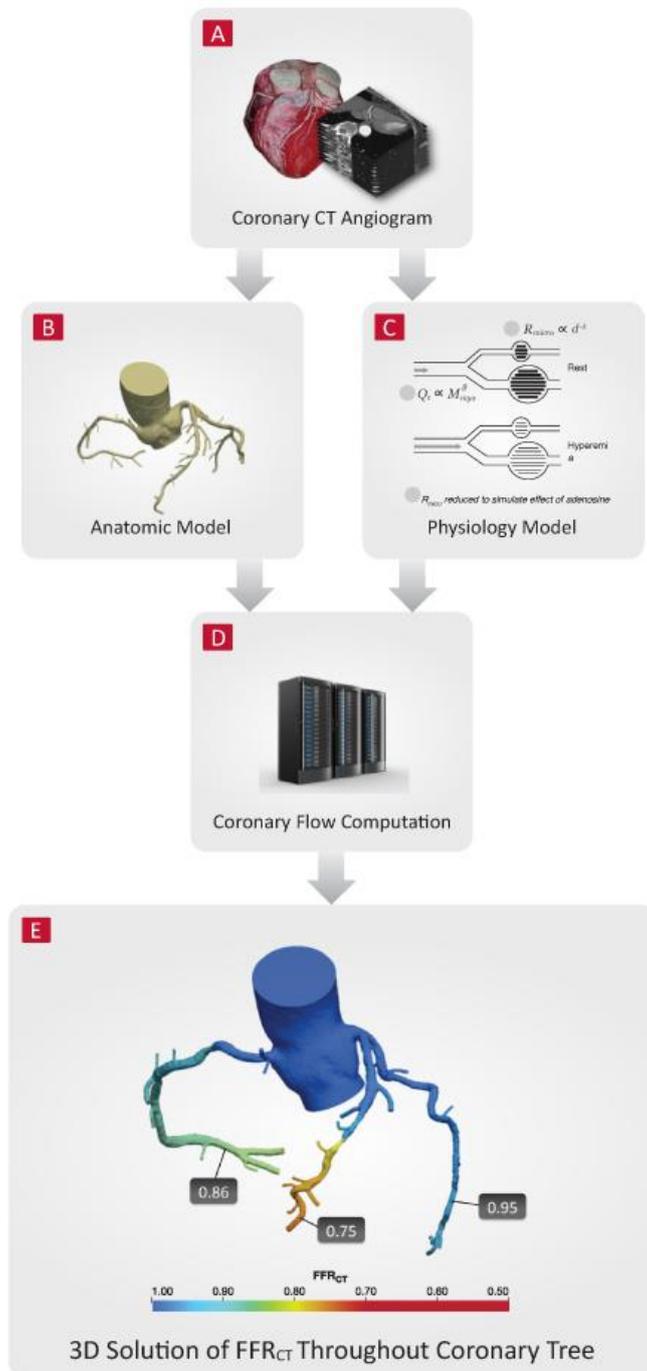


Figure 1: Schematic outline of the process for FFR<sub>CT</sub> analysis, provided on the manufacturer's website (<http://heartflow.com/>)

### 2.1.3. Overview of relevant clinical guidelines

The sponsor identified UK and European guidelines relevant to the technology. These were broadly divided in 3 categories.

- The management of stable angina and chest pain.

- Tests relevant to the model supporting the comparative costs and performance of FFR<sub>CT</sub> in the decision pathway for the management of stable chest pain.
- Interventions for patients with significant blood flow restriction in one or more coronary arteries.

The most relevant of these guidelines is [Chest pain of recent onset: Assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin](#) (NICE guidelines, CG95, March 2010). A partial update of this guideline is scheduled by NICE after a recent review in December 2014. The guideline recommends a strategy with which to approach the diagnosis of CAD (*Figure 2*). The guideline emphasises the importance of the pre-test likelihood to inform the choice of appropriate diagnostic investigations and avoid unnecessary investigations. NICE recommends using the modified Duke Clinical Score, published in 1993, to assess the pre-test likelihood of CAD (Pryor et al. 1993). This takes into account both clinical history and the presence of recognised cardiovascular risk factors. The principles outlined in CG95 were reiterated in the 2012 American Heart Association/American College of Cardiology (AHA/ACC) guideline (Fihn et al. 2012) and the 2013 ESC guideline (Montalescot et al. 2013) on patients with stable chest pain.

The ESC guideline recommends a stepwise approach for decision making in patients with suspected stable CAD. Initially, patients are assessed clinically to determine their pre-test likelihood of CAD. The guideline suggests that patients with intermediate pre-test likelihood should be offered non-invasive testing to establish the diagnosis of CAD or non-obstructive atherosclerosis (typically by performing carotid ultrasound). Once the diagnosis of stable CAD has been made, medical therapy is started and risk stratification for subsequent events is carried out, usually on the basis of available non-invasive tests, to select patients who may benefit from invasive investigations and revascularisation (Montalescot et al. 2013).

The AHA/ACC guideline states that after the completion of a clinical evaluation the clinician must determine whether the probability of CAD is sufficient to recommend further testing, often an exercise stress test. According to the AHA/ACC the use of diagnostic testing is most valuable when the pre-test probability of CAD is intermediate (Fihn et al. 2012). It is necessary to note, however, that these probabilities relate solely to the presence of obstructive CAD and do not pertain to ischaemia due to microvascular disease or other causes. They also do not reflect the likelihood that a non-obstructing plaque could become unstable and cause ischaemia.

The apparent diagnostic accuracy of a test can be altered substantially by the pre-test likelihood of CAD (Diamond and Forrester 1979, Rozanski et al. 1983, Douglas 1997), making the accurate assessment of pre-test likelihood and appropriate patient selection essential for assessing the diagnostic accuracy of a test (Fihn et al. 2012).

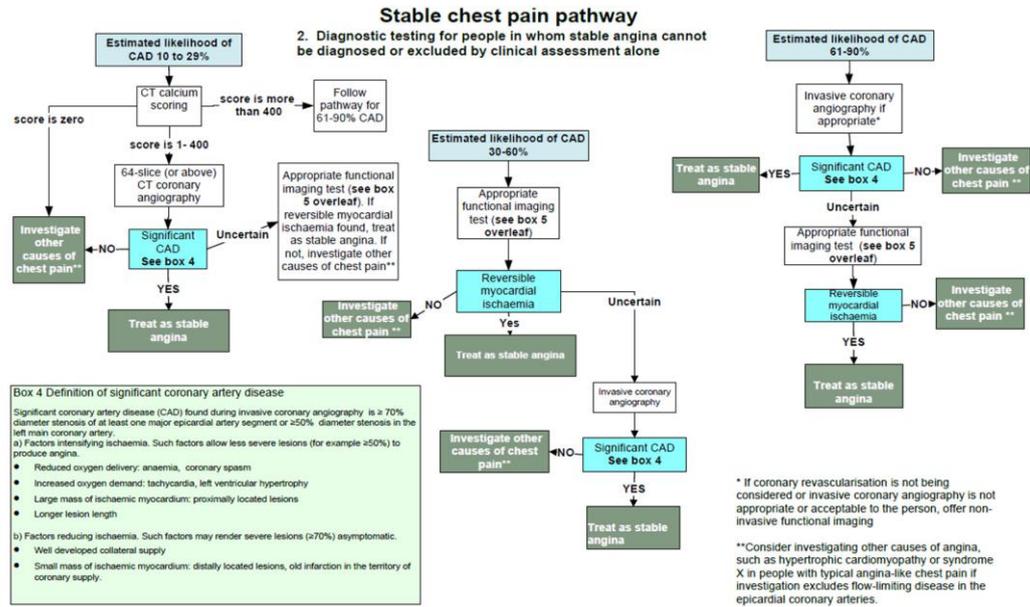


Figure 2: NICE's diagnostic pathway for stable chest pain based on the likelihood of CAD (CG95)

### 2.1.4. Critique of the sponsor's description of the clinical context

The sponsor's submission described the clinical context using background data from the NHS Choices content on CAD<sup>3</sup> and the 2012 British Cardiovascular Intervention Society audit on adult interventional procedures<sup>4</sup>. The sponsor's submission emphasised the difficulty in establishing the presence of CAD due to the frequent ambiguity of symptoms. According to the sponsor this difficulty, combined with a lack of consensus regarding the diagnostic pathway, often results in the patient being referred for multiple tests and invasive procedures in order to complete the diagnostic evaluation. This claim is supported by recently published evidence on the implementation of NICE CG95 (Whitaker J 2014).

<sup>3</sup> <http://www.nhs.uk/Conditions/Coronary-heart-disease/Pages/Introduction.aspx>

<sup>4</sup> [http://www.bcis.org.uk/resources/BCIS\\_Audit\\_2012\\_for\\_web\\_V2\\_14-10-20131.pdf](http://www.bcis.org.uk/resources/BCIS_Audit_2012_for_web_V2_14-10-20131.pdf)

In addition, the sponsor notes the unsatisfactory sensitivity and specificity of the testing methods currently available. However, the sponsor does not name these tests and does not provide further evidence on their claimed diagnostic accuracy. The sponsor's claim, although valid for some of the diagnostic modalities such as SPECT, shown to have only a modest sensitivity 0.74 and specificity of 0.79 (Takx et al. 2015), is not valid for other modalities. For example, a published systematic review and meta-analysis reported a pooled sensitivity of 0.90 and specificity of 0.87 for perfusion MRI (Li et al. 2014).

Currently, the gold standard for assessing the functional severity of coronary artery stenosis and making decisions about the need for revascularisation is invasive FFR (Tonino et al. 2009, De Bruyne et al. 2012). It has been shown that patients treated with coronary revascularisation on the basis of their FFR value experience fewer adverse clinical events and incur lower healthcare-related costs than patients treated on the basis of information gleaned from conventional diagnostic tools such as ICA (Tonino et al. 2009, De Bruyne et al. 2012). However, FFR measurement is an invasive procedure that requires the patient to be catheterised and is, therefore, associated with risks and adverse events. As a result, a technology that could accurately estimate FFR non-invasively has a clear advantage. To this end, the non-invasive estimation of FFR<sub>CT</sub> could complement the anatomical information provided by CCTA and minimise the number of unnecessary invasive procedures conducted in patients with functionally insignificant coronary artery stenosis.

### ***2.1.5. Issues relating to current practice***

Despite the NICE CG95 recommendations, it is recognised that there is widespread heterogeneity in clinical practice within the UK. Although the reasons for this are complex, it is likely that this reflects local referrer preferences along with individual accessibility, availability and user experience of the various functional and anatomical imaging modalities. The main issue with such clinical practice variability is the risk of unnecessary layering of investigations that can increase costs and delay diagnosis.

NICE's CG95 recognises this variability in clinical practice and advises clinicians to take account of locally available technology and expertise, the patient and their preferences, and the existence of any contraindications when deciding on the non-invasive functional imaging method. Although the sponsor's clinical submission acknowledges the existence of this variability, in the proposed pathway submitted in the economic submission it is assumed that SPECT will be used in 95% of cases where patients have intermediate pre-test likelihood requiring functional imaging.

Figures reported in a UK-based audit provide a different picture of clinical reality, one that is more in line with the picture provided by NICE CG95. Specifically, for patients with intermediate to-moderate pre-test likelihood of CAD (defined as those with pre-test likelihood of 30–60%), 34% of cardiologists report using exercise stress test as their first-choice investigation, 26% use stress echocardiography, 20% use nuclear stress test, 11% use CCTA and 9% use cardiac MRI (Whitaker J 2014). Stress echocardiography was more likely to be used by imaging cardiologists as their first investigation (53%) compared with interventional cardiologists (24%). Exercise stress test was more likely to be used by interventional cardiologists (41%) as a first choice of investigation than by imaging cardiologists (13%). If there were no restrictions on the availability of investigations, then the preferred methods of investigation would be stress echocardiography (30%), cardiac MRI (25%), cardiac CT (18%), nuclear stress test (14%) and exercise stress test (13%) (Whitaker J 2014).

#### **2.1.6. Potential changes to the pathway introduced by FFR<sub>CT</sub>**

According to the sponsor, FFR<sub>CT</sub> technology in conjunction with CCTA would be used in patients with a pre-test likelihood of CAD between 10% and 90%.

Specifically, the sponsor proposed that FFR<sub>CT</sub> in combination with CCTA would replace the following tests.

- CCTA in the pathway for pre-test disease likelihood between 10-29%.
- Appropriate functional imaging tests in the pathway for pre-test disease likelihood 30-60%.
- ICA in the pathway for pre-test disease likelihood 61-90%.

In all of the above cases the patient will have a CCTA acquired in line with pre-specified guidelines (Abbara et al. 2009). The CCTA will be reviewed locally for evidence of CAD with plaque which might be causal of ischaemia, following which the data will be sent to HeartFlow. The results of the FFR<sub>CT</sub> will then be returned to the clinician to assist in further decision-making.

The sponsor does not, at this point, provide further detail on the assessment of 'evidence of CAD with plaque which might be causal of ischaemia'. Further information is, however, provided in the sponsor's economic submission which provides a more detailed outline of the proposed pathway. It proposes that CT calcium scoring is performed in the first instance. CT calcium scoring is a method to quantify the calcification of the coronary arteries, a sign of

atherosclerotic disease, which does not require intravenous (IV) contrast<sup>5</sup>. If the result is >400 Agatston units the patient should be referred for ICA, if it is between 1 and 400 then the patient should be referred for CCTA and if it is 0 then other causes of chest pain should be explored.

Patients referred for CCTA will need to have an additional CT scan (with IV contrast). The CCTA data will be reviewed for the presence of significant CAD. Although not clarified by the sponsor, the assumption is that this will be based on the visual identification of coronary artery stenosis using a pre-specified threshold. For both these steps the diagnostic accuracy will be limited by the performance of CT calcium scoring and CCTA. According to the American College of Cardiology Foundation, non-contrast CT for calcium scoring is appropriate for intermediate- and selected low-risk patients (Taylor et al. 2010).

According to the sponsor,  $FFR_{CT}$  does not require any additional tests or investigations other than those discussed in section 3.5 of the submission. It also does not require additional facilities or technologies apart from the IT infrastructure required to enable transmission of CCTA data to HeartFlow through a secure, encrypted connection. HeartFlow's Connect software can be installed using a virtual machine server (VMware) on any hospital network. The minimum system specifications required for the virtual machines to run VMware are present in most NHS-based computers. The sponsor claims that the radiologists performing CCTA can also interpret the reported  $FFR_{CT}$  analyses along with trained general, interventional, or imaging cardiologists. The EAC agrees that while the generation of results is a centralised service performed at HeartFlow, the interpretation of these results is not centralised. It is performed by clinicians involved with patient care.

Finally, the sponsor cites a recent publication by Rajani et al. based at Guy's and St Thomas' Hospital in London (Rajani et al. 2015) to support the claim that the adoption of  $FFR_{CT}$  would result in fewer exercise and functional imaging stress tests. Consequently, the use of these resources could be made available for other conditions and tests.  $FFR_{CT}$  will not substitute these diagnostic tests completely, as they will still be indicated for patients who do not have intermediate pre-test likelihoods or for patients who are unsuitable to undergo CCTA. Rajani et al. (2015) also state that the application of  $FFR_{CT}$  results in fewer unnecessary ICA and Percutaneous Coronary Intervention (PCI) procedures, freeing up time and resources for other effective procedures. The sponsor has submitted evidence to support this, taken from

---

<sup>5</sup> The reported radiation dose of a CT calcium scoring has been 1.5–3.0 mSv, however, the doses will vary depending on equipment and technique used and patient size ([NICE CG95 calcium scoring factsheet](#)).

the preliminary results of the PLATFORM (Prospective Longitudinal Trial of FFR<sub>CT</sub>: Outcome and Resource Impacts) study.

Based on the above the EAC considers the sponsor's description of the clinical context to be appropriate and relevant to the decision problem under consideration. The EAC has highlighted the uncertainty and lack of evidence associated with some of the sponsor's claims in the appropriate sections below.

## **2.2 Overview of sponsor's description of ongoing studies**

In their submission the sponsor states that there is currently 1 ongoing study with FFR<sub>CT</sub>, the aforementioned PLATFORM study<sup>6</sup>. This is an international, multicentre cohort study aiming to compare clinical outcomes, resource utilisation, Major Adverse Cardiovascular Events (MACE), cumulative radiation exposure and quality of life (QOL) of FFR<sub>CT</sub>-guided evaluation versus standard practice evaluation in patients with suspected CAD. The study completed recruitment in November 2014. Freeman Hospital in Newcastle and University Hospital Southampton are participating in this Study.

The sponsor's submission included outcome data from 90 days of follow-up. The study also involves follow-up of patients at 180 and 365 days, but this has not been completed yet. This trial is listed on Clinicaltrials.gov (identifier number [NCT01943903](https://clinicaltrials.gov/ct2/show/NCT01943903)). The EAC requested and subsequently received the full protocol of the study from the sponsor. PLATFORM is the only study currently investigating clinical outcomes associated with the intervention. Previous studies with FFR<sub>CT</sub>, all of which have published their results, have looked at the technology's diagnostic accuracy (Koo et al. 2011, Min et al. 2012b, Norgaard et al. 2014).

The sponsor has also submitted unpublished data from the FFR<sub>CT</sub> RIPCORD study, a post-hoc analysis of 200 sequential patients from the HeartFlowNXT trial. The aim of this retrospective analysis was to assess changes in patient management following the introduction of FFR<sub>CT</sub> in patients undergoing CCTA and referred for ICA. The EAC has not found an online registration record of this study.

The EAC identified 1 additional ongoing study from its literature search. The EMERALD trial ([NCT02374775](https://clinicaltrials.gov/ct2/show/NCT02374775)) is an international multicentre study aiming to explore plaque rupture in patients with acute MI using CCTA and computational fluid dynamics. The population includes patients who presented

---

<sup>6</sup> <https://clinicaltrials.gov/ct2/show/NCT01943903>

with acute MI and definite evidence of plaque rupture who had undergone CCTA between 1 month and 2 years prior to the event (retrospectively searched). The estimated study completion date is September 2015. Although the study uses FFR<sub>CT</sub>, it is only one of many fluid dynamic parameters investigated, and is a secondary outcome. In addition, the study is retrospective and exploratory in nature. As a result, the EAC's view is that it is unlikely to affect the decision for FFR<sub>CT</sub> use as outlined in this assessment report.

### **2.3 Critique of sponsor's definition of the decision problem**

#### **Population**

The population described by the sponsor was '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%'. If the pre-test likelihood of CAD is <10% or >90%, further diagnostic testing is not required.

This definition is in accordance with the population identified in the scope and with the NICE CG95 guideline that recommends a diagnostic algorithm based on pre-test probability of significant CAD. However, the population described does not match the patient cohorts included in the diagnostic accuracy studies identified by the sponsor. Although all the studies included patients with stable angina, not all studies selected the participants based on their pre-test likelihood of CAD as defined by NICE CG95 or any other existing risk models (Jensen et al. 2012). The population in the 22 studies included in the sponsor's meta-analysis can be categorised as follows.

- Patients with coronary artery narrowing of unspecified degree in whom invasive FFR was performed at the interventional cardiologist's discretion (Meijboom et al. 2008, Ko et al. 2014, Rossi et al. 2014).
- Patients with coronary artery stenosis identified during ICA above a predefined threshold of 30% (Park et al. 2012, Kang et al. 2013, Cho et al. 2014, Wong et al. 2014), 50% (Ragosta et al. 2007, Melikian et al. 2010, Koo et al. 2011, Choi et al. 2012, Ko et al. 2012, Kamiya et al. 2014), 40-70% (Sahiner et al. 2013), 50-75% (Rieber et al. 2004, Hacker et al. 2005), or 'intermediate' (Jung et al. 2008).
- Patients with intermediate probability of CAD determined by reference to a clinical risk score (Stuijzand et al. 2014).
- Patients clinically indicated to undergo ICA (Costa et al. 2007, Bernhardt et al. 2012, Min et al. 2012b, Norgaard et al. 2014).

As a result the studies included in the submission include either mixed populations of intermediate-high risk populations or purely high risk populations with the exception of (Stuijzand et al. 2014) which includes an intermediate pre-test likelihood population.

## Intervention

The sponsor describes the intervention as '*HeartFlow noninvasive FFR<sub>CT</sub>*'. Different versions of the software exist, for example in the HeartFlowNXT trial (Gaur et al. 2013) v1.4 of the software for FFR<sub>CT</sub> analysis was used, whilst in the DeFACTO study (Min et al. 2011) an older version (v1.2) was used. The sponsor holds a CE mark that covers all FFR<sub>CT</sub> v1.X (v1.2–1.7). The original CE mark was issued on July 26, 2011 for FFR<sub>CT</sub> version 1.x but the technical file has since been updated to include subsequent releases, including HeartFlow's most recent commercial release, version 1.7. The current CE mark is valid until July 25, 2017. The Instructions for Use provided by the sponsor apply to v1.7. According to the sponsor there were only minor differences between versions, all of which were intended to address usability and support issues. The sponsor claims that none of these changes impacted upon the intended use or principles of operation. In brief, changes made to the software include the following.

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

HeartFlow FFR<sub>CT</sub> technology has also received regulatory approval in the following locations outside the UK.

- United States, FDA de novo 510K Clearance, November 2014; DEN130045.

- Australia, Therapeutic Goods Administration Approval, April 2013.

### **Comparator(s)**

Among the non-invasive and invasive tests that are able to detect CAD, CCTA and ICA assess coronary anatomy, whereas other comparators assess coronary function. This involves either stress myocardial perfusion scintigraphy using single photon computed emission tomography (SPECT) or cardiac MRI, or using MRI or echocardiography (ECHO) to conduct stress myocardial wall motion analysis. The sponsor correctly states, in line with NICE CG95, that the decision of which comparator to use will vary depending on the pre-test likelihood of coronary artery disease, on whether coronary revascularisation is being considered, and on local expertise and infrastructure. The following comparators were listed by the sponsor.

- CCTA imaging without  $FFR_{CT}$  estimation.
- Invasive coronary angiography (ICA) combined with invasive measurement of FFR using a pressure wire.
- Myocardial perfusion scintigraphy with SPECT.
- Other functional imaging (such as stress echocardiography (ECHO) or MR techniques (MRI)).
- For diagnostic accuracy, the reference standard is invasive measurement of FFR using a pressure wire.

It is important to note that for each non-invasive imaging comparator listed above, there are multiple ways to analyse the data. Therefore, the EAC has provided below a brief summary for each comparator regarding the specifications required for inclusion in the assessment report.

#### **Coronary CT angiography**

CCTA is an imaging method that uses a CT scanner for the non-invasive assessment of coronary arteries. Both anatomical (degree of vessel stenosis) and functional (presence of myocardial ischaemia or haemodynamic significance of a specific coronary stenosis) analysis techniques are possible with CCTA data (Choi et al. 2012, De Cecco et al. 2015). However, functional analysis techniques are predominantly used in research and are very seldom used clinically, whereas visual anatomical analysis is routine in clinical practice. As a result, a study is only eligible for inclusion in this report if it reports diagnostic accuracy results based on visual analysis of CCTA data.

A study reporting both visual and quantitative assessment can be included as long as the visual assessment is reported separately (Choi et al. 2012). A characteristic example is the systematic review and meta-analysis by Takx et al. (Takx et al. 2015) where all the included CCTA studies are measuring perfusion rather than coronary stenosis.

Systematic reviews comparing the diagnostic accuracy of CCTA with invasive FFR and FFR<sub>CT</sub> (Li et al. 2015) and with functional imaging (Nielsen et al. 2014) in patients with suspected or confirmed CAD have been published.

## MRI

Different approaches exist to detect CAD with MRI. These include direct visualisation of coronary arteries (magnetic resonance coronary angiography), the characterisation of myocardial tissue (delayed enhancement) and the visualisation of the effects of induced ischaemia (wall motion analysis or perfusion measurements) (Paetsch et al. 2005). Myocardial perfusion can be used to characterise myocardial blood flow at rest and after exercise or pharmacologically induced (with vasodilators or dobutamine) stress. Only studies that have performed stress perfusion MRI measurements are considered relevant to the scope of this assessment.

Systematic reviews comparing the diagnostic accuracy of perfusion MRI with invasive FFR (Li et al. 2014, Takx et al. 2015) and with other functional imaging modalities (Chen et al. 2014) in patients with suspected or confirmed CAD have been published.

## SPECT

SPECT is another imaging modality that can be used to assess myocardial perfusion. It can be used to characterise myocardial blood flow at rest and after exercise or pharmacologically induced (with vasodilators or dobutamine) stress. The most common SPECT tracers used are the <sup>99m</sup>Tc-sestamibi or Thallium-201 tracers and these were considered relevant for inclusion in the assessment.

Systematic reviews comparing the diagnostic accuracy of perfusion SPECT with invasive FFR (Zhou et al. 2014, Takx et al. 2015) and with other functional imaging modalities (Takx et al. 2015) in patients with suspected or confirmed CAD have been published.

## ECHO

Stress echocardiography is an established technique that encompasses two-dimensional (2D)-echo imaging of wall motion and thickening, as well as pulsed wave, continuous wave and colour Doppler. Stress echo can be

performed in combination with exercise or pharmacological agents such as vasodilators or dobutamine. The focus of stress ECHO has predominantly been for assessment of the impact of stress on regional wall motion in patients with known or suspected ischaemic heart disease. The induction of reduced regional systolic wall thickening is specific to CAD.

One systematic review comparing the diagnostic accuracy of stress echo with invasive FFR and other functional imaging modalities (Takx et al. 2015) in patients with suspected or confirmed CAD has been published.

### **Outcomes**

The outcomes listed in the scope, and their reporting in the included studies, are listed in Table 12 and Table 13. The sponsor's submission included studies covering all the outcomes described in the scope. For the diagnostic accuracy the sponsor did not include individual studies but listed a number of systematic reviews and meta-analyses on the diagnostic accuracy of FFR<sub>CT</sub> and its comparators.

### **Cost analysis**

The cost analysis provided by the sponsor assessed the impact of the technology (FFR<sub>CT</sub>) and its comparators, based on the NICE CG95 guideline, in the patient population specified by the scope. The time horizon for the model is sufficient to assess the impact of the technology. The EAC concludes that the sponsor has appropriately included the technology and comparators with regards to the cost analysis, however, the sponsor included costs associated with a pre-test likelihood of <10% and >90% which should be excluded to appropriately estimate the cost-savings of the technology compared to current practice.

### **Subgroups**

There are no subgroups specified in the final scope.

### **Special considerations, including issues related to equality**

No special considerations related to equality.

### 3 Clinical evidence

#### 3.1 Critique of the sponsor's search strategy

The sponsor provided the full search strategies used in appendices 1 and 2 of their submission. The sponsor conducted 3 separate searches; 1 for diagnostic accuracy of all comparators listed in the scope, using invasive FFR as a reference test, 1 for the clinical outcomes and 1 for adverse events related to FFR<sub>CT</sub>.

The EAC replicated the sponsor's searches and found some discrepancies between the number of studies listed in the PRISMA flowchart and the number of studies retrieved. Specifically, the numbers presented in the PRISMA flowchart (Figure B1.1, page 29 of the clinical submission) were lower than the numbers retrieved when the searches listed in Appendix 1 were re-run. Consequently, the EAC requested the sponsor clarify the exact search strategy and any additional limits used. Table 2 shows the additional filters applied by the sponsor for the diagnostic accuracy and clinical outcomes searches.

**Table 2: Additional filters used for the sponsors' literature searches**

Search strategy	Database	Filter
Diagnostic accuracy	PubMed	Humans, clinical trial
Diagnostic accuracy	Web of Science	cardiac cardiovascular systems, article
Clinical outcomes	PubMed	Humans, last 10 years
Clinical outcomes	Web of Science	cardiac cardiovascular systems, article

The EAC considered the date limits chosen by the sponsor (1995 to current for the diagnostic accuracy, 2005 to current for the clinical outcomes) to be adequate. The EAC, however, considers that although the sponsor attempted to construct search strategies that had enough sensitivity to capture the relevant literature, more keywords could have been used to describe the intervention and the comparators. The EAC, therefore, tailored the diagnostic accuracy search strategy submitted by the sponsor to include more intervention and comparator keywords to increase the search's sensitivity.

The EAC also added keywords related to the diagnostic accuracy to increase specificity (Appendix 2). The EAC’s search strategy aimed to identify literature related to the diagnostic accuracy of FFR<sub>CT</sub>, SPECT, CCTA, MRI, ICA and ECHO, using invasive-FFR as reference.

In addition, the EAC designed a search strategy to identify literature related to the clinical outcomes of FFR<sub>CT</sub>, SPECT, CCTA, MRI, ICA and ECHO. The EAC tailored the search strategy submitted by the sponsor to include more keywords related to comparators and outcomes to increase the sensitivity (Appendix 2).

The EAC considered the sponsor’s search strategy for finding studies that have reported adverse events with FFR<sub>CT</sub> technology to be adequate.

Finally, for searches of unpublished evidence the sponsor provided a general description of their methodology:

‘The strategy to retrieve unpublished clinical data relevant to the performance, outcome and clinical use of FFR<sub>CT</sub> and other diagnostic testing modalities included communication with investigators conducting clinical studies, monitoring ongoing clinical trials, attending professional meetings and monitoring online publications.’

However, no details as to which databases were searched for the monitoring of ongoing clinical trials, or which professional meetings and online publications were monitored to gather the abstracts and scientific meeting presentations were provided.

### **3.2 Critique of the sponsor’s study selection**

Diagnostic accuracy

The sponsor used the criteria outlined in *Table 3* for selecting the relevant diagnostic accuracy studies.

**Table 3: Sponsor’s selection criteria for published diagnostic accuracy studies**

<b>Inclusion criteria:</b>	
<b>Population</b>	People with stable chest pain with possible CAD with pre-test likelihood of 10-90%
<b>Interventions</b>	FFR <sub>CT</sub> , CCTA, ICA, SPECT, ECHO, and MRI
<b>Comparator</b>	Invasively measured FFR as the reference standard

<b>Outcomes</b>	SN, SP, PLR, NLR, and AUC
<b>Study design</b>	Cross sectional studies, meta-analyses; when studies reflected overlapping populations, the study with the largest population was included
<b>Language restrictions</b>	English
<b>Search dates</b>	January 1995 to February 2015
<b>Exclusion criteria</b>	
<b>Population</b>	People with unstable chest pain, ACS and pre-test likelihood >90%
<b>Interventions</b>	PET, CT perfusion, TAG
<b>Comparator</b>	Invasive FFR not used as reference standard
<b>Outcomes</b>	Absent or insufficient data to determine SN, SP, PLR, NLR and/or AUC
<b>Study design</b>	Studies of <30 patients and commentaries
<b>Language restrictions</b>	Not English
<b>Search dates</b>	Prior to January 1995

Although the sponsor stated that the inclusion criterion for the population was patients with intermediate pre-test likelihood of CAD (10-90%), they did not provide any additional details of how the status of the population was assigned in cases where this was not reported. The EAC requested further clarification from the sponsor regarding this. According to the sponsor, they extrapolated the patients' pre-test likelihood from information retrieved from the inclusion/exclusion criteria and the study design. Although most studies did not explicitly report the pre-test likelihood of CAD, all studies included patients who underwent ICA with measurement of FFR as the reference standard. In other words, each patient was determined, on the basis of clinical assessment, to be in need of ICA and thus was deemed to be of intermediate or high risk of CAD. Pre-test likelihood can have an effect on diagnostic accuracy and, therefore, the sponsor's approach is considered to be flawed (Diamond and Forrester 1979, Rozanski et al. 1983, Douglas 1997).

To be considered for inclusion, the sponsor required the diagnostic accuracy studies to provide measurements in more than 75% of vessels included in the analysis. The sponsor's view is that failing to measure FFR in all the vessels could bias the results since it is known that vessels with <50% stenosis can have  $FFR \leq 0.80$  and that vessels with >50% stenosis may have  $FFR$  values  $>0.80$ . However, in clinical practice a cut-off for the degree of stenosis based on visual CCTA or ICA is sometimes applied before proceeding with FFR

measurements. The use of a cut-off is also supported by the sponsor's proposed changes in the pathway where the degree of stenosis in CCTA is used to decide on further analysis of the data with  $FFR_{CT}$ . As a result the EAC does not consider this criterion to be representative of clinical practice.

The EAC agrees with all other criteria listed by the sponsor.

#### Clinical outcomes

The sponsor used the criteria outlined in Table 4 for selecting the relevant clinical outcomes studies.

**Table 4: Sponsor's selection criteria for published clinical outcomes studies**

<b>Inclusion criteria:</b>	
<b>Population</b>	People with stable chest pain with possible CAD with pre-test likelihood of 10-90%
<b>Interventions</b>	$FFR_{CT}$ , CCTA, ICA, SPECT, ECHO, and MRI
<b>Comparator</b>	NA
<b>Outcomes</b>	Rates of ICA and revascularization, mortality, MACE, radiation exposure, adverse events and QOL
<b>Study design</b>	Randomised trial, cross-sectional study, meta-analysis, clinical trial when studies reflected overlapping populations, the study with the largest population was included
<b>Language restrictions</b>	English
<b>Search dates</b>	January 2005 to February 2015
<b>Exclusion criteria</b>	
<b>Population</b>	People with unstable chest pain, ACS and pre-test likelihood >90%, non-human
<b>Interventions</b>	PET, CT perfusion, TAG
<b>Comparator</b>	NA
<b>Outcomes</b>	Absent or insufficient data to determine outcome measures
<b>Study design</b>	Studies of <30 patients, reviews, commentaries
<b>Language restrictions</b>	Not English
<b>Search dates</b>	Prior to January 2005

The sponsor adopted a similar strategy to the one outlined above (for the diagnostic accuracy studies) to determine the population's pre-test likelihood

of CAD. The pre-test likelihood can have a significant effect on clinical outcomes, with high pre-test probability associated with worse outcomes. Similarly to the diagnostic accuracy studies selection, the EAC considers this to be a limitation of the sponsor's study selection strategy.

The EAC agrees with all other criteria listed by the sponsor.

### **3.3 Included and excluded studies**

#### **Diagnostic accuracy**

The sponsor's submission included 29 possibly relevant studies for diagnostic accuracy, 28 of which are published in full-text (table B3.1 and B14.4 of the submission) and 1 of which is unpublished (Table B4.1 of the submission). Of these, 6 were meta-analyses and 23 were primary studies. In total, the sponsor included 28 studies after excluding one meta-analysis (Desai and Jha 2013). The sponsor stated that their reason for exclusion was that only 1 paper (a limited, retrospective study) was included in the excluded meta-analysis (Desai and Jha 2013) that was not included in the (Li et al. 2014) meta-analysis. See below for details of the included and excluded studies.

Three studies assessed the diagnostic accuracy of FFR<sub>CT</sub> (Koo et al. 2011, Min et al. 2012b, Norgaard et al. 2014), 3 of MRI (Costa et al. 2007, Bernhardt et al. 2012, Kamiya et al. 2014), 10 of CCTA (Meijboom et al. 2008, Koo et al. 2011, Ko et al. 2012, Min et al. 2012b, Ko et al. 2014, Norgaard et al. 2014, Rossi et al. 2014, Stuijzand et al. 2014, Wong et al. 2014), 6 of SPECT (Rieber et al. 2004, Hacker et al. 2005, Ragosta et al. 2007, Melikian et al. 2010, Sahiner et al. 2013, Kamiya et al. 2014) and 3 of ECHO (Rieber et al. 2004, Jung et al. 2008, Kamiya et al. 2014)(Table 12). Three of the studies included involved a direct comparison of FFR<sub>CT</sub> with CCTA (Koo et al. 2011, Min et al. 2012b, Norgaard et al. 2014) and 1 of FFR<sub>CT</sub> with CCTA and ICA (Norgaard et al. 2014).

All 29 studies addressed the scope in terms of the comparators, the reference test and the outcomes. However, none of the meta-analyses and only 1 of the selected studies defined the population as patients with intermediate pre-test likelihood of CAD. The majority of the studies included a mixture of patients with intermediate and high pre-test likelihood of CAD or patients with high pre-test likelihood only (Table 12). Only 1 of the included studies (Stuijzand et al. 2014) recruited a population with an intermediate pre-test likelihood of CAD. This study employed no pre-selection criteria based on scan findings and excluded patients with a prior cardiac history. Another study included a population with an intermediate risk of CAD (mean PROCAM score of 42.7); however, this was not explicitly defined in the methods section (Bernhardt et al. 2012). Finally, Norgaard et al. 2014 studied a population with a

predominantly (87%) intermediate pre-test likelihood of CAD, as stated in the patient characteristics table). Consequently, the EAC excluded 20 out of the 23 primary studies included by the sponsor.

In addition, 7 of the studies accepted by the sponsor had potentially overlapping cohorts. These were as follows.

- (Meijboom et al. 2008) overlapping with (Rossi et al. 2014).
- (Rieber et al. 2004) overlapping with (Hacker et al. 2005).
- (Kang et al. 2013) and (Cho et al. 2014) overlapping with (Park et al. 2012).

The EAC also reviewed all the studies included in the 5 meta-analyses identified by the sponsor. All studies which did not recruit a population with intermediate pre-test likelihood of CAD were excluded from further review. The meta-analyses all included mixed patient populations and, therefore, the EAC considers their pooled results to be irrelevant to the scope. The EAC agrees with the sponsor's decision to exclude Desai et al. (Desai and Jha 2013) because of the study overlap with Li et al. (Li et al. 2014).

Finally, the EAC included 7 diagnostic accuracy studies that fulfilled the inclusion and exclusion criteria outlined in Table 5. For a summary of the EAC's included studies, including those accepted by the sponsor, please see section 3.9, Table 6.

### **Clinical Outcomes**

The sponsor's submission included 31 possibly relevant studies for clinical outcomes, 27 of which are published (table B3.2 of the submission) and 4 unpublished (Table B4.2 of the submission). Of these, 6 were meta-analyses and 25 were primary studies. In total, the sponsor included 20 studies after excluding 4 meta-analyses and 7 primary studies (Table 13).

The EAC reviewed all the primary studies and meta-analyses identified by the sponsor. All studies that did not recruit a population with intermediate pre-test likelihood of CAD were excluded from further review. For a summary of the EAC's included studies, including those accepted by the sponsor, please see section 3.9, Table 8.

### **3.4 Overview of methodologies of all included studies**

#### **Diagnostic accuracy**

The sponsor-identified studies included different comparators, study designs and populations. The EAC reviewed the methodologies of the 28 sponsor-identified studies, outlined below.

- The studies employed a mixture of designs: retrospective/prospective cross-sectional, observational cohort and meta-analyses. There were no RCTs. Both single and multi-centre studies were included.
- Three studies evaluated the intervention specified in the scope (Koo et al. 2011, Min et al. 2012b, Norgaard et al. 2014). The rest investigated the comparators listed in the scope (Table 12).
- The studies used the same reference standard (invasive FFR) but different comparators (Table 12). No single study compared the intervention with all the comparators and the reference standard.
- The studies were performed on patients with known and unknown CAD. One study recruited patients with only intermediate pre-test likelihood of CAD (Stuijzand et al. 2014). The remaining studies recruited subjects with both intermediate and high pre-test likelihood. The patient population defined in the scope is: *'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%.* Therefore, the EAC considers that the majority of the studies included patient populations that were outside the scope.
- The majority of the studies reported confidence intervals with the exception of (Rieber et al. 2004, Hacker et al. 2005, Jung et al. 2008, Melikian et al. 2010, Wong et al. 2014).
- All included studies were full text publications.
- Several of the studies provided adequate baseline characteristics of the study populations, including symptoms, cardiovascular risk factors such as diabetes and hypertension, BMI, single or multi-vessel disease and medication.

## Clinical outcomes

The sponsor-identified studies included different comparators, study designs and populations. The EAC reviewed the methodologies of the 20 sponsor-identified studies, outlined below.

- The studies employed a mixture of designs: retrospective/prospective cross-sectional, observational cohort, RCTs and meta-analyses. Both single and multi-centre studies were included.
- Only 4 studies (2 unpublished and 2 abstracts) evaluated the intervention specified in the scope (PLATFORM study, FFRCT RIPCARD, Radiation FFRCT, (Gaur S 2015)). The rest investigated the comparators listed in the scope (table 12).
- The studies investigated different comparators (table 12). No single study compared the intervention with all the comparators.
- The studies were performed on patients with known and unknown CAD. Studies including unstable patients, patients with acute coronary syndromes, or acute MI were excluded. Two published studies recruited patients with primarily intermediate pre-test likelihood of CAD (Hachamovitch et al. 2012, Douglas et al. 2015). In addition the PLATFORM study recruited patients with intermediate pre-test likelihood of CAD. The remaining studies recruited subjects with various degrees of pre-test likelihood. The patient population defined in the scope is: *'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%'*. Therefore, the EAC considers that the majority of the studies included patient populations that were outside the scope.
- The majority of the studies reported confidence intervals.
- With the exception of 2 abstracts presented as posters, the rest of the included studies were full text publications.
- Several of the studies provided adequate baseline characteristics of the study populations, including symptoms, cardiovascular risk factors such as diabetes and hypertension, BMI, single or multi-vessel disease and medication.

### **3.5 Overview and critique of the sponsor's critical appraisal**

#### Diagnostic accuracy

The sponsor critically appraised all of the included diagnostic accuracy studies using the QUADAS-2 (revised Quality Assessment of Diagnostic Accuracy Studies) tool (Whiting et al. 2011). This tool is available from the QUADAS website ([www.quadas.org](http://www.quadas.org)) and is recommended for critically appraising diagnostic accuracy studies. The tool assesses the risk of study bias (internal validity) in four domains (patient selection, index test, reference standard, flow and timing), and the applicability of the study to the decision problem (external validity or generalisability) in three domains (patient selection, index test, and reference standard). All domains are categorised as low (risk of bias or applicability), high, or unclear, and no attempt is made to formally grade the strength of evidence the study provides. The critical appraisal of primary studies was not provided with the sponsor's original submission but it was requested and submitted to the EAC separately.

The appraisal criteria used by the sponsor are as follows.

1. Patient selection: prospective/retrospective, consecutive patients, FFR only for intermediate lesions, small subsample of "difficult to diagnose" intermediate lesions, exclusion of patients with coronary stenosis <50% or >90%.
2. Index test: was the index test interpreted without knowledge of the result of the reference standard (blinding)? Was the index test performed after angiography? Was the threshold of the test result pre-specified or selected after the angiography/FFR result was known? Did index test methods vary – i.e. 1.5 vs 3.0 tesla for MRI, new experimental technique used?
3. Reference standard: was FFR interpreted with prior knowledge of the results of the index test? Was the decision to perform FFR dictated by the index test? Was the reference standard FFR value of 0.75 or 0.80 pre-specified? Was the index test performed after angiography/FFR?
4. Flow and timing: was there an appropriate interval between the index and reference test? Did all patients have the same reference standard (an FFR cut off of 0.75 vs 0.80)? Did the index test influence the decision to perform reference standard? Were all patients included in the analysis or was this a sub-selected group of patients?

Critical appraisals of included meta-analyses were provided in the sponsor's submission. The EAC notes that the checklist used by the sponsor for the critical appraisal of the meta-analyses was designed for cohort studies, and, therefore, is not appropriate. NICE provides a comprehensive checklist for the

methodological quality assessment of different study designs, including meta-analyses ( <http://publications.nice.org.uk/the-guidelines-manual-appendices-bi-pmg6b>). The sponsor failed to identify and address as a limitation and possible confounding factor the inclusion of studies with patients without intermediate pre-test likelihood of CAD. Instead, in answering the question '*Was the cohort recruited in an acceptable way?*' the sponsor solely focuses on whether the PRISMA guidelines were used and not on the characteristics of the included population and whether or not they fit the scope. However, the EAC notes that the sponsor provided some information on potential bias in the included meta-analyses, namely the following.

- Whether or not 95% CI were reported for all outcome measures
- Whether sensitivity and publication bias analysis were performed
- Whether FFR was measured for all vessels

### **Clinical Outcomes**

The sponsor conducted a critical appraisal of all the studies included in their submission. Checklists for cohort studies or RCTs were used depending on the study design.

The critical appraisal of the studies provided adequate information on several aspects of bias. The sponsor commented on all major study design, technical and statistical methods used to minimise bias. However, the EAC notes that there was variability in what was considered as adequate to score these items as negative for bias. This may reflect the lack of tailored criteria for scoring the checklist items and the variability of study design and outcomes included in the studies.

In the majority of the studies the sponsor considered the reporting of patient clinical characteristics as adequate for identifying confounding factors in the study. When analysis included more than one subgroup, the presence of non-statistically significant baseline characteristics was required for this item to be scored as positive. In the PLATFORM study the recruitment of consecutive patients from a large multicentre study was regarded as adequate to minimise confounding factors.

Finally for all included studies the sponsor commented on the presence of adequate follow up and the precision of the results with the reporting of p-values and confidence intervals.

### **3.6 Results**

#### Diagnostic accuracy

The sponsor summarised and presented the results for the 5 published meta-analyses of diagnostic accuracy studies in submission Table B9. In addition the sponsor presented the results of the 22 studies included in the sponsor's meta-analysis in Table B14.6. The individual results from the 22 studies included in the sponsor's meta-analysis were not provided in the submission. More information on the sponsor's meta-analysis can be found in section 3.8.

The EAC accepted 3 of the sponsor's primary studies as eligible for inclusion in the assessment report (Bernhardt et al. 2012, Norgaard et al. 2014, Stuijzand et al. 2014). The results from the 3 primary diagnostic accuracy studies included by the sponsor and accepted by the EAC are provided in Table 7 in section 3.9.

#### **Clinical outcomes**

The sponsor summarised and presented the results of the 16 published and 4 unpublished studies related to clinical outcomes in submission Tables B9.2a to B9.2t.

From the submitted evidence by the sponsor only 4 studies fitted the scope and were subsequently accepted by the EAC. These were 2 of the published studies (Hachamovitch et al. 2012, Douglas et al. 2015) and 2 of the unpublished studies (PLATFORM, Radiation FFR<sub>CT</sub>). The results from the 4 clinical outcomes studies included by the sponsor and accepted by the EAC are provided in Table 9 in section 3.9. The rest of the studies included by the EAC were either excluded or not identified by the sponsor. Only the 2 unpublished studies included the patient population, intervention, comparators and outcomes as defined in the final scope. The remaining studies included various comparators, but not the intervention itself.

### **3.7 Description of the adverse events reported by the sponsor**

The intervention uses previously acquired CCTA data and, therefore, there are no adverse events associated with its use, beyond those associated with the CCTA IV contrast. The sponsor reports unpublished data from the PLATFORM study in relation to adverse events associated with the invasive procedures performed as part of the study. There are 16 adverse events listed by the sponsor.

- Allergic reaction to CCTA IV contrast (n=1).
- Haematoma in the access area of the ICA catheter (n=6).
- Artery puncture during placement of venous sheath (n=1).
- Myocardial infarction (n=2).
- Artery dissection during ICA (n=1).
- Coronary artery dissection (n=2)
- Neurological deficit after ICA (n=1)
- Progressive dyspnoea and chest pain during ICA (n=1)

The EAC does not believe that the adverse events reported by the sponsor raise any safety concerns for FFR<sub>CT</sub>.

### **3.8 Description and critique of evidence synthesis and meta-analysis carried out by the sponsor**

The sponsor performed a meta-analysis of 22 primary diagnostic accuracy studies. The inclusion/exclusion criteria described in Table 4 were used to identify these studies. In addition, the studies were required to have measured more than 75% of the vessels (per patient) with invasive FFR as described in section 3.2.

The EAC reviewed all the meta-analysis data presented by the sponsor. Several discrepancies were noted between tables B14.5 and table B14.6 in terms of the total number of patients listed. Further clarifications were requested from the sponsor. The reasons the sponsor provided for these discrepancies were as follows.

- some studies included more than one comparator test and, as a result, the total number of patients was greater than the number of patients in the 22 studies.
- the sponsor included in Table B14.6 only studies that reported per patient analyses, and not all studies did so.

All the sponsor's analyses were performed using Meta-DiSc 1.4 (Zamora et al. 2006). This package is considered by the EAC to provide accurate calculations. The sponsor provided the study level information required to repeat their meta-analyses. Using the same package, the EAC was able to replicate the sponsor's results for FFR<sub>CT</sub>, CCTA, ICA, and ECHO. The results for SPECT could not be replicated. The sponsor provided further clarification on this matter correcting the diagnostic accuracy values used in 1 of the studies (Melikian et al. 2010). According with the sponsor:

*'In reviewing our submission, we note that for the Melikian 2010 study, we have incorrectly entered the per-patient FP as 10 rather than 16, and the TN value as 16 rather than 10 , resulting in a "correct" value for Se of 76%, but an incorrect value for Sp (62%) according to the values presented in the manuscript text. We believe that the correct per patient values for SPECT in the Melikian study should be as follows: TP=31, FP=16, TN=10, FN=10 with Sensitivity 76% and Specificity 38%. We are in agreement with Zhou and plan to make this correction in our meta-analysis.'*

The EAC also requested further clarifications on the meta-regression analysis performed. According to the sponsor, meta-regression was performed when significant heterogeneity was present to identify pre-defined sources of heterogeneity (age, gender, prevalence of diabetes, prevalence of hypertension, prior MIs, prior revascularisations, and multi-vessel disease). This was done without access to individual patient data. The EAC's assumption was that the mean values reported in each study were used instead. The sponsor did not perform any statistical comparison of the diagnostic accuracy outcomes for the different comparators listed in table B14.6.

The meta-analysis performed by the sponsor included only per-patient analysis. According to the sponsor, per-vessel analysis does not fit within the scope, which looks at decisions on a per-patient level. The EAC disagrees with the sponsor's decision, as per-vessel analysis will potentially influence decisions on the need for revascularisation. Having said this, a per-vessel meta-analysis must be treated with some caution, as the inclusion of several vessels per patient means that this analysis strictly contravenes the principle of statistical independence of observations, and the resulting confidence

intervals for the pooled estimates are likely to be too conservative. With this caveat, a per-vessel analysis may still provide some helpful information.

### **3.9 Additional work carried out by the External Assessment Centre in relation to clinical evidence**

The EAC selected the studies based on the criteria identified in the scope (Table 5). The EAC considered the main issue with the studies identified by the sponsor to be the inclusion of studies with patient populations outside the scope. In order to fall within the scope as having recruited a population with an intermediate pre-test likelihood of CAD, the paper should fulfil the following criteria.

- State this explicitly in the inclusion criteria or study design outline.
- Provide the estimated likelihood in the patients' characteristics table.
- If the population is mixed, more than 75% of the patients included should have an intermediate probability.
- The mean and standard deviation should fall within the intermediate pre-test likelihood category.

The findings of all the EAC-accepted papers for diagnostic accuracy and clinical outcomes studies are presented in Table 7 and Table 9.

**Table 5: Selection criteria used by the EAC to identify relevant published studies.**

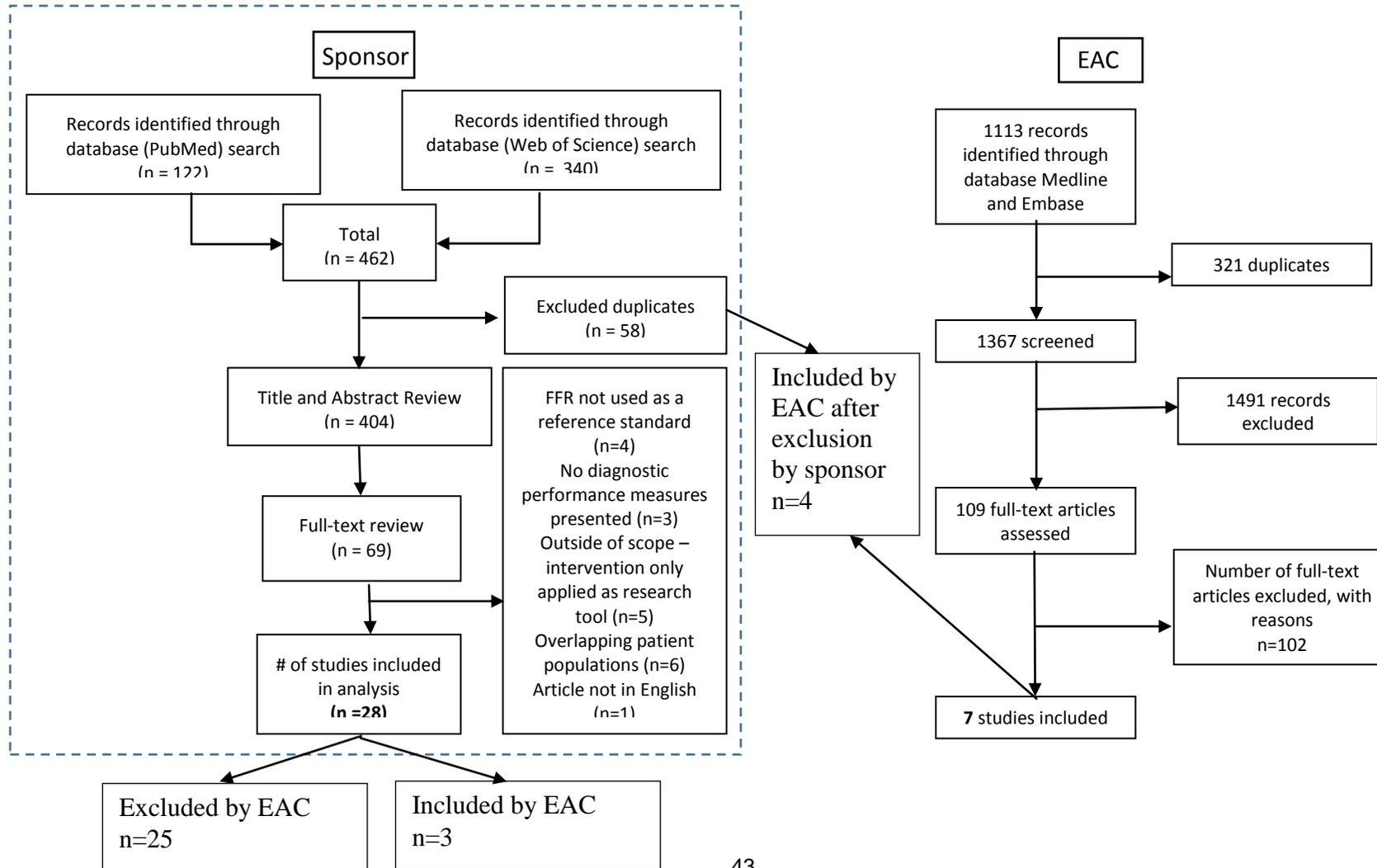
Inclusion criteria	
Population	People with stable chest pain who require investigation for possible CAD, and have a pre-test likelihood of CAD in the range 10-90%.
Intervention	HeartFlow non-invasive FFRCT applied to standard CCTA image data
Comparator	<ul style="list-style-type: none"> <li>- CCTA</li> <li>- ICA combined pressure-wire measured</li> </ul>

	<p>FFR</p> <ul style="list-style-type: none"> <li>- SPECT</li> <li>- ECHO</li> <li>- MRI</li> <li>- Reference standard for diagnostic accuracy is invasive measurement of FFR using pressure wire.</li> </ul>
<p>Outcomes</p>	<p>The outcome measures to consider will include:</p> <ul style="list-style-type: none"> <li>• Sensitivity (SN) and specificity (SP) in determining functional significance of coronary artery disease.</li> <li>• Positive (PLR) and negative likelihood ratios (NLR )and area-under-curve (AUC) versus invasive FFR measurement as the reference standard.</li> <li>• Rates of undertaking diagnostic coronary angiography</li> <li>• Rates of revascularization by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)</li> <li>• Medical radiation exposure</li> <li>• Mortality</li> <li>• Invasive test related adverse events</li> <li>• Major adverse cardiac events (MACE)</li> <li>• Use of noninvasive functional tests</li> <li>• Quality of life (QOL)</li> <li>• Device-related adverse events</li> </ul>
<p>Study design</p>	<p>Diagnostic accuracy studies</p>

	Outcome studies
Language restrictions	<ul style="list-style-type: none"> <li>• English language only</li> <li>• Foreign language papers with English abstracts could be included</li> </ul>
Cost analysis	<ul style="list-style-type: none"> <li>• Costs will be considered from an NHS and personal social services perspective.</li> <li>• Sensitivity analysis of costs will be considered for units with and without access to a CCTA system.</li> <li>• The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared.</li> <li>• 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.</li> </ul>
Search dates	<p>1995 – Current (diagnostic accuracy)</p> <p>2005 – Current (clinical outcomes)</p>
Exclusion criteria	
Population	People with unstable chest pain, ACS and pre-test likelihood <10% or >90%
Interventions	PET, CT perfusion, TAG
Comparator	Invasive FFR not used as reference standard (diagnostic accuracy only)

Outcomes	Absent or insufficient data to determine SN, SP, PLR, NLR and/or AUC
Language	Not English
Study design	Case reports, narrative reviews, letters to the editor

Figure 3.1: PRISMA flow diagram showing the sponsor and EAC's search results – diagnostic accuracy



## Diagnostic accuracy

### Bernhardt 2012

Bernhardt et al. (2012) compared the diagnostic performance of 1.5 vs. 3 T MRI scanners using FFR as a reference standard in patients (n=34) with stable angina and suspected or known CAD. The authors studied an intermediate risk population with a mean PROCAM score of 42.7. The patients were categorised as intermediate risk using the PROCAM score that estimates the 10-year risk of developing a coronary event. FFR measurements were performed in all patients in the left anterior descending, left circumflex, and right coronary artery during maximal hyperaemia (n=102 arteries). The analysis using data acquired with the 3T MRI showed 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 (ROC) analysis on a per-vessel basis for FFR  $\leq$ 0.8 yielded results for the left anterior descending (AUC 0.941, sensitivity=89.5%, specificity=100%); left circumflex (AUC 0.808, sensitivity=75.0%, specificity=96.2%); and right coronary artery (AUC 0.941, sensitivity=90.9%, specificity=100%). The study concluded that the diagnostic accuracy of a 3 T MRI scanner is superior to 1.5 T for the detection of hemodynamic significant stenosis. However, this is in disagreement with other published studies and meta-analyses (Li et al. 2014, Takx et al. 2015).

#### *Critical appraisal*

This study has a low risk of bias for flow and timing and unclear risk for the index and reference test. The PROCAM score uses different variables from the NICE proposed algorithm for assigning a pre-test likelihood of CAD<sup>7</sup>. As a result, there are some concerns about the applicability of patient selection. The reported sensitivity of 1.5T MRI is significantly lower than reported in other published studies and meta-analyses (Li et al. 2014, Takx et al. 2015). A recent meta-analysis (Li et al. 2014) has shown that omitting these results from the meta-analysis leads to non-statistically significant heterogeneity (Q=4.19; I<sup>2</sup>=0.00%; p=0.69). Therefore, the EAC only used the results presented for 3T in our meta-analysis. CIs and sample size calculations were not reported.

### Norgaard 2014

Norgaard et al. (2014) compared invasive FFR, FFR<sub>CT</sub> (v1.4), and CCTA for the diagnosis of myocardial ischaemia in patients (n=254) with suspected

---

<sup>7</sup> [http://www.chd-taskforce.com/coronary\\_risk\\_assessment.html](http://www.chd-taskforce.com/coronary_risk_assessment.html)

stable CAD scheduled to undergo ICA. The authors studied a predominantly intermediate risk population (87% of the patients). Invasive FFR was measured in all vessels (n=484). The study reported diagnostic performance of ICA, FFR<sub>CT</sub>, and CCTA for diagnosis of ischaemia on a per-patient and per-vessel basis, using ICA as the reference standard. The per-patient diagnostic accuracy was 53% for CCTA, 81% for FFR<sub>CT</sub>, and 77% for ICA. The per-vessel diagnostic accuracy was 65%, 86%, and 82% for CTA, FFR<sub>CT</sub>, and ICA, respectively. Per-vessel FFR<sub>CT</sub> was correlated to FFR (Pearson's correlation coefficient 0.82, p>0.001), with a slight underestimation of FFR<sub>CT</sub> compared with FFR. This study concluded that FFR<sub>CT</sub> has high diagnostic performance can identify patients with hemodynamically significant CAD with high sensitivity and specificity and that the addition of FFR<sub>CT</sub> to CCTA leads to a marked increase in specificity.

### *Critical appraisal*

This study has a low risk of bias for flow and timing, index and reference test. This was a large prospective study providing evidence on the diagnostic accuracy of FFR<sub>CT</sub> 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. One of the inclusion criteria was that patients had to have been referred or undergone ICA, therefore, this study was at high risk of patient selection bias. No other risks of bias and applicability concerns were identified. CIs and sample size calculations were reported.

### **Ponte 2014**

Ponte et al. (2014) compared diagnostic accuracy of CCTA and MRI for detection of functionally relevant CAD, using ICA with FFR as the reference standard in patients referred with clinical suspicion of CAD. Patients with a pre-test likelihood of CAD of 15-85% were included (n=95). Invasive FFR was measured in case of lesions with intermediate stenosis (40–90 %). Stenoses <40 % were assumed as irrelevant and stenoses >90 % were considered functionally significant. In comparison with CCTA MRI had lower sensitivity (100% vs. 88%) but higher specificity (59% vs. 89%). The authors concluded that although CCTA the anatomical is an effective rule-out test for significant CAD patients with stenosis >50 % or inconclusive results may best be investigated using a combined approach with a subsequent non-invasive functional test for confirmation of the hemodynamic significance of the disease.

### *Critical appraisal*

This study has a low risk of bias for patient selection, index and reference test. FFR was only measured in cases of lesions with intermediate stenosis (40–90 %). As a result, the study scored at high risk of bias for flow and timing, but no other risks of bias or applicability concerns were identified. 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. CIs were reported but sample size calculations were not.

### **Stuijzand 2014**

Stuijzand et al. (2014) evaluated the incremental value of transluminal attenuation gradient (TAG) over CCTA alone, using invasive FFR as the reference standard. Patients with an intermediate probability of CAD were included (n=85) and per-patient and per-vessel (n=253) analyses were conducted. FFR was measured in all major coronary arteries except for occluded or subtotal lesions. Fifty-nine lesions were graded as haemodynamically significant. Using a degree of stenosis threshold of 50%, coronary CCTA displayed an excellent sensitivity (95%) on a per-vessel and -patient basis, whereas specificity (75%) was moderate. The addition of TAG did not improve the diagnostic accuracy of CCTA. The results demonstrate that TAG does not evidently improve the diagnostic accuracy over 256-slice coronary CTA alone to diagnose hemodynamically-significant lesions.

### *Critical appraisal*

This study has a low risk of bias for patient selection, index, reference test and flow and timing. 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. CIs were reported but sample size calculations were not. The EAC considered this to be a study without any applicability concerns.

### **Neglia 2015**

Neglia et al. (2015) assessed the accuracy of several imaging techniques in patients with intermediate (20-90%) probability of CAD. A total of 475 patients were enrolled in the study and underwent CCTA, SPECT and/or ECHO. If at least one non-invasive imaging test was positive, patients also underwent ICA and FFR if stenosis was 30-70%. The analysis of the data was performed locally and in core laboratories. The diagnostic accuracy was 91% for CCTA, 70% for SPECT, and 68% for ECHO,. Within 30 days after ICA, 97 patients (20%) underwent revascularisation by PCI or CABG. Revascularisation was

performed 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. One patient had a stroke during PCI. Mean radiation exposure was  $11.2 \pm 8.1$  mSv for CTA,  $10.0 \pm 2.7$  mSv for SPECT,  $1.7 \pm 1.5$  mSv for PET, and  $12.8 \pm 14.8$  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 significant CAD as defined by ICA.

### *Critical appraisal*

This study has a low risk of bias for patient selection, index and reference test. 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. One of the limitations of this study is verification bias, as patients only underwent ICA and FFR if they had at least one positive non-invasive imaging test. After correction for verification bias, sensitivity of imaging modalities significantly decreased, whereas specificity and the relative performance were unchanged. CIs and sample size calculations were reported.

### **Danad 2013**

Danad et al. (2013) evaluated the diagnostic accuracy of CCTA in patients ( $n=120$ ) with clinically suspected CAD who underwent cardiac PET, CCTA and ICA. CCTA was performed using a hybrid PET/CT scanner (Gemini TF 64; Philips Healthcare). They included a population with a predominantly intermediate pre-test likelihood for CAD. Although 49 patients had significant coronary artery stenosis ( $>50\%$ ) at ICA only 17 had undergone an FFR measurement. FFR measurements were not routinely performed in all patients with an intermediate coronary stenosis. CIs and sample size calculation were not reported. On a per-patient basis, the sensitivity and specificity of CTCA were 100% and 34%, respectively. The authors concluded that the addition of PET in CCTA improves the diagnostic accuracy of the latter for the detecting significant CAD, mainly by improving the specificity.

### *Critical appraisal*

This study has a low risk of bias for the index and reference test and unclear risk of bias for patient selection. Although 49 patients had significant coronary artery stenosis ( $>50\%$ ) at ICA only 17 underwent an FFR measurement. FFR measurements were also not routinely performed in all patients with an

intermediate coronary stenosis. This could introduce bias associated with the reference test.

### **Kajander 2010**

Kajander et al. (2010) evaluated the diagnostic accuracy of PET and CCTA in patients with a history of stable chest pain and 30% to 70% pre-test likelihood of CAD. All patients (n=107) underwent ICA independently of the non-invasive imaging results, and the treatment decisions were based on ICA and FFR. CCTA was performed using a hybrid 64-row PET/CT scanner (GE Discovery VCT). In a per-patient analysis CCTA had 95% sensitivity and 87% specificity. In a per-vessel analysis CCTA had 75% sensitivity and 95% specificity. The authors concluded that the addition of PET in CCTA improves the diagnostic accuracy of the latter for the detecting significant CAD, by improving the sensitivity and specificity.

#### *Critical appraisal*

This study has a low risk of bias for patient selection, index and reference test. All patients underwent ICA independently of the non-invasive imaging results, and the treatment decisions were based on ICA and FFR. FFR measurements were performed for stenoses >30%. However, 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 flow and timing of the study. CIs and sample size calculations were not reported.

#### **Critical appraisal summary**

All studies clearly reported how the index test and reference test were performed, which, in most cases, was in adherence with international guidelines. In addition, pre-specified cut-offs for the comparators and invasive FFR were reported in all included studies. As a result, all of the studies scored low for risk of bias for the index and reference test.

Four of the studies (Kajander et al. 2010, Danad et al. 2013, Ponte et al. 2014, Neglia et al. 2015) were considered at high risk of bias for flow and timing. This was as a result of the fact that not all patients received the same reference standard. Instead, some patients were assessed as having functionally significant CAD based on ICA findings and not invasive FFR. KiTEC requested the opinion of expert commentators regarding the assignment of functionally significant status to a stenosis based on the ICA findings alone. According to them, 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 studies (Bernhardt et al. 2012, Norgaard et al. 2014) were considered to be at risk of bias for patient selection. This was attributed to the fact that they included patients who had already been referred for ICA. However, the majority of patients included in these studies had an intermediate pre-test likelihood of CAD, supporting the generalisability of the findings. The EAC concluded that despite the limitations outlined above, all studies contributed to the decision problem and, therefore, provided data for synthesis in the EAC's meta-analysis.

Table 6: Summary of key points from all diagnostic accuracy studies accepted by the EAC (n=7).

Study	Study design (country) Follow-up	Population	Intervention and/or comparators	Outcomes considered	Usefulness to the decision problem
<p>Bernhardt et al (2012)</p> <p>Included by the sponsor</p> <p>Included by the EAC</p>	<p>Prospective Cross sectional diagnostic accuracy</p> <p>Single centre (Germany)</p> <p>Follow up: NA</p>	<p>34 patients with stable angina and suspected or known CAD (mean PRO-CAM score = 42.7).</p> <p>Patient characteristics:</p> <p>Age: 62.0 ± 10.9</p> <p>Gender (males): 26 (76.5%)</p> <p>BMI: NA</p> <p>Hypertension: 27 (79.4%)</p> <p>Diabetes: 5 (14.7%)</p> <p>Prior MI: NA</p> <p>Prior revasc: NA</p> <p>Multi-vessel CAD: NA</p>	<p>MRI perfusion at 1.5 and 3T</p>	<p>Diagnostic accuracy</p>	<p>High.</p> <p>Study was considered of adequate methodological quality to be included in the EAC's evidence synthesis.</p>

Study	Study design (country) Follow-up	Population	Intervention and/or comparators	Outcomes considered	Usefulness to the decision problem
<p>Danad et al. (2013)</p> <p>Excluded by the sponsor</p> <p>Included by the EAC</p>	<p>Prospective cohort, single centre – Netherlands.</p> <p>Follow up: NA</p>	<p>120 patients being evaluated for CAD, (with a predominantly intermediate pre-test likelihood), referred for CTCA, CAC scoring and PET measurements on PET/CT scanner.</p> <p>Patient characteristics:</p> <p>Age: 61.0 ± 10</p> <p>Gender (males): 77 (64)</p> <p>BMI: 28 ± 4</p> <p>Hypertension: 67 (56)</p> <p>Diabetes: 25 (21)</p> <p>Prior MI: NA</p> <p>Prior revasc: NA</p>	<p>CCTA</p>	<p>Diagnostic accuracy</p>	<p>High.</p> <p>Study was considered of adequate methodological quality to be included in the EAC's evidence synthesis.</p>

Study	Study design (country) Follow-up	Population	Intervention and/or comparators	Outcomes considered	Usefulness to the decision problem
		Multi-vessel CAD: NA			
Kajander et al. (2010)  Excluded by the sponsor  Included by the EAC	Prospective cohort, single centre – Finland.  Follow up: NA	107 patients with an intermediate (30% to 70%) pre-test likelihood of CAD.  Patient characteristics:  Age: 61.0 ± 10  Gender (males): 77 (64)  BMI: 28 ± 4  Hypertension: 67 (56)  Diabetes: 25 (21)  Prior MI: NA	CCTA	Diagnostic accuracy	High.  Study was considered of adequate methodological quality to be included in the EAC's evidence synthesis.

Study	Study design (country) Follow-up	Population	Intervention and/or comparators	Outcomes considered	Usefulness to the decision problem
		Prior revasc: NA  Multi-vessel CAD: NA			
Neglia 2015  Included by the EAC	Prospective cohort, multicentre - participants were recruited from 14 European centres.  Follow up: NA	475 patients with an intermediate probability of CAD (20%–90%) based on age, sex, symptoms, and exercise ECG participated.  Patient characteristics:  Age: 60.0 ± 9  Gender (males): 291 (61%)  BMI: NA  Hypertension: 291 (61%)  Diabetes: 115 (24%)	CCTA, SPECT, ECHO	Diagnostic accuracy	High.  Study was considered of adequate methodological quality to be included in the EAC's evidence synthesis.

Study	Study design (country) Follow-up	Population	Intervention and/or comparators	Outcomes considered	Usefulness to the decision problem
		<p>Prior MI: 5 (6%)</p> <p>Prior revasc: 85 (17%) (PCI)</p> <p>Multi-vessel CAD: 35 (7%)</p>			
<p>Norgaard 2014</p> <p>[NXT trial]</p> <p>Included by the sponsor</p> <p>Accepted by the EAC</p>	<p>Prospective cohort, multicentre - 10 international centres.</p> <p>Follow up: NA</p>	<p>254 patients; 220 (87%) of which had intermediate (20%–80%) pre- test likelihood of CAD.</p> <p>Patient characteristics:</p> <p>Age: 64.0 ± 10</p> <p>Gender (males): 162 (64)</p> <p>BMI: 26±3</p> <p>Hypertension: 174 (69)</p> <p>Diabetes: 58 (23)</p>	<p>FFR<sub>CT</sub></p> <p>CCTA</p> <p>ICA</p>	<p>Diagnostic accuracy</p>	<p>High.</p> <p>Study was considered of adequate methodological quality to be included in the EAC's evidence synthesis.</p>

Study	Study design (country) Follow-up	Population	Intervention and/or comparators	Outcomes considered	Usefulness to the decision problem
		<p>Prior MI: 5 (2)</p> <p>Prior revasc: 8 (10) (PCI)</p> <p>Multi-vessel CAD: NA</p>			
<p>Ponte 2014</p> <p>Excluded by the sponsor</p> <p>Included by the EAC</p>	<p>Prospective cohort, single centre – Portugal.</p> <p>Follow up: NA</p>	<p>95 patients with intermediate pre-test probability of CAD.</p> <p>Patient characteristics:</p> <p>Age: 62.0 ± 8.1</p> <p>Gender (males): 65 (68)</p> <p>BMI: NA</p> <p>Hypertension: 71 (75)</p> <p>Diabetes: 37 (39)</p> <p>Prior MI: NA</p>	<p>CCTA</p> <p>MRI</p>	<p>Diagnostic accuracy</p>	<p>High.</p> <p>Study was considered of adequate methodological quality to be included in the EAC's evidence synthesis.</p>

Study	Study design (country) Follow-up	Population	Intervention and/or comparators	Outcomes considered	Usefulness to the decision problem
		Prior revasc: NA  Multi-vessel CAD: 18 (19)			
Stuijzand 2014  Included by the	Prospective cohort, single centre – Netherlands.  Follow up: NA	85 patients with an intermediate probability of CAD, determined in accordance with the Diamond and Forrester probabilities.	CCTA	Diagnostic accuracy	High.  Study was considered of adequate methodological quality to be included in the EAC's evidence

Study	Study design (country) Follow-up	Population	Intervention and/or comparators	Outcomes considered	Usefulness to the decision problem
sponsor  Accepted by the EAC		Patient characteristics:  Age: 57.3 ± 9.7  Gender (males): 51 (60)  BMI: 27.1 ± 4.1  Hypertension: 31 (37)  Diabetes: 13 (16)  Prior MI: NA  Prior revasc: NA  Multi-vessel CAD: NA			synthesis.

**Table 7: Diagnostic accuracy results from Sponsor and EAC accepted studies.**

Study	Index tests	Per vessel	Per patient
Norgaard 2014 [NXT trial] <b>Included by the sponsor Accepted by the EAC</b>	FFRCT ICA CCTA	N=484:  ○ Sensitivity: 84  ○ Specificity: 86  ○ NPV: 95  ○ PPV: 61  ○ Accuracy: 86	N= 254:  ○ Sensitivity: 86  ○ Specificity: 79  ○ NPV: 93  ○ PPV: 65  ○ Accuracy: 81
Stuijzand 2014 <b>Included by the sponsor Accepted by the EAC</b>	CCTA	N=253  ○ Sensitivity: 100  ○ Specificity: 65  ○ NPV: 100  ○ PPV: 65	N=85  ○ Sensitivity: 86  ○ Specificity: 79  ○ NPV: 93  ○ PPV: 65

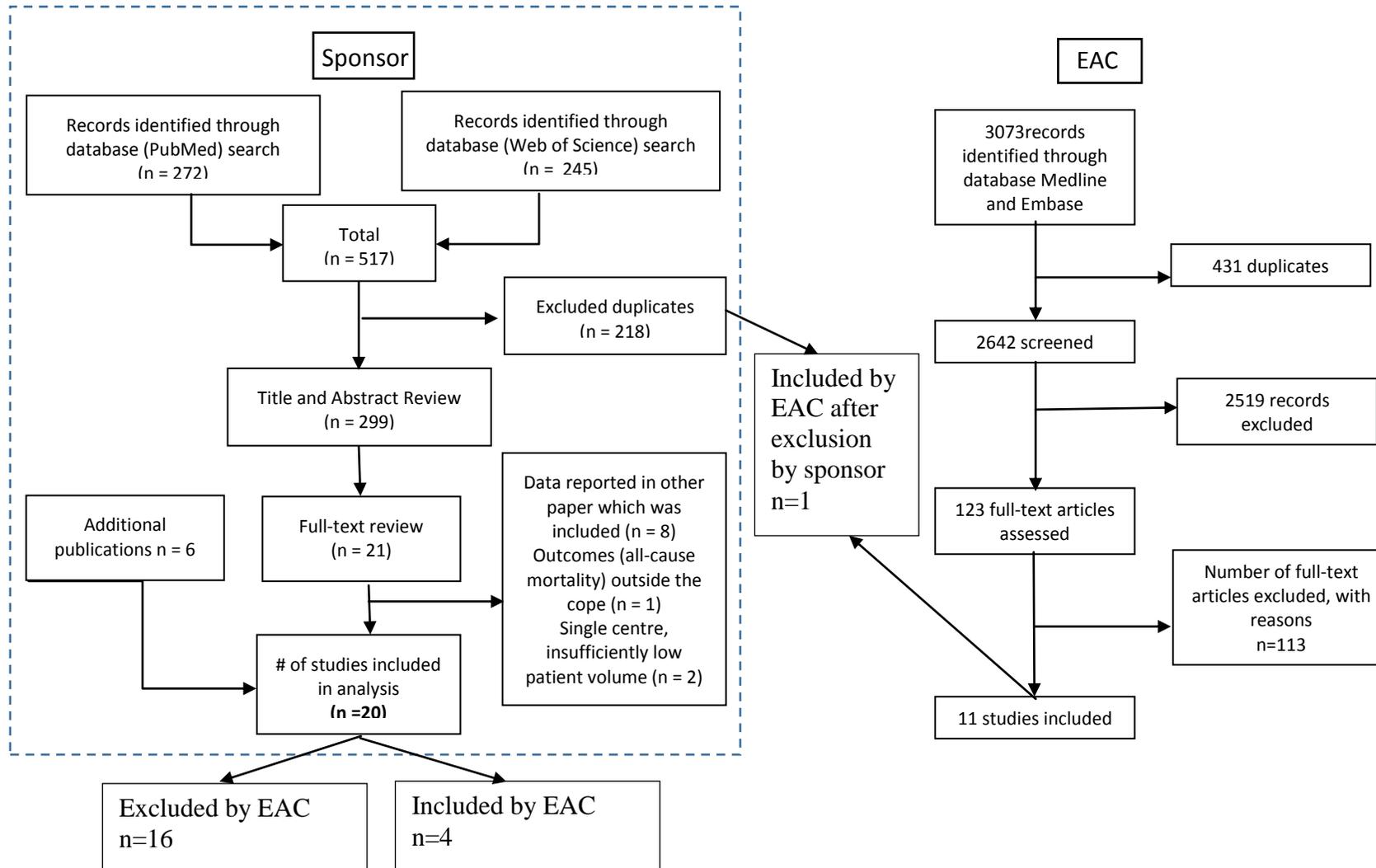
Study	Index tests	Per vessel	Per patient
Bernhardt et al 2012 <b>Included by the sponsor Accepted by the EAC</b>	MRI	<p>N=38 (of 102 total):</p> <p>At 1.5 T</p> <ul style="list-style-type: none"> <li>• Left anterior descending (LAD) (19): <ul style="list-style-type: none"> <li>○ Sensitivity: 64.8</li> <li>○ Specificity: 60.0</li> </ul> </li> <li>• Left circumflex (LCX) (8): <ul style="list-style-type: none"> <li>○ Sensitivity: 50.0</li> <li>○ Specificity: 92.3</li> </ul> </li> <li>• Right coronary artery (RCA) (11): <ul style="list-style-type: none"> <li>○ Sensitivity: 54.5</li> <li>○ Specificity: 100</li> </ul> </li> </ul> <p>At 3 T</p> <ul style="list-style-type: none"> <li>• LAD (19): <ul style="list-style-type: none"> <li>○ Sensitivity: 89.5</li> <li>○ Specificity: 100</li> </ul> </li> <li>• LCX (8):</li> </ul>	<p>N=34</p> <p>At 1.5 T</p> <ul style="list-style-type: none"> <li>○ Sensitivity: 61.9</li> <li>○ Specificity: 76.9</li> </ul> <p>At 3 T</p> <ul style="list-style-type: none"> <li>○ Sensitivity: 90.5</li> <li>○ Specificity: 100</li> </ul>

Study	Index tests	Per vessel	Per patient
		<ul style="list-style-type: none"> <li>○ Sensitivity: 75.0</li> <li>○ Specificity: 96.2</li> <li>• RCA (11): <ul style="list-style-type: none"> <li>○ Sensitivity: 90.9</li> <li>○ Specificity: 100</li> </ul> </li> </ul>	
<p>Ponte 2014  Excluded by the sponsor  Included by the EAC</p>	<p>CCTA  MRI</p>	<p><b>No per vessel analysis</b></p>	<p>For CCTA (N=95):</p> <ul style="list-style-type: none"> <li>○ Sensitivity: 100.0</li> <li>○ Specificity: 59.0</li> <li>○ NPV: 100.0</li> <li>○ PPV: 65.0</li> <li>○ Accuracy: 77.0</li> </ul> <p>For MRI (N=95):</p> <ul style="list-style-type: none"> <li>○ Sensitivity: 88.0</li> <li>○ Specificity: 89.0</li> <li>○ NPV: 91.0</li> <li>○ PPV: 86.0</li> <li>○ Accuracy: 88.0</li> </ul>

Study	Index tests	Per vessel	Per patient
Danad et al 2013 <b>Excluded by the sponsor Included by the EAC</b>	CCTA	Per vessel analysis: <ul style="list-style-type: none"> <li>○ Sensitivity: 90.0</li> <li>○ Specificity: 72.0</li> <li>○ NPV:96.0</li> <li>○ PPV:45.0</li> <li>○ Accuracy: 78.0.</li> </ul>	Per patient analysis: <ul style="list-style-type: none"> <li>○ Sensitivity: 100.0</li> <li>○ Specificity: 34.0</li> <li>○ NPV: 100.0</li> <li>○ PPV: 51.0</li> <li>○ Accuracy: 61.0</li> </ul>
Kajander et al. 2010 <b>Excluded by the sponsor Included by the EAC</b>	CCTA	N=428 <ul style="list-style-type: none"> <li>○ Sensitivity: 75.0</li> <li>○ Specificity: 95.0</li> <li>○ NPV: 94.0</li> <li>○ PPV: 76.0</li> <li>○ Accuracy: 91.0</li> </ul>	N=107 <ul style="list-style-type: none"> <li>○ Sensitivity: 95.0</li> <li>○ Specificity: 87.0</li> <li>○ NPV: 97.0</li> <li>○ PPV: 81.0</li> <li>○ Accuracy: 90.0</li> </ul>
Neglia 2015 <b>Excluded by the sponsor Included by the EAC</b>	CCTA SPECT ECHO	No per vessel analysis	For CCTA (n=475): <ul style="list-style-type: none"> <li>○ Sensitivity: 91.0</li> <li>○ Specificity: 92.0</li> <li>○ NPV: 96.0</li> <li>○ PPV: 83.0</li> </ul>

Study	Index tests	Per vessel	Per patient
			<ul style="list-style-type: none"> <li>○ Accuracy: 91.0</li> </ul> <p>For SPECT (n=293):</p> <ul style="list-style-type: none"> <li>○ Sensitivity: 73.0</li> <li>○ Specificity: 67.0</li> <li>○ NPV: 53.0</li> <li>○ PPV: 83.0</li> <li>○ Accuracy: 70.0</li> </ul> <p>For ECHO (n=261):</p> <ul style="list-style-type: none"> <li>○ Sensitivity: 45.0</li> <li>○ Specificity: 90.0</li> <li>○ NPV: 82.0</li> <li>○ PPV: 62.0</li> <li>○ Accuracy: 68.0</li> </ul>

Figure 3.2: PRISMA flow diagram showing the sponsor and EAC's search results – clinical outcomes



## Clinical Outcomes

### Douglas 2015

Douglas et al. (2015) compared health outcomes between CCTA and functional imaging (including stress ECHO). Patients (n=10,003) with a mean pre-test likelihood of CAD of 53.3%±21.4% were randomly assigned to either undergo CCTA or functional imaging as a first line diagnostic test. The composite primary end point was death, myocardial infarction, hospitalisation for unstable angina, or major procedural complication. Secondary end points included invasive cardiac catheterisation that did not show obstructive CAD and radiation exposure. Over a median follow-up period of 25 months, a primary end-point event occurred in 164 of 4996 patients in the CCTA group (3.3%) and in 151 of 5007 (3.0%) in the functional-testing group (adjusted hazard ratio, 1.04; 95% confidence interval, 0.83 to 1.29; p = 0.75). CCTA was associated with fewer catheterisations showing no obstructive CAD than functional imaging (3.4% vs. 4.3%, p = 0.02), although more patients in the CCTA group underwent catheterisation within 90 days of randomisation (12.2% vs. 8.1%). The median cumulative radiation exposure per patient was lower in the CCTA group than in the functional-testing group (10.0 mSv vs. 11.3 mSv), but 32.6% of the patients in the functional-testing group had no exposure, so the overall exposure was higher in the CCTA group (mean, 12.0 mSv vs. 10.1 mSv; P<0.001). The study concluded that in symptomatic patients with suspected CAD who required noninvasive testing, an initial strategy of CCTA was not associated with better clinical outcomes than functional testing over a median follow-up of 2 years.

#### *Critical appraisal*

This is a large prospective RCT with a median follow-up of 25 months. Study protocol is available with the publication. The study was planned so that in the event of a non-significant result in the comparison for superiority, there was sufficient power for a pre-specified non-inferiority assessment. All clinical events were evaluated by a committee unaware of the treatment assignment. Post-test management and resource utilisation can be affected by the health system's reimbursement policy and since this study was entirely based in the USA the results associated with resource utilisation might not be applicable to the NHS setting. As a result of relevance to the assessment report are only the results associated with MACE and radiation dose. By showing that there is no statistically significant difference between the rates of MACE events occurring in a diagnostic pathway that utilises CCTA vs. one that uses functional-testing it provides further evidence on the diagnostic pathway proposed by the sponsor. The effect the addition of FFR<sub>CT</sub> will have on resource utilisation and MACE cannot be inferred from this study and will

have to be based only on the results of the PLATFORM study submitted by the sponsor.

### **Hachamovitch 2012**

Hachamovitch et al. (2012) examined short-term cardiac catheterisation rates and medication changes after cardiac imaging. Patients (n=1703) were included if they had no previous history of CAD, an intermediate to high likelihood of CAD and were undergoing cardiac SPECT, PET, or 64-slice CCTA. Sample size calculation and CIs were reported for this study. 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.

#### *Critical appraisal*

This is a large prospective observational registry with a 90 day follow up, however, a sample size calculation is not reported. The authors used Bonferroni adjustment for multiple comparisons. Post-test management and resource utilisation can be affected by the health system's reimbursement policy and since this study was entirely based in the USA the results associated with resource utilisation might not be applicable to the NHS setting. As a result, conclusions on the impact of CCTA and SPECT on resource utilisation cannot be reached.

### **Cheezum 2011**

Cheezum et al. (2011) compared the clinical and cost outcomes of SPECT with CCTA in patients (n=241) without known CAD. The mean follow-up was  $30 \pm 7$  months. Sample size calculation and CIs were not reported for this study. No significant difference in the rates of major adverse cardiac events (0.4% versus 0.9%,  $p=0.54$ ) was found between CCTA (n=244) and SPECT (n=235). Of patients found to have obstructive disease on CCTA, subsequently confirmed by cardiac catheterisation (n=8), 2 underwent revascularisation. Similarly, of patients found to have ischaemia or infarction on SPECT and who had obstructive disease confirmed by cardiac catheterisation (n=6), 2 underwent revascularisation. No patients in either group were found to have confirmed cardiac death.

#### *Critical appraisal*

This is a medium sized retrospective study with a mean follow up of 30 months, which is considered adequate for the recording of MACE. Sample size calculations and CIs are not reported and according to the authors the study was under-powered to assess clinical outcomes. In addition, all patients analysed were military USA personnel, which considerably minimises the generalisability of the results and means that the population is not relevant to the decision problem. As a result, conclusions on the impact of CCTA and SPECT on resource utilisation and MACE cannot be reached.

### **Min 2008**

Min et al. (2008) examined health care expenditures and clinical outcomes of patients without known CAD who underwent CCTA (n=3331) or SPECT (n=138,043) for diagnostic coronary evaluation. Sample size calculation was not reported for this study. No 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 two groups. There were also no significant differences at 9-month follow-up in rates of CAD related hospitalisation, CAD related outpatient visits, post-test myocardial infarction, or new-onset angina between patients who underwent CCTA versus those who underwent SPECT.

#### *Critical appraisal*

This is a large retrospective study with a mean follow up of 9 months. A sample size calculation is not reported. The follow-up period is considered limited for adequate recording of MACE. The results from this study demonstrate the non-inferiority of CCTA in comparison with SPECT as the primary diagnostic modality for patients without known CAD. However, the authors used data from a large private USA database of >10 million members and the results associated with resource utilisation might not be applicable to the NHS setting. As a result conclusions on the impact of CCTA and SPECT on resource utilisation and MACE cannot be reached.

### **Min 2012a**

Min et al. (2012a) determined the near-term clinical effect and resource utilisation after CCTA compared with SPECT. Patients (n= 180) were characterised by low (12/180, 7%), intermediate (117/180, 65%), and high (51/180, 28%) likelihood of CAD. 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 underwent CCTA had increased aspirin (22% vs 8%; P = 0.04) and statin (7% vs -3.5%; P = 0.03) use, as well as increased revascularisation

(8% vs 1%; P = 0.03). Similar rates of CAD-related hospitalisation, ICA, and non-invasive cardiac imaging tests were reported for both CCTA and SPECT groups.

#### *Critical appraisal*

This is a medium sized prospective RCT. This study did not fulfil the population requirements for pre-test intermediate likelihood. As a result, only the conclusions related to radiation dose are considered relevant to this assessment report. Although sample size was calculated, this was only for the primary outcome and not the effective radiation dose. CIs were not reported. In contrast to Sahinarslan et al. (2013), who showed patients receive an effective radiation dose of 14.2mSv during CCTA, the authors report almost half the amount (7.4mSv). The effective radiation dose of CCTA was smaller than SPECT.

#### **Mouden 2014**

Mouden et al. (2014) assessed the impact and resulting clinical and prognostic implications of myocardial perfusion imaging (MPI) using SPECT. Patients (n = 282) were included if they had suspected CAD, low-to-intermediate risk of a coronary event and presented with a high CAC score ( $\geq 1,000$ ). On follow-up at 18 months invasive angiography, coronary revascularisation, nonfatal myocardial infarction and death were recorded. One patient (with non-ischaemic MPI) died from a cardiac cause, 1 patient (with ischaemic MPI) suffered a myocardial infarction and 92 patients (33 %) underwent revascularisation.

#### *Critical appraisal*

This is a retrospective study with a mean follow up of 24 months. Sample size calculations and CIs are not reported. Other limitations include the definition of obstructive CAD and the determination of the need for revascularisation based on visual assessment of the severity of coronary stenoses during ICA and not on FFR results. The results from this study showed that SPECT is a useful test for predicting coronary revascularisation. However, the population recruited had a very high CAC score ( $\geq 1,000$ ) and these are patients that are excluded from CCTA and FFR<sub>CT</sub> analysis. In addition, the data reported by Mouden is of limited utility as it did not include comparison with the intervention or any of the other comparators. As a result, conclusions on the impact of different diagnostic pathways (as outlined in CG95) on revascularisation rates and MACE cannot be reached.

## **Neglia 2015**

Neglia et al. (2015) recruited patients with symptoms of stable angina and an intermediate pre-test likelihood CAD. Patients underwent CCTA and 1 or more functional imaging tests. If  $\geq 1$  noninvasive anatomic or functional imaging study was abnormal, patients underwent ICA. Core laboratory analysis was performed in the patients who completed the protocol and for whom noninvasive and invasive images were made available and were judged as interpretable. The primary aim of the study was to compare the diagnostic accuracy of CCTA vs. non-invasive functional imaging. Secondary aims were radiation exposure, adverse events and revascularisation rates within 30 days of ICA. The diagnostic accuracy results associated with this study have been presented in the previous sections. No serious adverse events were reported during noninvasive imaging, but 4 patients had severe chest pain during CCTA. One patient had a stroke during percutaneous coronary intervention. Revascularisation rates were higher after positive CCTA (54%) than after positive SPECT (33%) or ECHO (48%).

### *Critical appraisal*

The secondary outcomes of the study addressed the scope by comparing the revascularisation rates, adverse events and radiation dose of non-invasive anatomical and functional imaging. Sample size calculations are reported, however, the study was powered for the primary outcome of diagnostic accuracy only. As a result, its usefulness in addressing the decision problem is poor.

## **Ovrehus 2013**

Ovrehus et al. (2013) evaluated the influence of CCTA as a first-line diagnostic test on treatment and prognosis in patients ( $n = 1055$ ) with low-to-intermediate risk of CAD. The patients were followed for a median of 18 months. No patients without CAD, 0.9% of patients with non-obstructive CAD, and 1.9% of patients with obstructive CAD met the primary end point (cardiovascular death and myocardial infarction,  $p = 0.008$ ). No patients without CAD, 1.5% of patients with non-obstructive CAD, and 30% patients with obstructive CAD met the secondary end point (cardiovascular death, myocardial infarction, and coronary revascularisation,  $p < 0.0001$ ).

### *Critical appraisal*

This is a large prospective study with a mean follow up of 18 months, however, sample size calculations and CIs are not reported. The follow-up period is considered limited for the adequate recording of MACE and this might have contributed to the low rate of serious cardiac events reported in

the study. Another limitation includes the definition of obstructive CAD and the determination of the need for revascularisation based on visual assessment of the severity of coronary stenoses during ICA and not on FFR results. The results from this study demonstrate the safety of using CCTA as a diagnostic gatekeeper. However, the data reported by Ovrehus is of limited utility as it does not include comparison with the intervention or any of the other comparators. As a result conclusions on the impact of different diagnostic pathways (as outlined in CG95) on revascularisation rates and MACE cannot be reached.

### **Sahinarslan 2013**

Sahinarslan et al. (2013) compared the radiation exposure between CCTA and ICA in patients with stable angina. Patients were divided into 2 groups, one of which was investigated with CCTA (n = 36) and the other with ICA (n = 36). Sample size calculation and CIs were not reported for this study. None had undergone CCTA or ICA prior to the study. The effective radiation dose was found to be higher for CCTA than for ICA ( $14.2 \pm 2.7$  vs.  $6.4 \pm 31.1$ ,  $p < 0.001$ ).

#### *Critical appraisal*

This is a small prospective study without follow up. Sample size calculations and CIs are not reported. 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. As a result, the conclusions on the impact of CCTA and ICA radiation dose on the short term radiation-induced genetic damage are of limited utility. Having said this, the study's conclusion that patients undergoing CCTA receive a higher dose than those undergoing ICA is relevant to this assessment report.

### **The PLATFORM study**

This is a post-market, prospective, controlled, multicentre, study comparing clinical outcomes, resource utilization, and quality of life of FFRCT-guided evaluation versus standard practice evaluation in patients with suspected CAD. The study comprises of 2 cohorts:

- Cohort 1: Pre-FFRCT versus practice incorporating CCTA and FFRCT
- Cohort 2: FFRCT-guided in subjects with suspected stable CAD who have no contraindications to CCTA.

The study enrolled the 2 cohorts sequentially with each site completing enrolment objectives for Cohort 1 prior to commencing Cohort 2.

The primary endpoint of the PLATFORM Study is the 90-day rate of coronary angiogram showing either:

- no obstructive disease (no stenosis  $\geq 50\%$  in a vessel  $\geq 2.0$  mm by quantitative coronary angiography (QCA), or
- no invasively-measured FFR  $\leq 0.80$  in a segment distal to a stenosis in a vessel  $\geq 2.0$  mm by QCA).

Secondary endpoints include a comparison of Major Adverse Cardiovascular Events (MACE) and MACE + vascular complications, resource utilization, quality of life (QOL) assessment (90 day, 180 day, 365 day), and cumulative radiation exposure at 365 days.

The study recruitment started in September 2013 and was completed in November 2014. In total 584 patients were enrolled, 287 in Cohort 1 and 297 in Cohort 2. In addition, the PLATFORM study recruited patients with intermediate pre-test likelihood of CAD. The sponsor has provided preliminary data from 90 days of follow-up for this study.

### *Critical appraisal*

All angiography measurements were evaluated at a dedicated core lab. Baseline characteristics were comparable for the 2 cohorts. The study is powered for the primary outcome and secondary outcome of MACE. CIs and p values are presented for all outcomes. Patient follow up has not been completed yet. The primary endpoint is at 90 days. At time of submission, 546 / 584 patients enrolled in the study have reached the 90 day time point. Of these, baseline data is fully monitored and query-free in 461 patients (79%) and 90 day data is fully monitored and query-free in 300 patients (51%). Final database lock is anticipated in early April, and the manufacturer states that any changes to the data will be supplied to NICE promptly. After consulting the clinical experts it was highlighted that 90 days is too short an interval to assess clinical outcomes such as MACE. As a result, it is considered that the evidence submitted so far by the sponsor can support the sponsor's claim regarding resource utilisation, rate of ICA and PCI, and QoL, but not MACE events.

### Radiation (FFR<sub>CT</sub>) study

This is a single centre modelling study submitted by the sponsor as an abstract, investigating the potential impact of FFR<sub>CT</sub> on radiation dose exposure and downstream clinical event rate. The clinical pathway utilising CCTA+ FFRCT as initial diagnostic test was compared with 3 clinical pathways utilising SPECT, ECHO and CCTA as initial diagnostic tests. The population included are stable, symptomatic patients (n=100) with suspected CAD with intermediate disease burden (34%), distributed in 3 risk profile categories: 50% low, 40% moderate and 10% high risk. There was no clinical follow up for this study. The primary outcome was the estimated

radiation dose and the secondary was death/MI estimates at one year after the test. Of the 4 diagnostic pathways studied, ECHO had the lowest radiation dose (5.3 mSv) but had a higher clinical event rate related to both false positive and false negative findings. The FFR<sub>CT</sub> pathway had lower cumulative radiation exposure (9.4 mSv) than SPECT (26.4 mSv) or CCTA (13.9 mSv) and also had the lowest clinical adverse event rate for low and intermediate risk patients. For high risk patients, the lowest clinical event rate was with ICA.

### *Critical appraisal*

This is a simulation/modelling study submitted as an abstract. Given the lack of detail regarding the investigators methodology, robust conclusions cannot be extracted and, consequently, its usefulness is limited.

### **Critical appraisal summary**

Based on the EAC's critical appraisal, only 1 study, the unpublished PLATFORM study submitted by the sponsor, is considered useful for assessing the impact of FFR<sub>CT</sub> on resource utilisation. One further study (Douglas et al. 2015) demonstrates that there is no statistically significant difference between the rates of MACE events occurring between a diagnostic pathway that utilise CCTA vs. one that uses functional imaging. However, the effect on resource utilisation and MACE that the addition of FFR<sub>CT</sub> into this pathway will have, cannot be inferred from this study and will, therefore, have to be based on the results of the PLATFORM study alone. Finally, 5 of the included studies (Neglia et al. 2015, Ovrehus et al., Min et al. 2012a, Douglas et al. 2015, Radiation FFR<sub>CT</sub>) provide evidence on the radiation dose from CCTA in comparison with either SPECT or ICA.

The main limitations of the studies regarded as low usefulness to the decision problem were concerns regarding:

- Applicability and generalisability of the results from studies based in the USA since post-test management and resource utilisation can be affected by the health system's reimbursement policy (Douglas et al. 2015, Hachamovitch et al. 2012, Cheezum et al. 2011, Min et al. 2008).
- Patient characteristics outside the scope (Min et al. 2012a)
- Lack of comparison with the intervention or other comparators (Mouden et al. 2014, Ovrehus et al. 2011)
- Limited follow up (Sahinarslan et al. 2013)

- Modelling study without detailed reporting of methodological aspects (Radiation FFR<sub>CT</sub>)

**Table 8: Summary of key points from all clinical outcomes studies accepted by the EAC (n=11).**

Study	Study design (country) Follow up	Population	Intervention and/or comparators	Outcomes considered	Usefulness to decision problem
<p>Douglas (2015)</p> <p>The PROMISE study</p> <p><a href="https://clinicaltrials.gov/ct2/show/study/NCT01174550">NCT01174550</a></p>	<p>Prospective RCT, multi- centre, United States.</p> <p>Follow-up: 25 months</p>	<p>10,003 symptomatic patients with suspected, but undiagnosed CAD.</p> <p>Mean pre-test likelihood of CAD = 53.4±21.4%, indicating an intermediate risk of CAD.</p> <p>Patient characteristics:</p> <p>Age: CTA group 60.7±8.3</p> <p>Functional testing group 60.9±8.3</p> <p>Gender (males): CTA</p>	<p>ECHO</p> <p>SPECT</p> <p>CCTA</p>	<p>Resource utilisation</p> <p>MACE</p> <p>Radiation dose</p>	<p>Medium.</p> <p>This study was considered to be of most relevance to informing the decision problem. By showing that there is no statistically significant difference between the rates of MACE events occurring between a diagnostic pathway that utilise CCTA vs. one that uses functional-testing it provides further evidence on the utilisation of a diagnostic pathway based on CCTA, such as the one proposed by the sponsor. The effect on resource utilisation and</p>

Study	Study design (country) Follow up	Population	Intervention and/or comparators	Outcomes considered	Usefulness to decision problem
		<p>group 2401 (48)</p> <p>Functional testing group 2332 (47)</p> <p>BMI: CTA group 30.5±6.1</p> <p>Functional testing group 30.5±6.1</p> <p>Hypertension: Both groups 30.5 ± 6.1</p> <p>Diabetes: CTA group 1065 (21.3)</p> <p>Functional testing group 1079 (21.5)</p> <p>Prior MI: NA</p>			<p>MACE the addition of FFR<sub>CT</sub> will have, cannot be extrapolated from the results of this study and will have to be based on the results of the PLATFORM study submitted by the sponsor.</p>

Study	Study design (country) Follow up	Population	Intervention and/or comparators	Outcomes considered	Usefulness to decision problem
		Prior revasc: NA  Multivessel CAD: NA			
Hachamovitch 2012  The SPARC study  <a href="https://clinicaltrials.gov/ct2/show/study/NCT00321399">NCT00321399</a>	Prospective observational registry, multicentre – North America.  Follow-up: 90 days	1,717 consecutive patients without previous CAD with an intermediate to high CAD likelihood. (CCTA 0.41±0.39, SPECT 0.38±0.29).  Patient characteristics:  Age: CCTA group 58±11.4  SPECT group 60±11.0  Gender (males):	CCTA  SPECT	Referral for ICA within 90 days of the index study  Referral to revascularization within 90 days after noninvasive procedures	Low.  Post-test management and resource utilisation can be affected by the health system's reimbursement policy and since this study was entirely based in the USA the results associated with resource utilisation might not be applicable to the NHS setting. As a result conclusions on the impact of CCTA and SPECT on resource utilisation cannot be

Study	Study design (country) Follow up	Population	Intervention and/or comparators	Outcomes considered	Usefulness to decision problem
		CCTA group 308 (52)  SPECT group 279 (49)  BMI: CCTA group 29±6  SPECT group 30±7  Hypertension: CCTA group 328 (56)  SPECT group 371 (66)  Diabetes: CTA group 94 (16)  SPECT group 173 (31)			reached.

Study	Study design (country) Follow up	Population	Intervention and/or comparators	Outcomes considered	Usefulness to decision problem
		Prior MI: NA Prior revasc: NA Multi-vessel CAD: NA			
Cheezum (2011)	Retrospective cohort, single centre - United States.  Follow-up= 30±7 months	241 consecutive patients without known CAD who underwent MPS for possible angina.  84% of patients had intermediate (10-90%) risk of CAD.  Patient characteristics:  Age: 53.0 ± 10  Gender (males): 135	CCTA  SPECT	Resource utilisation  MACE	Low  All patients analysed were USA military personnel minimising the generalisability of the results and making the population not relevant to the decision problem. In addition, resource utilisation can be affected by the health system's reimbursement policy and since this study was entirely based in the USA

Study	Study design (country) Follow up	Population	Intervention and/or comparators	Outcomes considered	Usefulness to decision problem
		(56)  BMI: 25 ± 5  Hypertension: 151 (60)  Diabetes: 28 (11)  Prior MI: NA  Prior revasc: NA  Multi-vessel CAD: NA			the results associated with resource utilisation might not be applicable to the NHS setting.
Min 2008	Retrospective cohort (registry), multicentre – United states.  Follow-up=9	Patients, without known CAD, who underwent CCTA (N = 1,938) were matched to those who underwent SPECT (N = 7,752). Patients had	CCTA  SPECT	Resource utilisation  MACE  Revascularisation rates	Low.  The authors used data from a large private USA database of >10 million members and the results associated with resource

Study	Study design (country) Follow up	Population	Intervention and/or comparators	Outcomes considered	Usefulness to decision problem
	months	<p>intermediate prevalence of traditional cardiovascular risk factors.</p> <p>Patient characteristics:</p> <p>Age: Both groups 52.1±8.7</p> <p>Gender (males): both groups 56.8%</p> <p>BMI: NA</p> <p>Hypertension: Both groups 34.8%</p> <p>Diabetes: Both groups 8.6%</p>			<p>utilisation might not be applicable to the NHS setting. As a result conclusions on the impact of CCTA and SPECT on the diagnostic pathways (as outlined in CG95) on resource utilisation and MACE cannot be reached.</p>

Study	Study design (country) Follow up	Population	Intervention and/or comparators	Outcomes considered	Usefulness to decision problem
		Prior MI: NA  Prior revasc: NA  Multi-vessel CAD: NA			
Min 2012	Prospective RCT, multicentre – United States.  Follow-up= 55±34 days	180 patients presenting with stable chest pain and suspected CAD. Patients had low (n = 38), intermediate (n = 65), and high (n = 76) pre-test likelihood of CAD.  Patient characteristics:  Age: CCTA group 55.9±10	CCTA  SPECT	Radiation dose	Medium.  This study did not fulfil the population requirements for pre-test intermediate likelihood. As a result only the conclusions related to radiation dose are considered relevant to this assessment report.

Study	Study design (country) Follow up	Population	Intervention and/or comparators	Outcomes considered	Usefulness to decision problem
		<p>SPECT group 58.9±9.5</p> <p>Gender (males): CCTA group 53 (58)</p> <p>SPECT group 38 (43)</p> <p>BMI: NA</p> <p>Hypertension: Both groups NA</p> <p>Diabetes: CCTA group 21(23)</p> <p>SPECT group 19(21)</p> <p>Prior MI: NA</p> <p>Prior revasc: NA</p> <p>Multi-vessel CAD: NA</p>			

Study	Study design (country) Follow up	Population	Intervention and/or comparators	Outcomes considered	Usefulness to decision problem
Mouden 2014	<p>Retrospective cohort, single centre – Germany.</p> <p>Follow-up: Mean=24 months</p>	<p>282 patients without a history of CAD with suspected stable angina referred for MPI (low (12%)/intermediate (88%) risk of CAD).</p> <p>Patient characteristics:</p> <p>Age: 69±9</p> <p>Gender (males): 63%</p> <p>BMI: NA</p> <p>Hypertension:71%</p> <p>Diabetes: 28%</p>	SPECT	Revascularisation rates	<p>Low.</p> <p>The data reported by Mouden is of limited usefulness as it did not include comparison with the intervention or any of the other comparators. As a result, conclusions on the impact of different diagnostic pathways (as outlined in CG95) on revascularisation rates and MACE cannot be reached. Therefore, the results should be interpreted with caution.</p>

Study	Study design (country) Follow up	Population	Intervention and/or comparators	Outcomes considered	Usefulness to decision problem
		Prior MI: NA  Prior revasc: NA  Multi-vessel CAD: NA			
Ovrehus 2011	Prospective registry, single centre – Denmark.  Follow-up: 18 months	1055 patients with suspected stable angina pectoris and a low (n=277, 24%) to intermediate (n=833, 72%) pre-test likelihood of CAD.  Patient characteristics:  Age: 56±11  Gender (males): 520 (45)	CCTA	Resource utilisation  MACE  Radiation dose	Low.  The data reported by this study is of limited utility as it did not include comparison with the intervention or any of the other comparators. As a result conclusions on the impact of different diagnostic pathways (as outlined in CG95) on revascularisation rates and MACE cannot be reached.

Study	Study design (country) Follow up	Population	Intervention and/or comparators	Outcomes considered	Usefulness to decision problem
		BMI: 26±4 Hypertension: 476 (41) Diabetes: 69 (6) Prior MI: NA Prior revasc: NA Multi-vessel CAD: NA			
Sahinarslan 2013	Prospective cohort, single centre – Turkey. Follow-up: None	72 patients presenting with stable angina, who had not previously undergone ICA or CCTA.  Patient	CCTA, ICA	Radiation dose	Low.  Although a biological measure of radiation dose damage was analysed this was done immediately after the procedure not allowing the assessment of more

Study	Study design (country) Follow up	Population	Intervention and/or comparators	Outcomes considered	Usefulness to decision problem
		characteristics:  Age: CCTA group 54±9  ICA group 57±8  Gender (males): CCTA group 56%  ICA group 56%  BMI: CCTA group 28.8±4  ICA group 28.3±4  Hypertension: CCTA group 58%  ICA group 58%  Diabetes: CCTA			relevant outcomes of radiation exposure. As a result, the conclusions on the impact of CCTA and ICA radiation dose on the short term radiation-induced genetic damage are of limited utility. On the contrary of relevance to this assessment report is the results associated with the radiation dose in patients undergoing CCTA and ICA.

Study	Study design (country) Follow up	Population	Intervention and/or comparators	Outcomes considered	Usefulness to decision problem
		group 14% ICA group 28% Prior MI: NA Prior revasc: NA Multi-vessel CAD: NA			

Study	Study design (country) Follow up	Population	Intervention and/or comparators	Outcomes considered	Usefulness to decision problem
Neglia 2015 <a href="#">NCT00979199</a>	Prospective cohort, multicentre - participants were recruited from 14 European centres.  Follow-up: 30 days	475 Patients with an intermediate probability of CAD (20%–90%) based on age, sex, symptoms, and exercise ECG (when available) participated. Patient characteristics: Age: 60.0 ± 9 Gender (males): 291 (61) BMI: NA Hypertension: 291 (61) Diabetes: 115 (24) Prior MI: 5 (6) Prior revasc: 85 (17) (PCI) Multi-vessel CAD: 35 (7)	CCTA  SPECT  ECHO	Adverse events  Revascularisation rates  Radiation dose	Low.  The secondary outcomes of the study addressed the scope by comparing the revascularisation rates, adverse events and radiation dose of non-invasive anatomical and functional imaging. However, the study was powered for the primary outcome of diagnostic accuracy.

Study	Study design (country) Follow up	Population	Intervention and/or comparators	Outcomes considered	Usefulness to decision problem
PLATFORM	<p>Post-market, prospective, controlled, sequential cohort, multicentre, study</p> <p>Follow-up: 90, 180 and 365 days</p>	<p>Patients at intermediate likelihood of obstructive CAD (20% - 80%)</p> <p>Group 1A and 2A: Patients referred for noninvasive test for suspected CAD</p> <p>Group 1B and 2B: Patients referred for ICA</p> <p>In total 584 patients were enrolled, 287 in Cohort 1 and 297 in Cohort 2. Baseline characteristics were similar between the 2 cohorts.</p>	<p>FFR<sub>CT</sub> vs standard of care</p> <p>88</p>	<p>Primary: 90-day rate of coronary angiogram showing no obstructive disease</p> <p>Secondary: (MACE) and MACE + vascular complications, all cause death, non-fatal MI, resource utilization, quality of life (QOL) assessment (90 day, 180 day, 365 day), and cumulative radiation exposure at 365 days.</p>	<p>High.</p> <p>The sponsor has provided preliminary data from 90 days of follow-up for this study.</p> <p>The study is powered for the primary outcome and secondary outcome of MACE. After consulting the experts it was highlighted that 90 days is too short interval to assess MACE.</p>

Study	Study design (country) Follow up	Population	Intervention and/or comparators	Outcomes considered	Usefulness to decision problem
Radiation FFR <sub>CT</sub>	Modelling study  (Canada)  No follow-up	Symptomatic (n=200) patients with stable angina and suspected CAD with intermediate disease burden (34%), distributed in 3 risk profile categories: 50% low, 40% moderate and 10% high risk	Intervention (n = 100): clinical pathway utilizing CCTA+ FFR <sub>CT</sub> as initial diagnostic study  Comparator(s) (n = 100): 3 clinical pathways utilizing SPECT, ECHO and CCTA as initial diagnostic study	Radiation dose  Death/MI estimates at 1 year	Low.  This is a simulation/modelling study submitted as an abstract. Given the lack of detail regarding the investigators methodology, robust conclusions cannot be extracted.

**Table 9: Clinical outcomes results from Sponsor and EAC accepted studies.**

Study	Index test(s)	Resource utilisation	MACE/Adverse events	Revascularisation rates	Radiation dose	QOL
Douglas (2015) (Douglas et al. 2015) The PROMISE study <a href="https://clinicaltrials.gov/ct2/show/study/NCT01174550">NCT01174550</a>	CCTA SPECT ECHO	Over a median follow-up period of 25 months negative CCTA was associated with less ICAs showing no obstructive CAD than was functional testing (3.4% vs. 4.3%, P = 0.02), although more patients in the CCTA group underwent catheterisation within 90 days of randomisation (12.2% vs.	There was no statistically significant difference between the rate of primary end-point events occurring in the CCTA group and the functional-testing group (3.3% vs. 3.0%, P = 0.75). Primary end points were: death, myocardial infarction, hospitalisation for unstable angina,	NA	The median cumulative radiation exposure per patient was lower in the CCTA group than in the functional-testing group (10.0 mSv vs. 11.3 mSv), but 32.6% of the patients in the functional-testing group had no exposure, so the overall exposure was higher in the CCTA group (mean, 12.0 mSv vs. 10.1 mSv;	NA

Study	Index test(s)	Resource utilisation	MACE/Adverse events	Revascularisation rates	Radiation dose	QOL
		8.1%).	or major procedural complication.		P<0.001).	
Hachamovitch 2012 (Hachamovitch et al. 2012)  The SPARC study <a href="https://clinicaltrials.gov/ct2/show/study/NCT00321399">NCT00321399</a>	CCTA  SPECT	Risk-adjusted analyses revealed that, compared with SPECT, 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-	NA	NA	NA	NA

Study	Index test(s)	Resource utilisation	MACE/Adverse events	Revascularisation rates	Radiation dose	QOL
		obstructive and mildly abnormal test results.				
Cheezum (2011) (Cheezum et al. 2011)	CCTA SPECT	During a mean follow-up of 30±7 months no difference was found between CCTA and SPECT in per-patient composite rates of downstream clinical resource utilisation, 24.6% versus 27.7% (p=0.44).  After excluding patients with true positive	There was no difference in the rates of MACEs in patients undergoing CCTA and SPECT (0.4% vs. 0.9%; p =0.54).	NA	NA	NA

Study	Index test(s)	Resource utilisation	MACE/Adverse events	Revascularisation rates	Radiation dose	QOL
		<p>initial imaging confirmed by ICA, CCTA patients had lower utilisation of invasive angiography (3.3% vs. 8.1%; <math>p = 0.02</math>) and a non-statistically significant trend towards reduced downstream cardiac testing (11.5% vs 17.0%; <math>P=0.08</math>).</p>				

Study	Index test(s)	Resource utilisation	MACE/Adverse events	Revascularisation rates	Radiation dose	QOL
Min 2008 (Min et al. 2008)	CCTA  SPECT	No significant differences were found in CAD medication use between patients who underwent CCTA and those who underwent SPECT.	No differences were observed for rates of adverse cardiovascular events, including CAD hospitalisations (4.2% vs. 4.1%, p = NS), CAD outpatient visits (17.4% vs. 13.3%, p = NS), MI (0.4% vs 0.6%, p = NS), and new-onset angina (3.0% vs. 3.5%, p = NS) between patients who underwent CCTA and those	No significant differences existed between patients who underwent CCTA and those who underwent SPECT in rates of percutaneous transluminal coronary angioplasty alone (0.1% vs. 0.1%, p=NS), intracoronary stent placement (1.4% vs. 1.0%, p=NS), any percutaneous intervention (1.4% vs. 1.1%,	NA	NA

Study	Index test(s)	Resource utilisation	MACE/Adverse events	Revascularisation rates	Radiation dose	QOL
			who underwent SPECT.	p=NS), coronary artery bypass surgery (0.6% vs. 0.5%, p=NS), or any coronary artery revascularisation (2.1% vs. 1.5%, p=NS)		

Study	Index test(s)	Resource utilisation	MACE/Adverse events	Revascularisation rates	Radiation dose	QOL
Min 2012 (Min et al. 2012a)	CCTA  SPECT	NA	NA	NA	Compared to SPECT the CCTA group had a significantly lower total estimated effective radiation dose (7.4 mSv [IQR, 5.0–14.0 mSv] vs. 13.3 mSv [IQR, 13.1–38.0 mSv]; $P < 0.0001$ ) with no difference in induced radiation.	NA
Mouden 2014 (Mouden et al.	SPECT	NA	NA	On a mean follow-up of 24 months: In	NA	NA

Study	Index test(s)	Resource utilisation	MACE/Adverse events	Revascularisation rates	Radiation dose	QOL
2014)				<p>patients with a coronary artery calcium score <math>\geq 1,000</math>, SPECT-related ischaemia is observed in approximately 30% of the cases and is a strong predictor of coronary revascularisation (odds ratio 13.1; 95 % CI 7.1–24.3; <math>p &lt; 0.001</math>). However, non-ischaemic SPECT does not exclude revascularisation, and patients with persisting</p>		

Study	Index test(s)	Resource utilisation	MACE/Adverse events	Revascularisation rates	Radiation dose	QOL
				complaints should be considered for invasive angiography.		
Ovrehus 2011 (Ovrehus et al. 2011)	CCTA	The patients were followed for a median of 18 months.  Additional testing (mainly ICA) was performed in 2% of patients with normal CCTA findings, in 7% with non-obstructive and in 82% of patients with	No patients without CAD, 0.9% of patients with non-obstructive CAD, and 1.9% of patients with obstructive CAD met the primary end point (cardiovascular death and myocardial infarction, p = 0.008).	NA	The mean±SD estimated radiation dose was 1.6±1 mSv for the calcium score scans and 6.6±4 mSv for the CCTA studies.	NA

Study	Index test(s)	Resource utilisation	MACE/Adverse events	Revascularisation rates	Radiation dose	QOL
		obstructive CAD.	No patients without CAD, 1.5% of patients with non-obstructive CAD, and 30% patients with obstructive CAD met the secondary end point (cardiovascular death, myocardial infarction, and coronary revascularisation, $p < 0.0001$ ).			
Sahinarslan 2013 (Sahinarslan	CCTA ICA	NA	NA	NA	The mean $\pm$ SD effective dose was higher in CCTA tests than	NA

Study	Index test(s)	Resource utilisation	MACE/Adverse events	Revascularisation rates	Radiation dose	QOL
et al. 2013)					<p>in ICA tests (<math>14.2 \pm 2.7</math> vs. <math>6.4 \pm 3.1</math>, <math>p &lt; 0.001</math>). The sister chromatid exchange (SCE) level from the blood samples increased significantly after both angiography methods (<math>p &lt; 0.001</math>). When the change in SCE after angiography was compared, no significant difference among the groups was observed (<math>2.73 \pm 1.6</math> vs.</p>	

Study	Index test(s)	Resource utilisation	MACE/Adverse events	Revascularisation rates	Radiation dose	QOL
					2.54±1.22, p=NS)	
Neglia 2015 (Neglia et al. 2015)	CCTA SPECT ECHO	NA	No serious adverse events were reported during non-invasive imaging, but 4 patients had severe chest pain during CCTA. One patient had a stroke during PCI.	Within 30 days of ICA, 97 patients (20%), corresponding to 69% of patients with significant coronary stenoses, underwent myocardial revascularisation by PCI (17% of patients) or coronary artery bypass grafting (3% of patients). Revascularisation was performed in 54% of patients	Mean±SD radiation exposure was 11.2±8.1 mSv for CCTA, 10.0±2.7 mSv for SPECT, 1.7±1.5 mSv for PET, and 12.8±14.8 mSv for ICA, including revascularisation when performed.	NA

Study	Index test(s)	Resource utilisation	MACE/Adverse events	Revascularisation rates	Radiation dose	QOL
				with positive CCTA, 37% of patients with positive MPI (33% SPECT and 60% PET), and 50% of patients with positive wall motion index (48% ECHO and 56% MRI).		
PLATFORM	FFRCT ICA	Among patients referred originally for ICA, 65% less underwent ICA in the group receiving CCTA and FFR <sub>CT</sub> compared to the rate undergoing	MACE event rates at 90 days were < 1% and were similar between the two groups.  Cohort 1: 0.4%, 95%CI: 0.01-	PCI rates were similar between the groups, indicating that in a pathway using CCTA and FFR <sub>CT</sub> , patients with functionally important CAD were not being	NA	QOL assessed via two different instruments (EQ5DL and SAQ) showed greater improvement in the group

Study	Index test(s)	Resource utilisation	MACE/Adverse events	Revascularisation rates	Radiation dose	QOL
		<p>standard management (Cohort 1B: 75%, 95% CI: 69-81% - Cohort 2B: 11%, 95%CI: 7-16%, p&lt;0.0001)</p> <p>The rate of ICA being performed only to discover no obstructive CAD (defined by a QCA core lab) fell from 75% in the standard care group (consistent with the literature) to 11% in the group managed</p>	<p>2.0%</p> <p>Cohort 2: 0.7%, 95%CI: 0.08-2.0%, p=NS</p> <p>MACE+ vascular complications:</p> <p>Cohort 1 (Current pathway): 1.1%, 95% CI: 0.2-3.0%</p> <p>Cohort 2 (Patients managed first with CCTA and for stenoses &gt; 30%, FFR<sub>CT</sub>): 2.4%, 95%CI: 1.0-5.0%, p=NS</p>	<p>under-diagnosed despite the lower rate of invasive angiography.</p> <p>Cohort 1B: 23% (42/180) vs. Cohort 2B: 24% (44/184), p=NS</p> <p>CABD rates:</p> <p>Cohort 1B: 9% (16/180)</p> <p>Cohort 2B: 4% (7/184)</p>		<p>managed via CCTA and FFR<sub>CT</sub> than in the control group managed according to standard care.</p> <p>SAQ Cohort 1: 14.0±18.9</p> <p>SAQ Cohort 2: 18.3±17.5</p> <p>EQ5DL Cohort 1: 0.04±0.13</p> <p>EQ5DL Cohort 2:</p>

Study	Index test(s)	Resource utilisation	MACE/Adverse events	Revascularisation rates	Radiation dose	QOL
		with knowledge of CCTA and FFR <sub>CT</sub> data.				0.070.13  SAQ Cohort 1 vs Cohort 2: p=0.009  EQ5DL Cohort 1 vs Cohort 2: p=0.017
Radiation FFRCT	FFRCT	NA	Anticipated mortality and MI rates in 12 months: <ul style="list-style-type: none"> <li>• FFR<sub>CT</sub> pathway 2.33%</li> <li>• SPECT pathway</li> </ul>	NA	Average radiation dose per patient: <ul style="list-style-type: none"> <li>• FFR<sub>CT</sub> pathway 9.4 mSv;</li> <li>• SPECT pathway 26.4 mSv;</li> </ul>	NA

Study	Index test(s)	Resource utilisation	MACE/Adverse events	Revascularisation rates	Radiation dose	QOL
			<p>2.6%</p> <ul style="list-style-type: none"> <li>• ECHO pathway 2.75%</li> <li>• CCTA pathway 2.38%</li> </ul> <p>The FFR<sub>CT</sub> pathway yielded the fewest clinical events for low and intermediate risk patients. However, for high risk patients, the lowest complication rate was in the ICA group.</p>		<ul style="list-style-type: none"> <li>• ECHO pathway 5.2 mSv;</li> <li>• CCTA pathway 13.9 mSv</li> </ul> <p>While the average amount of radiation received increased with increasing disease likelihood, there was no change in relative pathway performance. ECHO resulted in lowest level of radiation, while</p>	

Study	Index test(s)	Resource utilisation	MACE/Adverse events	Revascularisation rates	Radiation dose	QOL
					SPECT as first line test resulted in the highest level of radiation.	

## **Evidence synthesis and meta-analysis performed by the EAC**

The EAC conducted a new meta-analysis with the diagnostic accuracy results retrieved from the 7 studies listed in Table 6. The included studies were reviewed and population outcome data were extracted (Table 7 and Table 10). Where actual frequencies of TP, TN, FP, FN were not reported in the papers they were calculated using available study summary data (sensitivity, specificity, PPV, NPV, total number of patients/vessels). Random effects meta-analyses were used to calculate all pooled proportions for sensitivity, specificity, PLR, NLR and DOR. The meta-analyses were conducted using the Meta-Disc program (Zamora et al. 2006). For studies with a 0 value in any cell of the 2x2 table, 0.5 is added to all cells of that table.

z-tests were used to compare sensitivities and specificities. The significance test results should be treated as approximate, as they assume a normal distribution for these measures, and standard deviations were derived from the confidence intervals, which introduces a further degree of approximation. Further, the z-test assumes independent data, but the datasets include a mixture of paired data (where results for several comparators are included per study) and independent data. Further, the z-test assumes independent data, but the datasets include a mixture of paired data (where results for several comparators are included per study) and independent data.

Pooled values were calculated for CCTA and MRI for patient-level data, and for CCTA only for vessel-level data (table x). For the remaining comparators, where only a single study was available, confidence intervals were calculated using the Stata program for sensitivity and specificity (StataCorp 2013), and the Confidence Interval Analysis program for likelihood ratios and diagnostic odds ratio (Gardner MJ 1992).

**Table 10: '2x2 table' data underpinning the Heartflow diagnostic accuracy analysis**

<b>Per patient analysis</b>						
<b>Author</b>	<b>Intervention</b>	<b>TP</b>	<b>FP</b>	<b>FN</b>	<b>TN</b>	<b>N</b>
Danad 2013	CCTA	49	47	0	24	120
Kajander 2011	CCTA	38	9	2	58	107
Neglia 2015	CCTA	130	26	13	306	475
Norgaard 2014	CCTA	75	115	5	59	254
Ponte 2014	CCTA	41	22	0	32	95
Stuijzand 2014	CCTA	34	18	0	33	85
Neglia 2015	ECHO	31	19	38	172	260
Norgaard 2014	FFRCT	68	37	11	138	254
Norgaard 2014	ICA	51	30	29	144	254
Bernhardt, 2012	MRI	19	0	2	13	34
Ponte 2014	MRI	36	6	5	48	95
Neglia 2015	SPECT	72	64	27	130	293
<b>Per vessel analysis</b>						
<b>Author</b>	<b>Intervention</b>	<b>TP</b>	<b>FP</b>	<b>FN</b>	<b>TN</b>	<b>N</b>
Danad 2013	CCTA	88	107	10	275	480
Kajander 2011	CCTA	60	19	20	329	428
Norgaard 2014	CCTA	83	154	17	230	484
Stuijzand 2014	CCTA	57	48	3	145	253
Norgaard 2014	FFRCT	85	54	16	329	484
Norgaard 2014	ICA	55	38	45	346	484
Bernhardt, 2012	MRI	33	1	5	63	102

Results for FFR<sub>CT</sub> are presented for a single study (Norgaard et al. 2014). Compared with the gold standard of invasive FFR, FFR<sub>CT</sub> had a sensitivity of 86.1% (95% CI 76.5% - 92.8%) and a specificity of 78.9% (72.1% - 84.7%). A comparison of the diagnostic accuracy of FFR<sub>CT</sub> with five comparators is presented in Table 11.

- Compared with the diagnostic accuracy of CCTA vs. invasive FFR, obtained from a meta-analysis of six studies, FFR<sub>CT</sub> had lower sensitivity but higher specificity, for patient-based analysis. For the vessel-based analysis (based on four CCTA studies), FFR<sub>CT</sub> had a similar sensitivity and higher specificity.
- Compared with ECHO, FFR<sub>CT</sub> had higher sensitivity but lower specificity, for patient-based analysis. Vessel-based analysis was not available for ECHO.

- Compared with ICA, FFR<sub>CT</sub> had higher sensitivity and a similar specificity, for patient-based analysis. For the vessel-based analysis, FFR<sub>CT</sub> also had a higher sensitivity and a similar specificity.
- Compared with the diagnostic accuracy of MRI, obtained from a meta-analysis of two studies, FFR<sub>CT</sub> had a similar sensitivity and a lower specificity. For vessel-based analysis (single MRI study), FFR<sub>CT</sub> also had a similar sensitivity and a lower specificity.
- Compared with SPECT, FFR<sub>CT</sub> had higher sensitivity and specificity, for patient-based analysis. Vessel-based analysis was not available for SPECT.

Table 11 indicates which of these differences were statistically significant, before and after adjustment for multiple testing. However these significance test results should be treated as approximate, for the reasons described above. Note that a non-significant result does not imply that there is no true difference between two sensitivities or specificities, only that a difference cannot be demonstrated with these data.

Table 11: Results from meta-analyses, and individual studies (where only one study was included for a given comparator)

**Table 11: Results from meta-analyses, and individual studies (where only one study was included for a given comparator)**

Index test	N	Sensitivity (95% CI)	Sig vs FFRct?	Sig after adj?	Specificity (95% CI)	Sig vs FFRct?	Sig after adj?	PLR (95% CI)	NLR (95% CI)	DOR (95% CI)
<b>Patient-based analysis</b>										
<b>CCTA*</b> (6 studies)	1136	0.948 0.921 - 0.968	*		0.684 0.649 - 0.717	*	*	3.18 1.56 - 6.47	0.093 0.054 - 0.159	59.0 15.4 - 227
<b>ECHO</b> (Neglia, 2015)	261	0.449 0.329 - 0.574	*	*	0.901 0.849 - 0.939	*	*	4.52 2.74 - 7.45	0.612 0.492 - 0.761	7.39 3.78 - 14.4
<b>ICA</b> (Norgaard, 2014)	254	0.638 0.522 - 0.742	*	*	0.828 0.763 - 0.881			3.70 2.57 - 5.33	0.438 0.325 - 0.590	8.44 4.62 - 15.4
<b>FFRct</b> (Norgaard, 2014)	254	0.861 0.765 - 0.928			0.789 0.721 - 0.847			4.07 3.02 - 5.49	0.177 0.102 - 0.307	23.1 11.1 - 48.0
<b>MRI*</b> (2 studies)	129	0.887 0.781 - 0.953			0.910 0.815 - 0.966	*		8.59 4.12 - 17.9	0.130 0.066 - 0.256	69.2 21.5 - 223
<b>SPECT</b> (Neglia, 2015)	293	0.727 0.629 - 0.812	*		0.670 0.599 - 0.736	*		2.20 1.74 - 2.79	0.407 0.291 - 0.570	5.42 3.18 - 9.24
<b>Vessel-based analysis</b>										
<b>CCTA*</b> (4 studies)	1645	0.852 0.810 - 0.888			0.749 0.725 - 0.772	*	*	4.15 2.38 - 7.23	0.192 0.117 - 0.316	25.1 9.05 - 69.6

<b>ICA</b> <i>(Norgaard, 2014)</i>	484	0.550 0.447 - 0.650	*	*	0.901 0.867 - 0.929			5.56 3.92 - 7.89	0.499 0.401 - 0.622	11.1 6.64 - 18.7
<b>FFRct</b> <i>(Norgaard, 2014)</i>	484	0.842 0.756 - 0.907			0.859 0.820 - 0.892			5.97 4.60 - 7.75	0.184 0.117 - 0.290	32.4 17.6 - 59.4
<b>MRI</b> <i>(Bernhardt, 2012)</i>	102	0.868 0.719 - 0.956			0.984 0.916 - 1.000	*	*	55.6 7.92 - 390	0.134 0.059 - 0.303	416 46.6 - 3708

\*Results of meta-analysis

### **3.10 Conclusions on the clinical evidence**

The EAC considers that the sponsor's systematic review was comprehensive; however, the majority of studies included by the sponsor did not fit the scope set by NICE and should have been excluded from the review. From the 28 studies on diagnostic accuracy and 20 studies on clinical outcomes included by the sponsor, the EAC agreed with the inclusion of 3 and 4 studies, respectively. This reduced the available evidence submitted by the sponsor substantially.

The evidence provided covered all of the outcomes listed in the scope. The sponsor's interpretation of the available evidence was reasonable, and provided a fair assessment of the strengths and weaknesses. However, following the aforementioned exclusion of the majority of the sponsor's included studies; most of the outcomes were disregarded.

The sponsor performed a comprehensive and thorough meta-analysis of diagnostic accuracy studies. However, the inclusion criteria for selecting these studies were focused on eliminating the bias related to the reference test. As a result, most of the studies included in the meta-analysis were outside the scope. In addition, the sponsor submitted only patient-level results in their original submission. After consulting the expert advisers it was concluded that both patient and vessel-based estimates of diagnostic accuracy are important as vessel-based results will influence the further decision on the need for revascularisation. The EAC repeated the systematic review and performed a new meta-analysis. The EAC's systematic review identified 7 diagnostic accuracy studies, of which 3 had been included by the sponsor, and 4 had been excluded by the sponsor. The EAC concluded that despite the limitations associated with not all patients receiving the same reference test in some of the studies, all could contribute to the decision problem and provide data for synthesis in the EAC's meta-analysis.

The meta-analysis of the comparators to invasive FFR was carried out by the EAC to provide estimates on diagnostic accuracy with 95% confidence intervals. The pooled estimates of sensitivity and specificity were the parameters required for the economic modelling and were provided for the CCTA (6 studies) and MRI (2 studies). For each of the other comparators, data from only 1 study was available.

Compared with the gold standard of invasive FFR, FFR<sub>CT</sub> had a sensitivity of 86.1% (95% CI 76.5% - 92.8%) and a specificity of 78.9% (72.1% - 84.7%). Compared with CCTA, FFR<sub>CT</sub> had lower sensitivity but higher specificity for patient-based analysis. For the vessel-based analysis (based on four CCTA

studies), FFR<sub>CT</sub> had a similar sensitivity and higher specificity. Compared with ECHO, FFR<sub>CT</sub> had higher sensitivity but lower specificity for patient-based analysis. Vessel-based analysis was not available for ECHO. Compared with ICA, FFR<sub>CT</sub> had higher sensitivity and a similar specificity for patient-based analysis. For the vessel-based analysis, FFR<sub>CT</sub> also had a higher sensitivity and a similar specificity. Compared with MRI, FFR<sub>CT</sub> had a similar sensitivity and a lower specificity. For vessel-based analysis, FFR<sub>CT</sub> also had a similar sensitivity and a lower specificity. Compared with SPECT, FFR<sub>CT</sub> had higher sensitivity and specificity for patient-based analysis. Vessel-based analysis was not available for SPECT.

The EAC notes that caution must be taken when interpreting the results of the meta-analyses, as no adjustment was made for confounding variables such as patient characteristics. This is due to the lack of detailed information available in the included studies. In addition, since some of the studies included by the EAC did not measure invasive FFR in all the vessels, irrespective of degree of coronary stenosis, it is possible that the sensitivity and specificity values reported in the primary studies, especially at the vessel level, could have been affected.

Based on the EAC's critical appraisal, only 1 study, the unpublished PLATFORM study submitted by the sponsor, is considered useful for assessing the impact of FFR<sub>CT</sub> on resource utilisation. It was reported that among patients referred for ICA the diagnostic pathway utilising FFR<sub>CT</sub> was superior to standard of care, resulting in a drop of 65% in the rate of actual ICA being necessary. In addition, the FFR<sub>CT</sub> pathway was superior than standard pathway in regards to the rate of ICA being performed only to discover no obstructive CAD (75% in the standard care group (consistent with the literature) to 11% in the group managed with knowledge of CCTA and FFR<sub>CT</sub> data. It should be noted here that the sponsor has not provided a breakdown of the relevant percentages of diagnostic modalities involved in the description of the standard pathway.

Although the PLATFORM study reported additionally data on MACE (MACE event rates at 90 days were < 1% and were similar between the two groups) it was considered by the expert commentators that a 90-day time frame is not sufficient to adequately assess whether FFR<sub>CT</sub> has any impact on major adverse coronary events. This time frame is too short for a meaningful comparison since the event rate would be expected to be small within that time period and that 365 days of follow-up or more are necessary to detect differences in clinical outcomes in this cohort. One further study (Douglas et al. 2015) demonstrates that there is no statistically significant difference between the rates of MACE events occurring between a diagnostic pathway that utilise CCTA vs. functional-testing and supports a diagnostic pathway

based on CCTA as proposed by the sponsor. However, the effect the addition of FFR<sub>CT</sub> on this pathway will have on resource utilisation and MACE, cannot be inferred from this study and will have to be based on the results of the PLATFORM study submitted by the sponsor with the limitations highlighted above.

Regarding revascularisation rates the PLATFORM study showed that PCI rates were similar between the groups, indicating that in a diagnostic pathway using CCTA and FFR<sub>CT</sub> is non-inferior to its comparators and that patients with functionally important CAD are not being underdiagnosed despite the lower rates of ICA performed in this cohort. The FFR<sub>CT</sub> pathway also resulted in better QOL than in the control group managed according to standard care.

Finally the evidence on radiation dose was conflicting with some studies showing higher dose with CCTA than with SPECT and ICA and others lower. Since the radiation dose will vary significantly depending on the scanning acquisition parameters used firm conclusions on the differences between CCTA and its comparators cannot be drawn from the available evidence.

## **4 Economic evidence**

### **4.1 *Published economic evidence***

#### **Critique of the sponsor's search strategy**

The sponsor submitted a search strategy designed to retrieve relevant health economics studies from published and unpublished literature. The sponsor searched PubMed and Web of Science for studies published in English from 1985 to 2015. The search combined terms related to the population (obstructive, stable, or suspected CAD), the intervention (non-invasive FFR) or the comparator (CCTA, ICA, nuclear myocardial perfusion, magnetic resonance perfusion, MPS, SPECT, stress perfusion, stress myocardial perfusion, or ECHO) with economics terms.

In total, 159 publications were identified for title and abstract review. Based on inclusion and exclusion criteria, 22 were retrieved for further full text review and 4 of those were excluded. The sponsor added 4 unpublished studies and 2 additional studies (source unclear) to their review, thus including 24 studies in their final review.

The EAC reviewed the sponsor's search strategy and databases included and concluded that it could be improved in three ways. Firstly, the date span of the search could be restricted to a shorter time period than 1985 to 2015. Secondly, the search terms could be more comprehensive by including the search term 'coronary artery disease', rather than restricting the population search to 'obstructive CAD or stable CAD or stable coronary artery disease or suspected coronary artery disease'. Finally, the sponsor did not include any HTA databases, therefore the EAC considered that the Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database (HTA), NHS Economic Evaluation Database (NHS EED) and Econlit databases should have been included.

Given these issues, the EAC undertook a new search for economic evidence related to the technology and comparators. The databases included were Medline & Medline(R) In-Process & Other Non-Indexed Citations, Embase, CDSR, DARE, HTA, NHS EED, and Econlit and the search covered the time period 2005 to 2015. The detailed search strategies are included in appendix 2.

#### **Critique of the sponsor's study selection**

The sponsor selected studies based on the scope, including the following: population of people with stable chest pain with possible CAD pre-test likelihood from 10-90%; interventions (FFR<sub>CT</sub>, CCTA, ICA, MPS with SPECT,

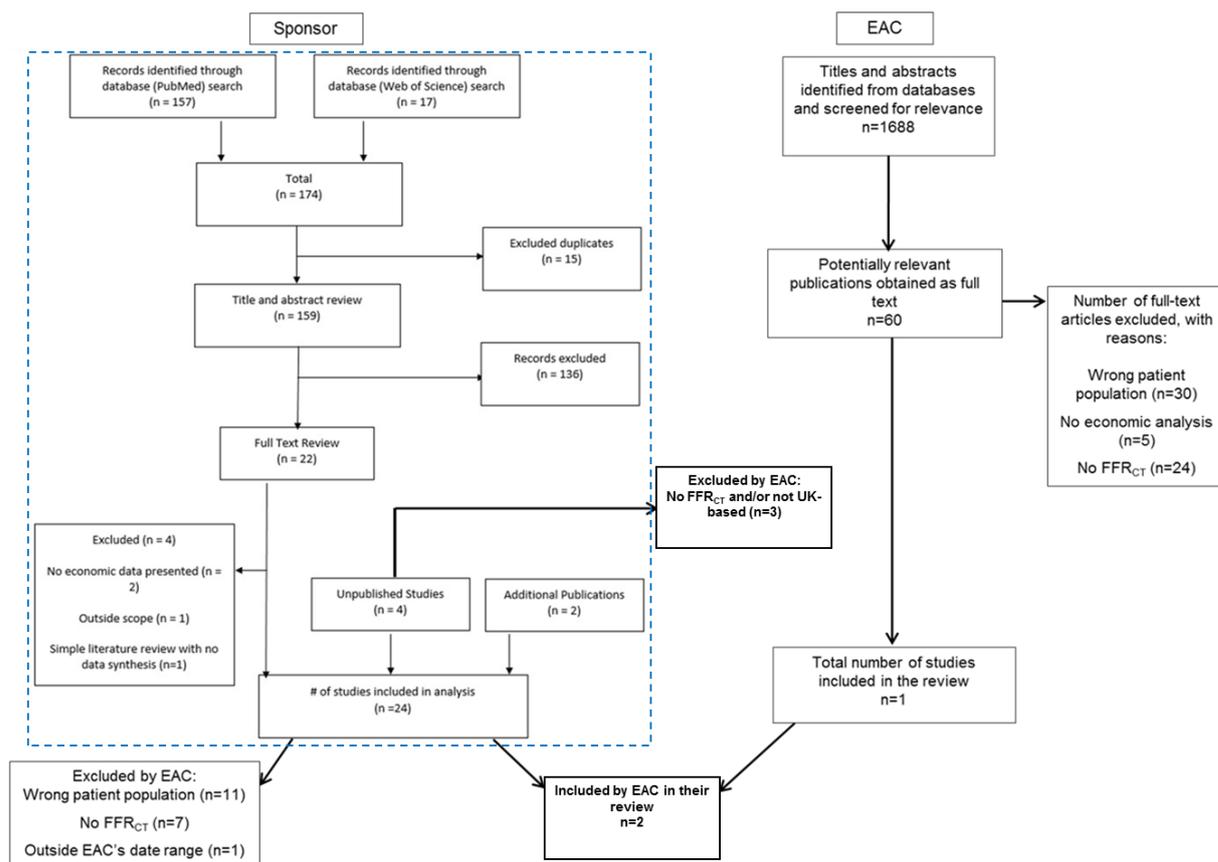
stress ECHO and stress MRI); outcomes (quality adjusted life years, incremental cost effectiveness ratio, cost savings, health care costs, cost analysis). Studies were included if they were in English. The exclusion criteria used were: population (patients with unstable chest pain or pre-test likelihood of <10% or >90%); and intervention (PET, CT perfusion, TAG).

The EAC reviewed the inclusion and exclusion criteria and determined that they were appropriate, except for the date of the search which could be shorter. The EAC used 2005 to 2015 as the span of search in its revised search strategy to reflect the differences in imaging technologies from 1985-2005. Similar to the clinical evidence literature search, the EAC tailored the sponsor's search strategy to include additional keywords related to the description of the functional imaging modalities to increase sensitivity.

### **Included and excluded studies**

The sponsor included 20 published and 4 unpublished studies Figure 3. Of the published studies, 19 were excluded by the EAC. Eleven were excluded because they did not meet the population specified in the scope, 7 did not include FFR<sub>CT</sub>, and 1 was published before the search date and did not include FFR<sub>CT</sub>. Of the unpublished studies, 3 were excluded because they did not include FFR<sub>CT</sub>, the specified population, or were not UK-based. One published study (Rajani et al. 2015) and one unpublished study (the PLATFORM study) included by the sponsor incorporated the appropriate patient population, and followed the pathway laid out in NICE guideline (CG95).

In its search, the EAC found 1688 abstracts, 60 of which were read in full Figure 3. Of these, 59 were excluded because they did not include the population specified by the scope (30) did not include FFR<sub>CT</sub> (24), or did not include an economic analysis (5). The EAC did not find any published studies in addition to Rajani et al. 2015 which included economic evidence related to the technology and relevant to the population.



**Figure 3: PRISMA flow diagram showing the sponsor's search (dotted box) and the EAC search results**

### Overview of methodologies of all included economic studies

Rajani et al. (2015) performed a single-centre retrospective cost analysis over a 12-month period. Patients were grouped into pre-test likelihood categories and diagnostic imaging tests were performed based on standardised protocols. A standardised unit cost for each test and procedure was taken from the NHS National Tariff 2013/2014 and compared to the cost of incorporating FFR<sub>CT</sub>. While the cost derivation is explicit, the details of the decision model structure in this study are unclear.

The PLATFORM study includes a patient population with pre-test likelihood of obstructive CAD of 20-80% and was conducted in the UK, France, Germany, Italy, Austria, and Denmark. It is a multicentre, prospective, controlled study comparing outcomes, resource utilisation, and quality of life following either standard treatment (Cohort 1) or FFR<sub>CT</sub> (Cohort 2). Costs were assigned from NHS National Tariff 2013/2014.

## **Overview and critique of the sponsor's critical appraisal for each study**

The sponsor used the tables recommended by NICE to summarise each study's location, model and comparators, patient population, costs, patient outcomes, and results.

The majority of the studies were prospective or retrospective cost analyses (13). Also included were 1 cost-effectiveness analysis; cost-utility analyses (4, which used quality adjusted life years as the utility measure); literature reviews (3, two of which included a cost-effectiveness analysis); or simulated cost-effectiveness analysis models (2).

Rajani et al. (2015) used a cost modelling approach to predict the cost of using CCTA, FFR<sub>CT</sub>, MPS, ICA, and PCI based on the volume of patients. The study found that the average savings per patient presenting with chest pain was £200 with FFR<sub>CT</sub> when compared to the current NICE pathway. The study did not mention whether a sensitivity analysis was performed.

The PLATFORM study predicted the cost of CCTA, MPI, ICA, PCI, CABG and FFR<sub>CT</sub>. Cohort 1 (following standard treatment) and Cohort 2 (following FFR<sub>CT</sub>) were further stratified by patients presenting for initial non-invasive testing (Cohorts 1A and 2A) and those already referred for ICA (1B and 2B). Preliminary results showed significant savings in average cost per patient using FFR<sub>CT</sub>. This was true across cohorts: Cohorts 1 and 2 (£3916 versus £2584); Cohorts 1A and 2A (£1101 and £1176); and Cohorts 1B and 2B (£5429 and £3351).

### **Does the sponsor's review of economic evidence draw conclusions from the data available?**

The sponsor concluded that while there is evidence regarding the cost of using FFR<sub>CT</sub>, there is currently no evidence which fulfils the scope by using the appropriate patient population and comparator (NICE clinical guideline CG95).

The EAC notes that Rajani et al. (2015) is most closely related to the NICE clinical guideline CG95. The study states that the economic model evaluates patients according to the NICE guidelines based on pre-test likelihood categories and compares it to the cost of adding FFR<sub>CT</sub> to the pathway. The study shows the use of FFR<sub>CT</sub> has a cost savings of £200 compared to the pathway laid out in the NICE guideline. However, it is unclear whether the model adequately captures the guideline within its structure. Similarly, the cost model is unclear from the submitted study protocol for the PLATFORM study, although it shows that the use of FFR<sub>CT</sub> has a cost savings of £1332. The study does not include patients with a pre-test likelihood ratio 10-20% or 80-90% and it is unclear how this affects the results.

## **4.2 De novo cost analysis**

The de novo cost analysis was submitted by the sponsor who claimed that there have been several publications on the cost consequences of patient care with FFR<sub>CT</sub>, including one in the UK (Rajani et al. 2015), but that none of these publications used the pathway laid out in the NICE CG95 as the comparator or otherwise matches the specific scope. The EAC has a slightly different view on this. In its systematic review of economic evidence, the EAC included only one published study (Rajani et al. 2015) with economic evidence related to the technology and relevant to the population. Although the study claims to depict an economic model structured in accordance with the NICE guidelines or with the FFR<sub>CT</sub> pathway, the results provide only the volume of patients (and cost savings) that would have CCTA, FFR<sub>CT</sub>, MPS, ICA, and PCI. It is not clear from the study if NICE CG95 was adequately used to estimate the cost savings. The paper also mentions that it has used data from one single-centre experience and “it would be useful to compare findings with similar services in the UK that shows greater adherence to the NICE guidelines”. This gives a reason to believe that Rajani et al (2015) might have differed from NICE CG95, but it is difficult to ascertain the extent of the deviation. This limitation supports the need for the de-novo cost analysis, which the sponsor has presented. The cost model submitted by the sponsor is based on the NICE guideline on stable chest pain pathway compared against the incorporation of the use of FFR<sub>CT</sub> in the pathway.

### **Patients**

The population specified by the scope includes 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%. The sponsor states that only this population (pre-test likelihood of 10-90%) has been considered for the cost model, however, the EAC found that the cost of pre-test likelihoods of <10% & >90% were also included. While the sponsor’s model includes patients outside the scope (pre-test likelihood of 10-90%), the sponsor does not recommend any change in treatment for these patients. We have excluded these patients from our revised model and results to accurately estimate the cost-savings of the technology compared to current practice.

### **Technology & Comparator(s)**

The comparator specified in the scope is the current practice depending on local treatment pathways and infrastructure and can include the following.

- CCTA imaging without FFR 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)

NICE CG95 (*Figure 2*) is a good representation of the current practice as specified in the scope. The sponsor has used this clinical guideline to develop a decision model. The cost model has then assessed the impact of incorporating the technology (FFR<sub>CT</sub>) into the clinical pathway (*Figure 2*). The EAC feels that this approach is adequate to compare the cost impact of the technology and comparators. Despite the fact that NICE expert advisers have confirmed that local treatment pathways may vary according to practice, taking a general approach to estimate cost savings is reasonable for this assessment.

### **Model structure**

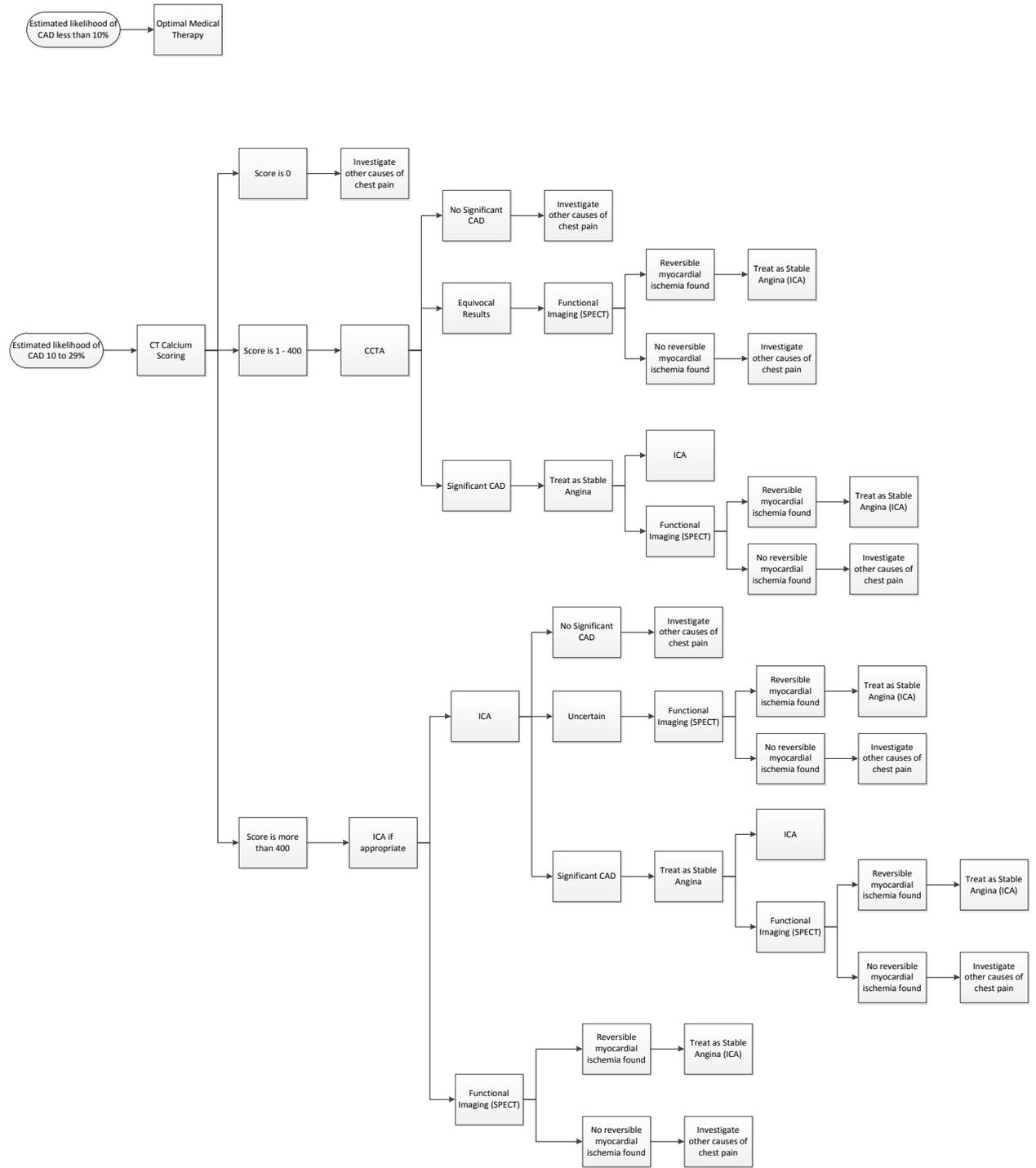
The sponsor submitted a decision tree model from the NHS and personal social services perspective, for estimating the cost associated with the technology (FFR<sub>CT</sub>) along with the comparator (current practice). The cost model is based on NICE CG95. It is proposed that HeartFlow's non-invasive FFR<sub>CT</sub> technology be used in conjunction with CCTA in place of CCTA in the pathway for likelihood of disease 10% to 29%; appropriate functional imaging tests in the pathway for likelihood of disease 30% to 60%; and ICA in the pathway for likelihood of disease 61% to 90%. The model structures used in the economic model are presented in *Figures 4 & 5*. The cost of treating patients by using the existing NICE CG95 for patients with stable chest pain compared to the cost of treating the same patient population while incorporating FFR<sub>CT</sub> technology has been estimated. The model has used diagnostic accuracy to estimate the probabilities and has also captured and quantified changes in the rates of death and MI at one year. It also quantifies the number of ICA and PCI procedures avoided through the use of FFR<sub>CT</sub>. The time horizon for the model is 1 year enabling the quantification of cost consequences of incorporating FFR<sub>CT</sub> into the treatment pathway at the time of treatment.

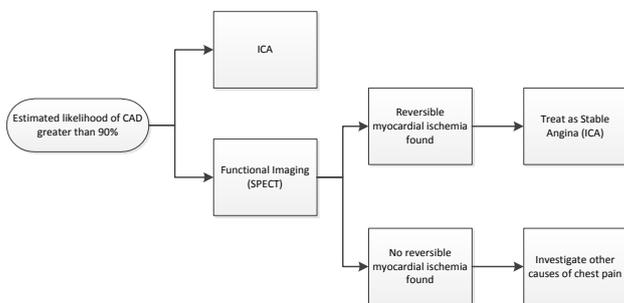
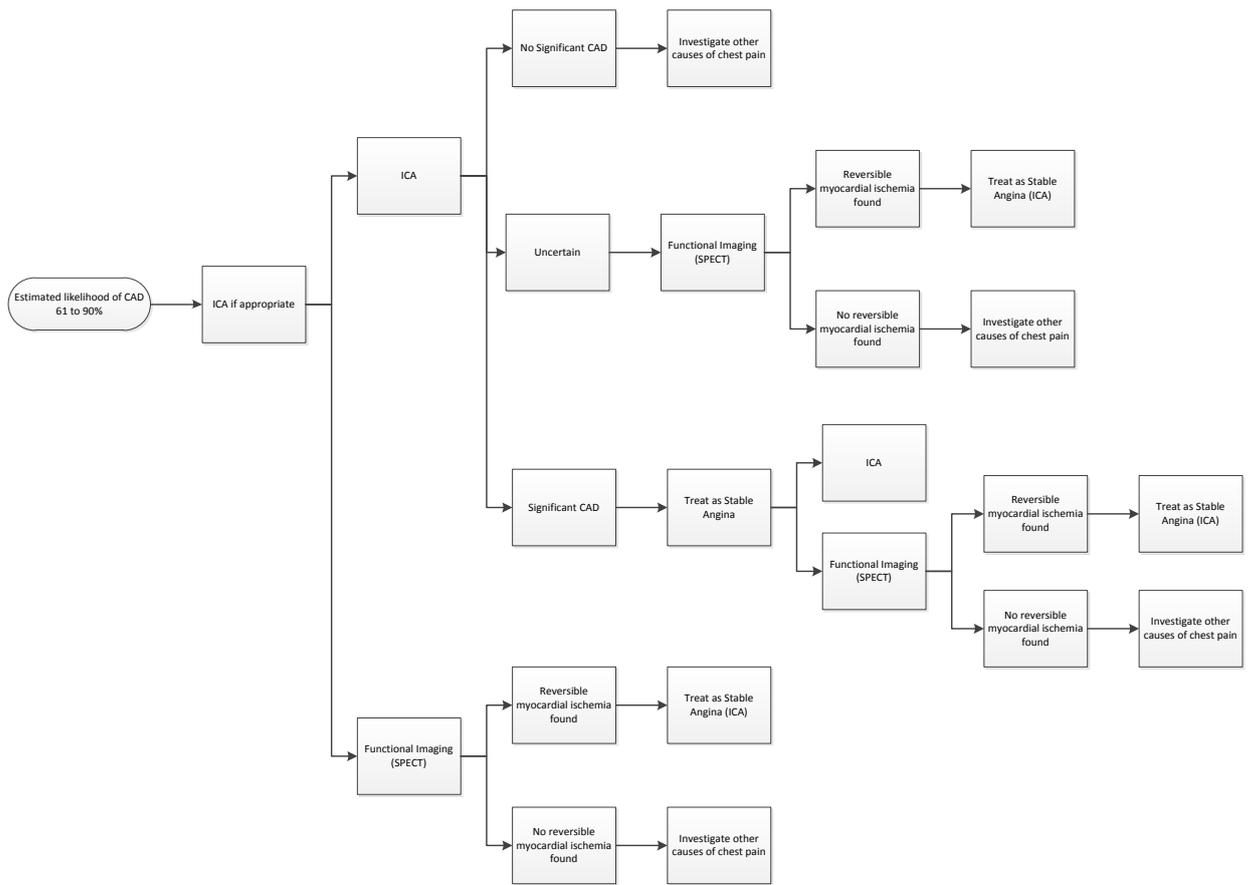
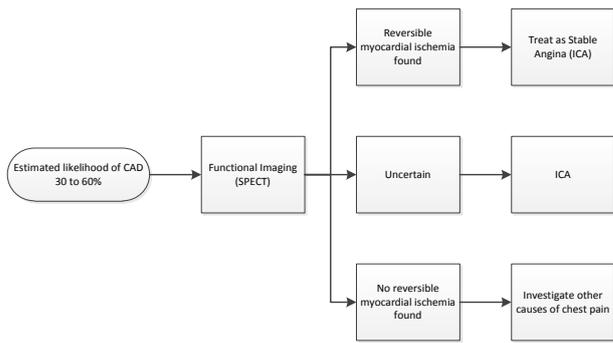
The EAC evaluated the proposed model structure against the pathway in NICECG95 (*Figure 2*) and concluded that the model structure captures the guideline in an appropriate manner for this evaluation. All aspects of the clinical guideline have been included in the model structure. The time horizon for the model (1 year) was appropriate for assessing the impact of the technology, since the consequence of diagnosis on the treatment provided will occur within a 1 year time horizon. Beyond this, the model would have needed to assess the outcomes of the treatment provided, which was not

required for this evaluation since treatment outcomes were not specified in the scope.

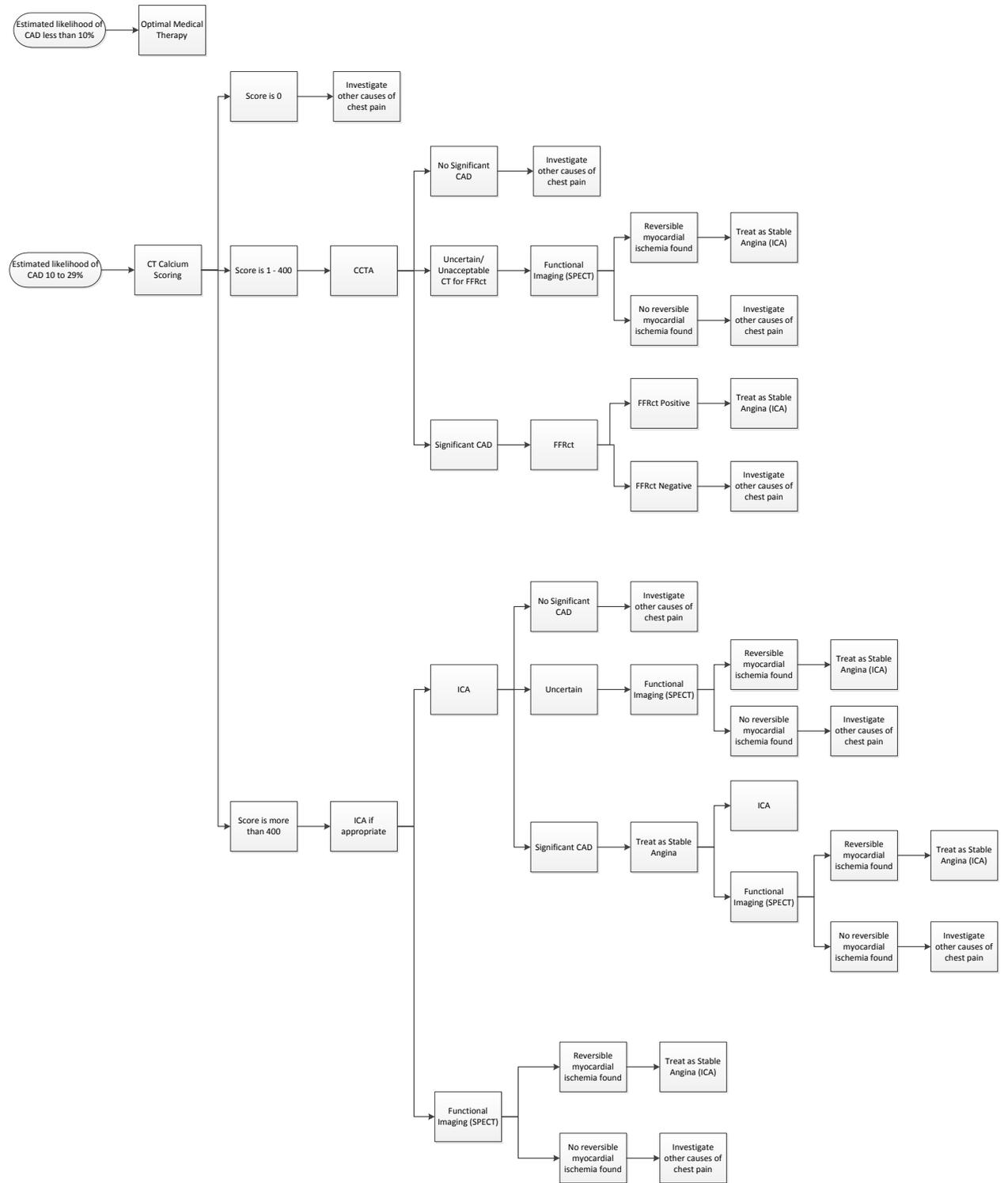
As stated above, the cost model included populations with pre-test likelihoods of <10% & >90%, which need to be excluded to estimate the cost-savings. In the cost model, the sponsor has used SPECT as the method of functional imaging. Though most practices might use SPECT as the functional imaging, other techniques (such as stress ECHO or MRI) are also used in the UK (Whitaker et al. 2014). The impact of using other functional imaging has not been considered in the cost model.

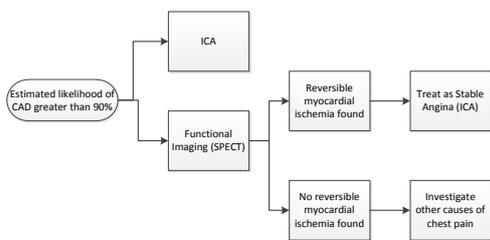
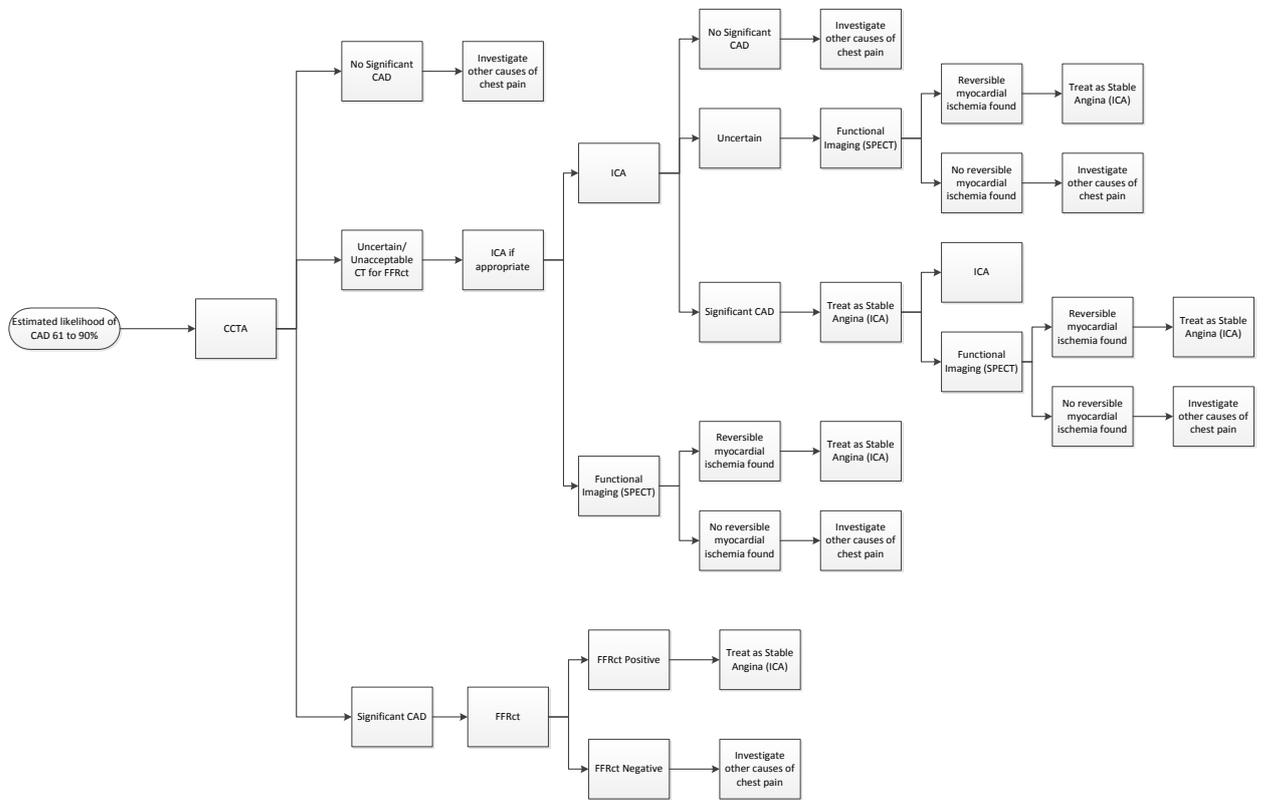
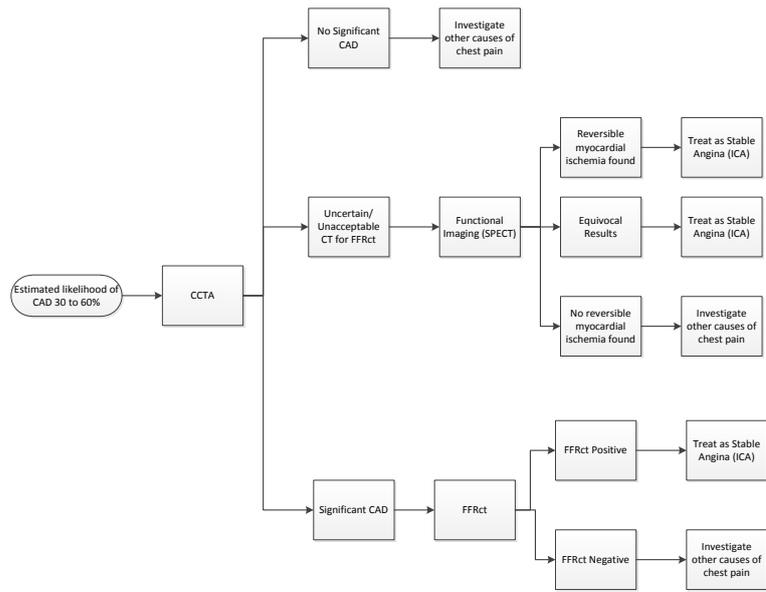
**Figure 4 Flow Chart of current NICE stable chest pain pathway used for economic model**





**Figure 5 Flow Chart of proposed FFR<sub>CT</sub> pathway used for economic model**





## Clinical parameters and variables

There are a number of assumptions around the clinical parameters and variables used in the model, which are described and critiqued below. The sponsor used 3 experts (one of whom is a NICE nominated expert adviser) to check the validity of the model structure, inputs and assumptions.

- The model simulates a cohort of 1000 people, allocating them according to the pre-test likelihood prevalence subsequently following the clinical pathway until treatment is received. The pre-test likelihood prevalence are based on estimates reported in literature (Rajani et al 2015), which is based on data from a rapid access chest pain clinic (RACPC) in the United Kingdom. Depending on the pathway followed, the cohort might receive CCTA, ICA, FFR<sub>CT</sub> or SPECT (as the chosen functional imaging) and their diagnostic accuracy (sensitivity and specificity) has been used to estimate the true and false positives and true and false negatives. Clinical outcomes such as rates of diagnostic angiography, revascularisation by PCI and the use of non-invasive functional tests have been captured in the model. The EAC thinks that the estimates (which are UK specific estimates) and the approach are reasonable.
- FFR<sub>CT</sub> is a diagnostic test with no direct adverse events other than the potential misdiagnosis of patients. These misdiagnoses (false positives and false negatives) have been tracked in the model for both the pathway following the NICE guidelines and proposed pathway using CCTA and FFR<sub>CT</sub>. The EAC thinks that misdiagnosis has been adequately included in the cost model.
- The model also captures and quantifies the change in the rate of death due to MI at 1year. The death and MI rate is based on whether each patient is appropriately or inappropriately diagnosed to receive PCI or optimal medical therapy. The likelihood of an event based on the appropriate or inappropriate diagnosis is based on literature (Pijls and Sels 2012). Event rates are reported and no monetary costs associated with these health states are included in the cost model. The sponsor has reported the change in event rates, however, it does not impact upon the cost model and the EAC agrees that event rates are not relevant for the NICE pathway cost model and for a cost-consequences approach.
- The sponsor has assumed SPECT is the preferred method of functional imaging in the cost model. This assumption might not be reasonable since a recent audit of preferences of functional imaging

amongst cardiologist in UK revealed that other techniques, such as stress echocardiography or MRI techniques are also preferred (Whitaker et al. 2014). The model, therefore, needs to be re-estimated to incorporate other functional imaging techniques. The EAC has used diagnostic accuracy from the meta-analysis it conducted to model the impact of these techniques.

- The per-patient diagnostic accuracy for CCTA, ICA, FFR<sub>CT</sub> or SPECT used in the cost model is based on literature (CCTA & ICA: Meijboom et al. 2008, FFR<sub>CT</sub>: Norgaard et al. 2014, SPECT: Melikian et al. 2010). Although the diagnostic accuracy for stress ECHO (Jung et al. 2008) is reported by the sponsor, this has not been used in the cost model. The sponsor has evaluated the quality of various studies, confirmed it with the meta-analysis estimates submitted and selected the most appropriate estimates of diagnostic accuracy for the model. The EAC feels that the justification for selection of diagnostic accuracy literature based on individual studies, given that a meta-analysis has been performed, is not adequate. The sponsor claims to have confirmed the estimates used with the meta-analysis performed but the process of confirmation is unclear. For example, the specificity of SPECT used in the model is 38% but the meta-analysis submitted by the sponsor reports it to be 75%. The EAC has re-estimated the cost impact using per-patient estimates from the meta-analysis it conducted.
- All of the estimates of diagnostic accuracy are per-patient level estimates. The EAC in its review of clinic evidence felt that both vessel-based diagnostic accuracy and the per-patient estimates can provide useful information for this technology and comparators. The EAC has used vessel-based diagnostic accuracy from its meta-analysis and re-estimated the costs.
- The primary endpoint for the model included appropriate treatment (PCI) or optimal medical therapy. The sensitivity and specificity of angiography (Meijboom et al. 2008) has been used at the model endpoints to estimate the proportion of those who would undergo PCI and optimal medical therapy. The EAC feels that this is a reasonable approach since the decision to perform a PCI is usually based on angiographic results. However, given that a meta-analysis has been performed, using estimates from an individual study is not adequate. The EAC has revised the cost model to include estimates from the meta-analysis it conducted.
- The cost model is based on costs incurred during the index management of new-onset stable chest pain. While there will be

ongoing economic benefits associated with clinical outcomes (such as lower rates of death and MI, nephrotoxicity from contrast media administration, vascular access site complications, sequelae from incremental radiation exposure, post-CABG events, and bleeding events related to antiplatelet medications following PCI), the sponsor has not included these in the model, as they mostly occur beyond the 1 year horizon of the model. The EAC agrees with the time horizon and the non-inclusion of treatment outcomes since it was not specified in the scope. Moreover, data on long term outcomes was limited to the PLATFORM study (only first 90 days of follow-up have been submitted by the sponsor).

- Assumptions on the results of CT calcium scoring (0 (15%), 1-400 (80%) and >400 (5%)) were sourced from literature (Rajani et al. 2015) and are considered reasonable for the model.
- The proportion (10%) of patients not eligible to undergo invasive angiography (inappropriate angiography) for 61-90% risk prevalence was based on expert opinion, which the EAC confirmed as reasonable from literature (Neglia et al. 2015). However, literature also reports that the proportion could be as high as 20% (Curzen et al. 2014). To address the uncertainty, the EAC subjected this assumption to a sensitivity analysis in its revised estimations.
- An assumption of 10% for the percentage of inconclusive CCTA results was based on expert opinion. In order to ascertain whether this was reasonable, the EAC checked the literature. Whilst the EAC agrees that this assumption could be used in the base case analysis, a sensitivity analysis was required since the literature also reports a higher proportion of 16% (Abdool et al. 2014). In its revised estimations, the EAC subjected this assumption to sensitivity analysis.
- An assumption of 10% uncertain proportion for functional test (SPECT) was based on expert opinion, which the EAC confirmed as reasonable from literature (Mouden et al. 2014). However, in its revised estimations, the EAC subjected this assumption to sensitivity analysis to address uncertainty.

### **Resource identification, measurement and valuation**

A number of assumptions on resource identification, measurement and valuation have been used to estimate the costs used in the model, which are described and critiqued below.

- The model uses the Payment by Results 2014-15 (DOH 2013) tariffs for the relevant activity as a proxy for cost. Tariffs represents a 'real' cost to NHS commissioners. The EAC agrees that using tariffs is a reasonable approach to estimate costs in the model.
- A cohort of 1000 patients are simulated through the model and the volume of patients in the decision arms are estimated and multiplied by the relevant NHS tariffs to estimate total costs. A per patient cost has been estimated by dividing the total costs by the total number of patients. The EAC considers using a cohort approach to estimate per patient cost to be appropriate. However, the model has included the cost of patients with pre-test likelihood of <10% and >90%, which need to be excluded to estimate the cost-savings in the specified population of 10-90%.
- The tariff for SPECT is HRG RA37Z (£220) - Nuclear Medicine - category 3, which the EAC considers as appropriate. As mentioned earlier, the cost model has used SPECT as the preferred functional imaging modality. Other functional imaging such as stress echocardiography and MRI has not been included. A recent audit of preferences of functional imaging amongst cardiologist in UK revealed that other techniques like stress echocardiography or MRI techniques are also equally preferred (Whitaker et al. 2014). The EAC estimated the model separately using the relevant tariffs; echocardiography, HRG RA60Z-Simple Echocardiogram (£74) and MRI, HRG RA03Z-Magnetic Resonance Imaging Scan, one area, pre and post contrast (£188).
- The tariff for CCTA is HRG RA14Z (£136) – Computerised Tomography Scan, more than three areas, which the EAC considers as appropriate.
- The tariff for calcium scoring is HRG RA08Z (£77) - Computerised Tomography Scan, one area, no contrast, which the EAC considers as appropriate. However, in the electronic model submitted, the EAC detected an error; a cost of £98 for calcium scoring was used for the FFR<sub>CT</sub> pathway, which the EAC rectified.
- The tariff for angiography is HRG EA36A (£1,241)-Catheter 19 years and over, which the EAC considers as appropriate.
- The tariff for PCI is a weighted average of two tariffs; HRG EA31Z (£2,704) - Percutaneous Coronary Intervention (0-2 Stents) and HRG EA49Z (£ 3,216)-Percutaneous Coronary Interventions with 3 or more Stents, Rotablation, IVUS or Pressure Wire. The two tariffs are weighted on the assumption that 25% of those requiring PCI will

require >2 stents. The EAC checked the recent NHS reference cost (DOH 2014) for number of activities for these 2 tariffs, and found that the assumption was reasonable to be used in the model. The weighted average tariff for PCI used in the model is £2,832. Patients who have a PCI also require medication (aspirin and antiplatelet drugs). The EAC thinks that the cost of these drugs should have been included with the PCI tariff. Upon query, the sponsor has mentioned that drug costs were not included because patients undergoing PCI and those not needing PCI (optimal medical therapy) would require medication and inclusion of these costs would not significantly affect the results. The EAC feels that the medications required for the two groups are different and hence need to be accounted for. The EAC estimated an annual cost of £33 (aspirin and clopidogrel) from the British National Formulary (BNF 2015) and used a cost of £ 2,865 (PCI tariff with drug costs) in its revised model.

- An appropriate cost for optimal medical therapy has not been included in the model. Expert advisers have advised the EAC that optimal medical therapy usually consists of aspirin, statins, nitrates and beta blockers. The EAC estimated an annual cost of £84 (aspirin, simvastatin, glyceryl trinitrate and propranolol hydrochloride) from the British National Formulary (BNF 2015) and used it in the EAC's revised model.

### **Technology and comparators' costs**

The cost model compares the pathway in NICE CG95 (current practice) with the incorporation of HeartFlow FFR<sub>CT</sub> technology into the pathway. Payment by Results 2014-15 tariffs for the relevant activity have been used in the pathways. For the technology cost, the listed price of the HeartFlow technology (£888) has been used in the model, which the EAC considers as appropriate.

### **Sensitivity analysis**

A deterministic sensitivity analysis on cost of FFR<sub>CT</sub> and accuracy (sensitivity and specificity) of diagnostic tests for the different pathways have been presented. A multi-way scenario (sensitivity and specificity) of FFR<sub>CT</sub> and SPECT has also been presented. The EAC considers the deterministic sensitivity analysis as appropriate since the impact of individual parameters is of relevance for this evaluation. However, a rationale for the multi-way scenario analysis is not provided. The EAC also thinks that additional sensitivity analysis on the percentage of inappropriate angiographies (for 61-90% risk prevalence) and inconclusive CCTA & functional imaging proportion

could have been undertaken, since it was based on expert opinion. The EAC included the sensitivity analysis as a part of its additional work undertaken.

### **4.3 Results of de novo cost analysis**

#### **Base-case analysis results**

The base-case reports a cost savings of £159 per patient for the adapted NICE pathway using FFR<sub>CT</sub> (£ 2,080) compared to current NICE recommended pathway (£2,239). These results, however include patients with pre-test likelihoods of <10% and >90%, which need to be excluded. The EAC excluded these populations and re-estimated the cost-savings. Furthermore, the diagnostic accuracy estimates used in the model are patient based. The EAC has used vessel based diagnostic accuracy to re-estimate the costs. Some cost parameters also needed to be revised. The functional imaging in the sponsor's model uses SPECT. The EAC has also re-estimated the costs using other functional imaging.

#### **Sensitivity analysis results**

The sensitivity analysis submitted by the sponsor on a wide range of sensitivity and specificity values for each diagnostic test (FFR<sub>CT</sub>, CCTA, SPECT, ICA) resulted in overall cost-savings for the use of FFR<sub>CT</sub>. In only 1 scenario, with very high specificity of SPECT (87%), there was decreasing cost-savings for the use of FFR<sub>CT</sub>. In the sensitivity analysis of the price of FFR<sub>CT</sub>, the break-even point was £1,226, which meant that if the price of FFR<sub>CT</sub> is more than this point, there would be decreased cost-savings for the use of FFR<sub>CT</sub>. If the price of FFR<sub>CT</sub> is less than the list price of £888, the cost-savings also increased.

#### **Subgroup analysis**

No subgroup analysis was required or performed. In their submission, the sponsor states that patients with pre-test likelihood of <10% and >90% are not considered. However, on scrutiny of the electronic model, costs have been estimated for these populations and are included in the final per patient cost estimations. Since the sponsor does not suggest any change in treatment for such patients, excluding them results in further increase in average cost savings due to FFR<sub>CT</sub>. The EAC has excluded these populations and re-estimated the costs.

#### **Model validation**

The sponsor has validated the model using scenarios that quantify the health and economic impact of utilising FFR<sub>CT</sub> technology in the place of a particular diagnostic test. There are 2 scenarios (all patients receive SPECT or CCTA and then FFR<sub>CT</sub>) that assume that one of the two simple pathways is followed. The EAC considers this validation approach as appropriate. However, the EAC detected the following errors in the electronic model, which was subsequently rectified before re-estimating the costs.

- In the calculation of TP, FP, TN & FN probabilities used to estimate the treatment volumes (PCI and OMT), there were a few errors in how the positives, negatives, total and disease % was calculated.
- In the FFR<sub>CT</sub> model, the 61-90% functional imaging (cells AV 77, 78, 80, 81) is multiplied by inputs sheets (cells E 29 – H29), which are the incorrect parameters and should have been M29 – P29 from the inputs sheet.
- A tariff of £98 (instead of £77) for calcium scoring has been used for the FFR<sub>CT</sub> pathway.

#### **4.4 Interpretation of economic evidence**

The sponsor has stated that the results from their submitted cost model are consistent with published literature. The published literature included 2 publications excluded by the EAC in the systematic review of economic evidence because they included a population that fell outside the one specified by the scope. Only one of the published studies was included by the EAC (Rajani et al. 2015). The sponsor also reports that the results are consistent with the results of unpublished PLATFORM study. The PLATFORM study does not include patients with a pre-test likelihood ratio of 10-20% or 80-90%, and the model structure used is unclear. In the systematic review of economic evidence, the EAC found only one published study (Rajani et al. 2015) that was closely related to the pathway in NICE CG95, although it only uses data from a single-centre. The study reported a cost saving of £200 for the use of FFR<sub>CT</sub> compared to NICE guidelines, which is consistent with the results (£159) from the cost model submitted by the sponsor.

#### **4.5 Additional work undertaken by the External Assessment Centre in relation to economic evidence**

The sponsor's cost model has a number of issues which required a re-estimation of cost savings against the specified comparator.

The following issues prompted the re-estimation.

- In the base-case estimation, the sponsor has included the pre-test likelihood populations of <10% and >90%
- Patient based diagnostic accuracy (sensitivity and specificity) were used instead of a vessel based estimates.
- The cost impact of using other functional imaging techniques (MRI and ECHO) instead of SPECT was not considered.
- A cost has not been assigned to optimal medical therapy.
- Some errors in the electronic model were detected (e.g. a cost of £98 for calcium scoring has been used for the FFR<sub>CT</sub> pathway)

### **Model Structure**

The EAC evaluated the submitted model structure against the pathway in NICE CG95 (Figure 2) and concluded that the model structure captured the guideline in an appropriate manner. The EAC only excluded the decision arms for pre-test likelihoods <10% and > 90% from the base-case cost-savings estimation. This meant that the cohort size used to estimate the per patient cost is 748 instead of 1000 used by the sponsor.

### **Assumptions**

The following assumptions have been used in the re-estimations.

- Diagnostic accuracy for CCTA, ICA, FFRCT, SPECT, MRI and ECHO for the base-case estimation is vessel based. These estimates are based on the meta-analysis conducted by the EAC (Table 12). In this meta-analysis, pooled vessel based diagnostic accuracy for SPECT and ECHO could not be calculated, since vessel based data was not available in any of the included studies. In the absence of these estimates, the EAC considered it reasonable to use vessel based estimates for SPECT and ECHO from the meta-analysis subsequently submitted by the sponsor. For completeness, results using patient based diagnostic accuracy have also been presented.
- Tariffs of £74 (ECHO) and £188 (MRI) have been used in the re-estimations.
- An annual drug cost of £33 has been included with the PCI tariffs, and a cost of £2,865 has been used in the revised model.
- An annual drug cost of £84 has been assigned for optimal medical therapy.

- Other tariffs are the same as those used by the sponsor.

## Sensitivity Analysis

As there was uncertainty surrounding some of the key variables (cost of FFR<sub>CT</sub>, diagnostic accuracy, inappropriate angiography proportion (61-90%), CCTA and functional test uncertain proportion) used in the cost model, deterministic sensitivity analysis was performed to check the robustness of cost saving estimates. Ranges used in the sensitivity analysis for diagnostic accuracy were the confidence intervals estimated in the EAC's meta-analysis. In the absence of vessel based estimates for SPECT and ECHO, the EAC used estimates submitted by the sponsor. Whilst confidence intervals were estimated for SPECT, they were not estimated for ECHO. Hence the range was arbitrarily chosen on the basis of patient estimates. The variables and ranges used in the sensitivity analysis for the vessel based and patient based models are presented in Table 13.1 & Table 13.2 respectively.

Table 13.1: Sensitivity analysis: variables and range (vessel based)

Variable	Base-case value	Range of values	Source
<b>Cost</b>			
FFR <sub>CT</sub>	£888	£700 – 1,300	Sponsor
<b>Sensitivity(SN) and Specificity(SP)</b>			
SN FFR <sub>CT</sub>	84%	76 – 91%	EAC Meta-analysis
SP FFR <sub>CT</sub>	86%	82 – 89%	EAC Meta-analysis
SN CCTA	85%	81 – 89%	EAC Meta-analysis
SP CCTA	75%	73 – 77%	EAC Meta-analysis
SN ICA	55%	45 – 65%	EAC Meta-analysis
SP ICA	90%	87 – 93%	EAC Meta-analysis
SN MRI	87%	72 – 96%	EAC Meta-analysis
SP MRI	98%	92 – 100%	EAC Meta-analysis
SN ECHO	50%	40 – 60%	Sponsor Meta-analysis
SP ECHO	90%	85 – 95%	Sponsor Meta-analysis
SN SPECT	59%	52 – 66%	Sponsor Meta-analysis
SP SPECT	76%	71 – 81%	Sponsor Meta-analysis
<b>Proportions</b>			
ANGIO INAPPROPRIATE	10%	1 – 20%	Sponsor's expert's opinion/literature (Neglia et al. 2015)

FUNCTIONAL UNCERTAIN	10%	1 – 20%	Sponsor's expert's opinion/literature (Mouden et al. 2014)
CCTA UNCERTAIN	10%	1 – 20%	Sponsor's expert's opinion/literature (Abdool et al. 2014)

Table 13.2: Sensitivity analysis: variables and range (patient based)

Variable	Base-case value	Range of values	Source
<b>Cost</b>			
FFR <sub>CT</sub>	£888	£700 – 1,300	Sponsor
<b>Sensitivity(SN) and Specificity(SP)</b>			
SN FFR <sub>CT</sub>	86%	76 – 93%	EAC Meta-analysis
SP FFR <sub>CT</sub>	79%	72 – 85%	EAC Meta-analysis
SN CCTA	95%	92 – 97%	EAC Meta-analysis
SP CCTA	68%	65 – 72%	EAC Meta-analysis
SN ICA	64%	52 – 74%	EAC Meta-analysis
SP ICA	83%	76 – 88%	EAC Meta-analysis
SN MRI	89%	78 – 95%	EAC Meta-analysis
SP MRI	91%	81 – 97%	EAC Meta-analysis
SN ECHO	45%	33 – 57%	EAC Meta-analysis
SP ECHO	90%	85 – 94%	EAC Meta-analysis
SN SPECT	73%	63 – 81%	EAC Meta-analysis
SP SPECT	67%	60 – 74%	EAC Meta-analysis
<b>Proportions</b>			
ANGIO INAPPROPRIATE	10%	1 – 20%	Sponsor's expert's opinion/literature (Neglia et al. 2015)
FUNCTIONAL UNCERTAIN	10%	1 – 20%	Sponsor's expert's opinion/literature (Mouden et al. 2014)
CCTA UNCERTAIN	10%	1 – 20%	Sponsor's expert's opinion/literature (Abdool et al. 2014)

## Results

### Base case (vessel based)

The average total cost per patient with the adapted NICE guideline using FFR<sub>CT</sub> compared to NICE recommended guidelines is presented in Table 14. Three separate model results using different functional imaging (SPECT, MRI and ECHO) have been estimated by the EAC. The cost saving results show that the adapted pathway using FFR<sub>CT</sub> is cost saving when SPECT (£151) or MRI (£229) is the functional imaging test used. The cost saving is greater for MRI than for SPECT. However, when ECHO is used as the functional imaging test, the adapted NICE guideline using FFR<sub>CT</sub> is not cost-saving (-£67).

Table 14: Base case results (vessel based)

	Average total cost per patient (vessel based)		
	(Functional Imaging: SPECT) Model	(Functional Imaging: MRI) Model	(Functional Imaging: ECHO) Model
NICE Recommended Guideline	£1,868	£1,946	£1,623
Adapted NICE Guideline using FFR <sub>CT</sub>	£1,717	£1,717	£1,690
Difference (cost saving)	£151	£229	-£67

### Sensitivity analysis (vessel based)

Tables 15.1 – 15.12 report the sensitivity analysis of a number of variables on the cost savings conclusion. Except for the price of FFR<sub>CT</sub>, none of the other parameters alter the cost-saving conclusion of the adapted guideline with FFR<sub>CT</sub> for the SPECT and MRI models. However, for the ECHO model, the sensitivity of FFR<sub>CT</sub> and ECHO along with the price of FFR<sub>CT</sub> affects the cost-saving conclusions. When a low range value (77%) of sensitivity for FFR<sub>CT</sub> or a high range value (59%) of sensitivity for ECHO is used in the model, the adapted guideline using FFR<sub>CT</sub> changes from being cost-incurring to cost saving. This is due to the fact that when the sensitivity of a test increases, more patients are identified and treated. This increases the average cost of treating patients and hence the change in cost-savings.

For the SPECT, MRI and ECHO models, the price of FFR<sub>CT</sub> is a major cost driver. The breakeven price for the technology is £1,203 (SPECT model), £1,365 (MRI model) and £748 (ECHO model). Any price above this breakeven price is not cost saving for the technology.

Table 15.1: Sensitivity analysis – price of FFR<sub>CT</sub>

**Cost savings by price of FFR<sub>CT</sub> (SPECT model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Price HeartFlow	£ 700	£183	£215	-£441	<b>-£241</b>
	£ 800	£209	£261	-£378	<b>-£193</b>
	£ 888	£233	£303	-£322	<b>-£151</b>
	£ 1,000	£263	£355	-£252	<b>-£97</b>
	£ 1,100	£290	£402	-£189	<b>-£49</b>
	£ 1,200	£316	£449	-£125	<b>-£2</b>
	£ 1,203	£317	£451	-£124	<b>£0</b>
	£ 1,300	£343	£496	-£62	<b>£46</b>

**Cost savings by price of FFR<sub>CT</sub> (MRI model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Price HeartFlow	£ 700	£222	£240	-£615	<b>-£319</b>
	£ 800	£248	£287	-£551	<b>-£271</b>
	£ 888	£272	£328	-£496	<b>-£229</b>
	£ 1,000	£302	£381	-£425	<b>-£175</b>
	£ 1,100	£328	£428	-£362	<b>-£127</b>
	£ 1,200	£355	£475	-£299	<b>-£79</b>
	£ 1,300	£382	£522	-£236	<b>-£31</b>
	£ 1,365	£399	£552	-£195	<b>£0</b>

**Cost savings by price of FFR<sub>CT</sub> (ECHO model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Price HeartFlow	£ 700	£239	£548	-£265	<b>-£23</b>
	£ 748	£252	£571	-£235	<b>£0</b>
	£ 800	£266	£595	-£202	<b>£25</b>
	£ 888	£289	£636	-£146	<b>£67</b>
	£ 1,000	£319	£689	-£75	<b>£121</b>
	£ 1,100	£346	£736	-£12	<b>£169</b>
	£ 1,200	£373	£783	£51	<b>£217</b>
	£ 1,300	£399	£830	£114	<b>£265</b>

Table 15.2: Sensitivity analysis – sensitivity of FFR<sub>CT</sub>

**Cost savings by Dx sensitivity of FFR<sub>CT</sub> (SPECT model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Sensitivity FFR <sub>CT</sub>	76%	£218	£229	-£451	-£230
	78%	£221	£247	-£419	-£211
	80%	£225	£265	-£388	-£192
	82%	£229	£283	-£357	-£172
	84%	£233	£303	-£322	-£151
	85%	£234	£310	-£310	-£143
	87%	£238	£328	-£279	-£124
	89%	£242	£346	-£248	-£105
	91%	£246	£364	-£216	-£85

**Cost savings by Dx sensitivity of FFR<sub>CT</sub> (MRI model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Sensitivity FFR <sub>CT</sub>	76%	£257	£255	-£624	-£308
	78%	£260	£273	-£593	-£289
	80%	£264	£291	-£561	-£269
	82%	£268	£309	-£530	-£250
	84%	£272	£328	-£496	-£229
	85%	£273	£335	-£483	-£221
	87%	£277	£353	-£452	-£202
	89%	£281	£371	-£421	-£182
	91%	£284	£389	-£390	-£163

**Cost savings by Dx sensitivity of FFR<sub>CT</sub> (ECHO model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Sensitivity FFR <sub>CT</sub>	76%	£274	£563	-£274	-£12
	77%	£276	£572	-£259	-£2
	78%	£278	£581	-£243	£7
	80%	£281	£599	-£212	£27
	82%	£285	£617	-£181	£46
	84%	£289	£636	-£146	£67
	85%	£291	£644	-£134	£75
	87%	£294	£661	-£102	£94
	89%	£298	£679	-£71	£114
	91%	£302	£697	-£40	£133

Table 15.3: Sensitivity analysis – specificity of FFR<sub>CT</sub>

**Cost savings by Dx specificity of FFR<sub>CT</sub> (SPECT model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Specificity FFR <sub>CT</sub>	82%	£241	£315	-£317	<b>-£142</b>
	83%	£239	£312	-£318	<b>-£144</b>
	84%	£237	£309	-£320	<b>-£147</b>
	85%	£235	£306	-£321	<b>-£149</b>
	86%	£233	£303	-£322	<b>-£151</b>
	87%	£230	£299	-£324	<b>-£154</b>
	88%	£228	£296	-£326	<b>-£156</b>
	89%	£226	£293	-£327	<b>-£158</b>

**Cost savings by Dx specificity of FFR<sub>CT</sub> (MRI model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Specificity FFR <sub>CT</sub>	82%	£280	£341	-£490	<b>-£220</b>
	83%	£278	£338	-£491	<b>-£222</b>
	84%	£276	£334	-£493	<b>-£224</b>
	85%	£274	£331	-£494	<b>-£227</b>
	86%	£272	£328	-£496	<b>-£229</b>
	87%	£269	£325	-£498	<b>-£231</b>
	88%	£267	£322	-£499	<b>-£234</b>
	89%	£265	£318	-£501	<b>-£236</b>

**Cost savings by Dx specificity of FFR<sub>CT</sub> (ECHO model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Specificity FFR <sub>CT</sub>	82%	£298	£649	-£140	<b>£76</b>
	83%	£296	£646	-£142	<b>£74</b>
	84%	£293	£642	-£143	<b>£72</b>
	85%	£291	£639	-£145	<b>£69</b>
	86%	£289	£636	-£146	<b>£67</b>
	87%	£287	£633	-£148	<b>£65</b>
	88%	£285	£630	-£149	<b>£62</b>
	89%	£282	£626	-£151	<b>£60</b>

Table 15.4: Sensitivity analysis – sensitivity of functional imaging test

**Cost savings by Dx sensitivity of SPECT (SPECT model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Sensitivity SPECT	52%	£237	£357	-£259	-£97
	53%	£236	£349	-£268	-£105
	55%	£235	£334	-£286	-£120
	57%	£234	£318	-£304	-£136
	59%	£233	£303	-£322	-£151
	62%	£231	£280	-£350	-£174
	64%	£230	£264	-£368	-£189
	66%	£229	£249	-£386	-£205

**Cost savings by Dx sensitivity of MRI (MRI model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Sensitivity MRI	72%	£280	£443	-£361	-£115
	75%	£278	£420	-£389	-£138
	79%	£276	£389	-£425	-£169
	83%	£274	£358	-£461	-£200
	87%	£272	£328	-£496	-£229
	89%	£271	£311	-£516	-£246
	94%	£268	£273	-£561	-£284
	96%	£267	£257	-£579	-£300

**Cost savings by Dx sensitivity of ECHO (ECHO model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Sensitivity ECHO	40%	£295	£714	-£55	£144
	42%	£294	£698	-£73	£129
	46%	£291	£667	-£110	£98
	48%	£290	£652	-£128	£83
	50%	£289	£636	-£146	£67
	54%	£287	£605	-£183	£36
	58%	£285	£574	-£219	£6
	59%	£284	£567	-£228	-£2
	60%	£284	£559	-£237	-£10

Table 15.5: Sensitivity analysis – specificity of functional imaging test

**Cost savings by Dx specificity of SPECT (SPECT model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Specificity SPECT	71%	£222	£255	-£338	-£178
	72%	£224	£265	-£335	-£172
	73%	£226	£274	-£332	-£167
	74%	£228	£284	-£329	-£162
	76%	£233	£303	-£322	-£151
	78%	£237	£322	-£316	-£140
	79%	£240	£331	-£313	-£135
	80%	£242	£341	-£310	-£130
	81%	£244	£350	-£307	-£124

**Cost savings by Dx specificity of MRI (MRI model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Specificity MRI	92%	£257	£268	-£515	-£263
	93%	£260	£277	-£512	-£258
	94%	£262	£287	-£509	-£252
	96%	£266	£306	-£503	-£242
	98%	£272	£328	-£496	-£229
	99%	£273	£334	-£494	-£226
	100%	£275	£343	-£491	-£220

**Cost savings by Dx specificity of ECHO (ECHO model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Specificity ECHO	85%	£278	£589	-£161	£41
	86%	£280	£599	-£158	£46
	87%	£283	£608	-£155	£51
	88%	£285	£617	-£152	£57
	90%	£289	£636	-£146	£67
	92%	£294	£655	-£140	£78
	93%	£296	£665	-£137	£83
	94%	£298	£674	-£134	£89
	95%	£300	£684	-£131	£94

Table 15.6: Sensitivity analysis – sensitivity of CCTA

**Cost savings by Dx sensitivity of CCTA (SPECT model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Sensitivity of CCTA	81%	£228	£250	-£412	<b>-£206</b>
	82%	£229	£263	-£391	<b>-£193</b>
	83%	£230	£275	-£370	<b>-£180</b>
	84%	£231	£288	-£348	<b>-£167</b>
	85%	£233	£303	-£322	<b>-£151</b>
	87%	£235	£325	-£284	<b>-£128</b>
	88%	£236	£338	-£263	<b>-£115</b>
	89%	£237	£350	-£241	<b>-£102</b>

**Cost savings by Dx sensitivity of CCTA (MRI model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Sensitivity of CCTA	81%	£266	£276	-£586	<b>-£283</b>
	82%	£267	£288	-£564	<b>-£270</b>
	83%	£269	£301	-£543	<b>-£257</b>
	84%	£270	£313	-£522	<b>-£244</b>
	85%	£272	£328	-£496	<b>-£229</b>
	87%	£274	£351	-£457	<b>-£205</b>
	88%	£276	£363	-£436	<b>-£192</b>
	89%	£277	£376	-£414	<b>-£179</b>

**Cost savings by Dx sensitivity of CCTA (ECHO model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Sensitivity of CCTA	81%	£283	£584	-£236	<b>£12</b>
	82%	£285	£597	-£215	<b>£26</b>
	83%	£286	£609	-£193	<b>£39</b>
	84%	£287	£621	-£172	<b>£52</b>
	85%	£289	£636	-£146	<b>£67</b>
	87%	£292	£659	-£108	<b>£91</b>
	88%	£293	£671	-£86	<b>£104</b>
	89%	£295	£684	-£65	<b>£117</b>

Table 15.7: Sensitivity analysis – specificity of CCTA

**Cost savings by Dx specificity of CCTA (SPECT model)**

Dx Specificity CCTA	Disease Burden			All
	10-29%	30-60%	61-90%	
73%	£230	£315	-£317	<b>-£145</b>
74%	£232	£308	-£320	<b>-£148</b>
75%	£233	£303	-£322	<b>-£151</b>
76%	£234	£296	-£326	<b>-£154</b>
77%	£236	£290	-£328	<b>-£157</b>

**Cost savings by Dx specificity of CCTA (MRI model)**

Dx Specificity CCTA	Disease Burden			All
	10-29%	30-60%	61-90%	
73%	£271	£340	-£490	<b>-£223</b>
74%	£271	£334	-£493	<b>-£226</b>
75%	£272	£328	-£496	<b>-£229</b>
76%	£272	£321	-£499	<b>-£232</b>
77%	£273	£315	-£502	<b>-£236</b>

**Cost savings by Dx specificity of CCTA (ECHO model)**

Dx Specificity CCTA	Disease Burden			All
	10-29%	30-60%	61-90%	
73%	£289	£648	-£141	<b>£74</b>
74%	£289	£642	-£144	<b>£70</b>
75%	£289	£636	-£146	<b>£67</b>
76%	£290	£630	-£149	<b>£64</b>
77%	£290	£623	-£152	<b>£60</b>

Table 15.8: Sensitivity analysis – sensitivity of ICA

**Cost savings by Dx sensitivity of ICA (SPECT model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Sensitivity of ICA	45%	£213	£285	-£265	-£141
	47%	£217	£288	-£276	-£143
	50%	£223	£294	-£294	-£146
	53%	£229	£299	-£311	-£149
	55%	£233	£303	-£322	-£151
	58%	£239	£308	-£340	-£154
	60%	£243	£312	-£351	-£156
	63%	£249	£317	-£369	-£159
	65%	£253	£321	-£380	-£161

**Cost savings by Dx sensitivity of ICA (MRI model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Sensitivity of ICA	45%	£250	£311	-£418	-£212
	47%	£255	£314	-£434	-£215
	50%	£261	£319	-£457	-£220
	53%	£267	£325	-£480	-£225
	55%	£272	£328	-£496	-£229
	58%	£278	£334	-£519	-£234
	60%	£283	£337	-£535	-£237
	63%	£289	£342	-£558	-£242
	65%	£293	£346	-£574	-£245

**Cost savings by Dx sensitivity of ICA (ECHO model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Sensitivity of ICA	45%	£268	£606	-£107	£65
	47%	£272	£612	-£115	£65
	50%	£278	£621	-£126	£66
	53%	£285	£630	-£138	£67
	55%	£289	£636	-£146	£67
	58%	£296	£646	-£158	£68
	60%	£300	£652	-£166	£68
	63%	£307	£661	-£178	£69
	65%	£311	£667	-£186	£70

Table 15.9: Sensitivity analysis – specificity of ICA

**Cost savings by Dx specificity of ICA (SPECT model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Specificity ICA	87%	£224	£287	-£340	-£165
	88%	£227	£292	-£334	-£161
	89%	£230	£297	-£329	-£156
	90%	£233	£303	-£322	-£151
	91%	£235	£307	-£317	-£147
	92%	£238	£312	-£312	-£142
	93%	£241	£317	-£306	-£138

**Cost savings by Dx specificity of ICA (MRI model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Specificity ICA	87%	£265	£313	-£515	-£243
	88%	£267	£318	-£509	-£239
	89%	£269	£323	-£503	-£234
	90%	£272	£328	-£496	-£229
	91%	£274	£333	-£490	-£225
	92%	£276	£338	-£484	-£220
	93%	£291	£373	-£440	-£187

**Cost savings by Dx specificity of ICA (ECHO model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Specificity ICA	87%	£283	£625	-£162	£56
	88%	£285	£629	-£157	£59
	89%	£287	£632	-£152	£63
	90%	£289	£636	-£146	£67
	91%	£291	£640	-£142	£71
	92%	£293	£643	-£137	£74
	93%	£295	£647	-£132	£78

Table 15.10: Sensitivity analysis – angiography inappropriate proportion

**Cost savings by angio inappropriate proportion(SPECT model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Angio inappropriate	1%	£231	£303	-£358	<b>-£165</b>
	5%	£232	£303	-£344	<b>-£159</b>
	7%	£232	£303	-£336	<b>-£156</b>
	10%	£233	£303	-£322	<b>-£151</b>
	12%	£233	£303	-£313	<b>-£147</b>
	15%	£234	£303	-£297	<b>-£141</b>
	20%	£235	£303	-£267	<b>-£130</b>

**Cost savings by angio inappropriate proportion (MRI model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Angio inappropriate	1%	£268	£328	-£482	<b>-£225</b>
	5%	£269	£328	-£491	<b>-£227</b>
	7%	£270	£328	-£494	<b>-£228</b>
	10%	£272	£328	-£496	<b>-£229</b>
	12%	£273	£328	-£496	<b>-£229</b>
	15%	£274	£328	-£495	<b>-£228</b>
	20%	£277	£328	-£487	<b>-£224</b>

**Cost savings by angio inappropriate proportion (ECHO model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Angio inappropriate	1%	£284	£636	-£236	<b>£33</b>
	5%	£286	£636	-£197	<b>£48</b>
	7%	£288	£636	-£177	<b>£55</b>
	10%	£289	£636	-£146	<b>£67</b>
	12%	£290	£636	-£125	<b>£75</b>
	15%	£292	£636	-£93	<b>£88</b>
	20%	£295	£636	-£38	<b>£109</b>

Table 15.11: Sensitivity analysis – functional test uncertain proportion

**Cost savings by functional test uncertain proportion (SPECT model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Functional uncertain	1%	£233	£385	-£322	<b>-£120</b>
	5%	£233	£349	-£322	<b>-£134</b>
	7%	£233	£330	-£322	<b>-£141</b>
	10%	£233	£303	-£322	<b>-£151</b>
	12%	£233	£284	-£322	<b>-£158</b>
	15%	£233	£257	-£322	<b>-£169</b>
	20%	£233	£211	-£322	<b>-£186</b>

**Cost savings by functional test uncertain proportion (MRI model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Functional uncertain	1%	£272	£411	-£496	<b>-£197</b>
	5%	£272	£374	-£496	<b>-£211</b>
	7%	£272	£356	-£496	<b>-£218</b>
	10%	£272	£328	-£496	<b>-£229</b>
	12%	£272	£310	-£496	<b>-£236</b>
	15%	£272	£283	-£496	<b>-£246</b>
	20%	£272	£237	-£496	<b>-£264</b>

**Cost savings by functional test uncertain proportion (ECHO model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Functional uncertain	1%	£289	£739	-£146	<b>£106</b>
	5%	£289	£694	-£146	<b>£89</b>
	7%	£289	£671	-£146	<b>£80</b>
	10%	£289	£636	-£146	<b>£67</b>
	12%	£289	£613	-£146	<b>£59</b>
	15%	£289	£579	-£146	<b>£45</b>
	20%	£289	£522	-£146	<b>£24</b>

Table 15.12: Sensitivity analysis – CCTA uncertain proportion

**Cost savings by CCTA uncertain proportion (SPECT model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
CCTA uncertain	1%	£253	£299	-£331	-£151
	5%	£244	£301	-£327	-£151
	7%	£240	£302	-£325	-£151
	10%	£233	£303	-£322	-£151
	12%	£228	£304	-£321	-£151
	15%	£222	£305	-£318	-£151
	20%	£211	£307	-£313	-£152

**Cost savings by CCTA uncertain proportion (MRI model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
CCTA uncertain	1%	£290	£328	-£520	-£234
	5%	£282	£328	-£509	-£231
	7%	£278	£328	-£504	-£230
	10%	£272	£328	-£496	-£229
	12%	£268	£328	-£490	-£228
	15%	£262	£329	-£482	-£226
	20%	£252	£329	-£469	-£223

**Cost savings by CCTA uncertain proportion (ECHO model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
CCTA uncertain	1%	£309	£667	-£143	£85
	5%	£300	£653	-£145	£77
	7%	£296	£646	-£145	£73
	10%	£289	£636	-£146	£67
	12%	£285	£630	-£147	£63
	15%	£278	£620	-£148	£58
	20%	£267	£603	-£149	£48

### Base case (patient based)

This section presents the estimated cost saving using patient based diagnostic accuracy. The average total cost per patient with the adapted NICE guideline using FFR<sub>CT</sub> compared to the NICE recommended guideline is presented in Table 16. As with the vessel based approach, three separate model results using different functional imaging techniques (SPECT, MRI and ECHO) have been estimated by the EAC. The results show that the adapted pathway using FFR<sub>CT</sub> is cost saving when SPECT (£167) and MRI (£140) is the functional imaging test used. Unlike the vessel based estimated, the cost saving is not higher for MRI compared to SPECT. With ECHO used as the functional imaging test, the adapted NICE guideline using FFR<sub>CT</sub> is not cost-saving (-£285). The costs incurred are higher than the vessel based estimate (-£67).

Table 16: Base case results (patient based)

	<b>Average total cost per patient (patient based)</b>		
	<b>(Functional Imaging: SPECT) Model</b>	<b>(Functional Imaging: MRI) Model</b>	<b>(Functional Imaging: ECHO) Model</b>
NICE Recommended Guideline	£2,211	£2,174	£1,708
Adapted NICE Guideline using FFR <sub>CT</sub>	£2,044	£2,034	£1,993
Difference (cost saving)	£167	£140	-£285

### **Sensitivity analysis (patient based)**

Tables 17.1 – 17.12 report the impact of sensitivity analysis of a number of variables on the cost savings conclusion. Except for the price of FFRCT, none of the parameters alter the cost-saving conclusion of the adapted guideline with FFRCT for the SPECT, MRI and ECHO models. The breakeven price for the technology is £1,193 (SPECT model), £1,144 (MRI model) and £367 (ECHO model). Any price below this breakeven price used in the model shows cost savings for the technology.

Table 17.1: Sensitivity analysis – price of FFR<sub>CT</sub>

**Cost savings by price of FFR<sub>CT</sub> (SPECT model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Price HeartFlow	£ 700	£158	£190	-£430	<b>-£270</b>
	£ 800	£190	£244	-£359	<b>-£215</b>
	<b>£ 888</b>	<b>£218</b>	<b>£292</b>	<b>-£296</b>	<b>-£167</b>
	£ 1,000	£253	£352	-£217	<b>-£106</b>
	£ 1,100	£285	£406	-£146	<b>-£51</b>
	£ 1,193	£315	£456	-£79	<b>£0</b>
	£ 1,200	£317	£460	-£74	<b>£4</b>
	£ 1,300	£349	£514	-£3	<b>£59</b>

**Cost savings by price of FFR<sub>CT</sub> (MRI model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Price HeartFlow	£ 700	£223	£333	-£499	<b>-£243</b>
	£ 800	£255	£387	-£428	<b>-£188</b>
	<b>£ 888</b>	<b>£283</b>	<b>£434</b>	<b>-£366</b>	<b>-£140</b>
	£ 1,000	£319	£495	-£286	<b>-£79</b>
	£ 1,100	£351	£549	-£215	<b>-£24</b>
	£ 1,144	£365	£573	-£184	<b>£0</b>
	£ 1,200	£383	£603	-£144	<b>£31</b>
	£ 1,300	£414	£657	-£73	<b>£86</b>

**Cost savings by price of FFR<sub>CT</sub> (ECHO model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Price HeartFlow	£ 367	£166	£621	-£247	<b>£0</b>
	£ 700	£272	£801	-£10	<b>£182</b>
	£ 800	£304	£855	£61	<b>£237</b>
	<b>£ 888</b>	<b>£332</b>	<b>£902</b>	<b>£124</b>	<b>£285</b>
	£ 1,000	£368	£963	£203	<b>£347</b>
	£ 1,100	£400	£1,017	£274	<b>£402</b>
	£ 1,200	£432	£1,071	£346	<b>£457</b>
	£ 1,300	£464	£1,125	£417	<b>£511</b>

Table 17.2: Sensitivity analysis – sensitivity of FFR<sub>CT</sub>

**Cost savings by Dx sensitivity of FFR<sub>CT</sub> (SPECT model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Sensitivity FFR <sub>CT</sub>	76%	£194	£182	-£487	-£286
	78%	£199	£203	-£450	-£262
	80%	£203	£225	-£412	-£239
	84%	£213	£269	-£336	-£192
	86%	£218	£292	-£296	-£167
	88%	£222	£312	-£260	-£145
	90%	£227	£334	-£222	-£121
	92%	£231	£356	-£185	-£98
	93%	£234	£367	-£166	-£86

**Cost savings by Dx sensitivity of FFR<sub>CT</sub> (MRI model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Sensitivity FFR <sub>CT</sub>	76%	£260	£324	-£557	-£259
	78%	£264	£346	-£519	-£235
	80%	£269	£368	-£481	-£212
	84%	£278	£412	-£405	-£165
	86%	£283	£434	-£366	-£140
	88%	£288	£455	-£330	-£118
	90%	£292	£477	-£292	-£94
	92%	£297	£499	-£254	-£71
	93%	£299	£509	-£235	-£59

**Cost savings by Dx sensitivity of FFR<sub>CT</sub> (ECHO model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Sensitivity FFR <sub>CT</sub>	76%	£309	£792	-£67	£167
	78%	£313	£814	-£30	£190
	80%	£318	£836	£8	£214
	84%	£327	£879	£84	£261
	86%	£332	£902	£124	£285
	88%	£337	£923	£160	£308
	90%	£341	£945	£198	£331
	92%	£346	£967	£235	£355
	93%	£349	£977	£254	£366

Table 17.3: Sensitivity analysis – specificity of FFR<sub>CT</sub>

**Cost savings by Dx specificity of FFR<sub>CT</sub> (SPECT model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Specificity FFR <sub>CT</sub>	72%	£239	£322	-£282	-£145
	73%	£236	£318	-£284	-£148
	74%	£233	£313	-£286	-£151
	77%	£224	£300	-£292	-£161
	79%	£218	£292	-£296	-£167
	81%	£211	£282	-£301	-£174
	83%	£205	£273	-£305	-£180
	85%	£198	£264	-£309	-£187

**Cost savings by Dx specificity of FFR<sub>CT</sub> (MRI model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Specificity FFR <sub>CT</sub>	72%	£305	£465	-£351	-£118
	73%	£302	£461	-£353	-£121
	74%	£299	£456	-£355	-£124
	77%	£289	£443	-£362	-£134
	79%	£283	£434	-£366	-£140
	81%	£277	£425	-£370	-£147
	83%	£270	£416	-£374	-£153
	85%	£264	£407	-£378	-£160

**Cost savings by Dx specificity of FFR<sub>CT</sub> (ECHO model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Specificity FFR <sub>CT</sub>	72%	£354	£933	£138	£308
	73%	£351	£929	£136	£305
	74%	£348	£924	£134	£301
	77%	£338	£911	£128	£292
	79%	£332	£902	£124	£285
	81%	£326	£893	£119	£279
	83%	£320	£884	£115	£272
	85%	£313	£875	£111	£266

Table 17.4: Sensitivity analysis –sensitivity of functional imaging test

**Cost savings by Dx sensitivity of SPECT (SPECT model)**

		Disease Burden			
		10-29%	30-60%	61-90%	All
Dx Sensitivity SPECT	63%	£225	£374	-£197	<b>-£85</b>
	65%	£223	£357	-£218	<b>-£102</b>
	68%	£221	£332	-£248	<b>-£127</b>
	71%	£219	£306	-£279	<b>-£153</b>
	73%	£218	£292	-£296	<b>-£167</b>
	76%	£215	£263	-£330	<b>-£195</b>
	79%	£213	£238	-£361	<b>-£220</b>
	81%	£211	£220	-£381	<b>-£237</b>

**Cost savings by Dx sensitivity of MRI (MRI model)**

		Disease Burden			
		10-29%	30-60%	61-90%	All
Dx Sensitivity MRI	78%	£291	£526	-£256	<b>-£50</b>
	80%	£290	£509	-£277	<b>-£67</b>
	83%	£288	£483	-£307	<b>-£92</b>
	85%	£286	£466	-£328	<b>-£109</b>
	89%	£283	£434	-£366	<b>-£140</b>
	91%	£281	£415	-£389	<b>-£160</b>
	93%	£280	£398	-£410	<b>-£177</b>
	95%	£278	£380	-£430	<b>-£194</b>

**Cost savings by Dx sensitivity of ECHO (ECHO model)**

		Disease Burden			
		10-29%	30-60%	61-90%	All
Dx Sensitivity ECHO	33%	£341	£1,004	£245	<b>£386</b>
	35%	£340	£987	£225	<b>£369</b>
	40%	£336	£944	£174	<b>£327</b>
	43%	£334	£919	£143	<b>£302</b>
	45%	£332	£902	£124	<b>£285</b>
	47%	£331	£884	£102	<b>£268</b>
	54%	£325	£824	£31	<b>£208</b>
	57%	£323	£799	£0	<b>£183</b>

Table 17.5: Sensitivity analysis – specificity of functional imaging test

**Cost savings by Dx specificity of SPECT (SPECT model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Specificity SPECT	60%	£196	£218	-£320	<b>-£209</b>
	61%	£199	£229	-£317	<b>-£203</b>
	63%	£205	£250	-£310	<b>-£191</b>
	65%	£212	£271	-£303	<b>-£179</b>
	67%	£218	£292	-£296	<b>-£167</b>
	69%	£224	£312	-£289	<b>-£155</b>
	71%	£230	£333	-£283	<b>-£143</b>
	73%	£236	£354	-£276	<b>-£131</b>
	74%	£239	£365	-£272	<b>-£125</b>

**Cost savings by Dx specificity of MRI (MRI model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Specificity MRI	81%	£253	£330	-£400	<b>-£201</b>
	84%	£262	£361	-£389	<b>-£183</b>
	87%	£271	£393	-£379	<b>-£164</b>
	89%	£277	£413	-£372	<b>-£152</b>
	91%	£283	£434	-£366	<b>-£140</b>
	93%	£289	£455	-£359	<b>-£128</b>
	94%	£292	£466	-£355	<b>-£122</b>
	95%	£295	£476	-£352	<b>-£116</b>
	97%	£301	£497	-£345	<b>-£104</b>

**Cost savings by Dx specificity of ECHO (ECHO model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Specificity ECHO	85%	£317	£849	£106	<b>£255</b>
	86%	£320	£859	£110	<b>£261</b>
	87%	£323	£870	£113	<b>£267</b>
	89%	£329	£891	£120	<b>£279</b>
	90%	£332	£902	£124	<b>£285</b>
	91%	£335	£912	£127	<b>£291</b>
	92%	£338	£922	£130	<b>£297</b>
	93%	£341	£933	£134	<b>£303</b>
	94%	£344	£943	£137	<b>£309</b>

Table 17.6: Sensitivity analysis – sensitivity of CCTA

**Cost savings by Dx sensitivity of CCTA (SPECT model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Sensitivity of CCTA	92%	£214	£254	-£361	<b>-£206</b>
	93%	£216	£267	-£338	<b>-£192</b>
	94%	£217	£281	-£315	<b>-£178</b>
	95%	£218	£292	-£296	<b>-£167</b>
	96%	£219	£308	-£268	<b>-£150</b>
	97%	£220	£321	-£245	<b>-£136</b>

**Cost savings by Dx sensitivity of CCTA (MRI model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Sensitivity of CCTA	92%	£279	£397	-£430	<b>-£180</b>
	93%	£281	£410	-£407	<b>-£165</b>
	94%	£282	£424	-£384	<b>-£151</b>
	95%	£283	£434	-£366	<b>-£140</b>
	96%	£285	£451	-£338	<b>-£123</b>
	97%	£286	£464	-£315	<b>-£109</b>

**Cost savings by Dx sensitivity of CCTA (ECHO model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Sensitivity of CCTA	92%	£328	£865	£59	<b>£246</b>
	93%	£329	£878	£82	<b>£260</b>
	94%	£331	£892	£105	<b>£274</b>
	95%	£332	£902	£124	<b>£285</b>
	96%	£334	£919	£152	<b>£302</b>
	97%	£336	£932	£175	<b>£317</b>

Table 17.7: Sensitivity analysis – specificity of CCTA

**Cost savings by Dx specificity of CCTA (SPECT model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Specificity CCTA	65%	£211	£317	-£285	-£155
	66%	£213	£309	-£288	-£158
	67%	£215	£302	-£292	-£162
	68%	£218	£292	-£296	-£167
	69%	£219	£287	-£298	-£169
	70%	£221	£280	-£302	-£173
	71%	£223	£272	-£305	-£176
	72%	£224	£265	-£309	-£180

**Cost savings by Dx specificity of CCTA (MRI model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Specificity CCTA	65%	£280	£459	-£354	-£127
	66%	£281	£452	-£357	-£131
	67%	£282	£445	-£361	-£135
	68%	£283	£434	-£366	-£140
	69%	£284	£430	-£368	-£142
	70%	£285	£423	-£371	-£146
	71%	£286	£415	-£374	-£150
	72%	£286	£408	-£378	-£154

**Cost savings by Dx specificity of CCTA (ECHO model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Specificity CCTA	65%	£332	£927	£135	£299
	66%	£332	£920	£132	£295
	67%	£332	£913	£128	£291
	68%	£332	£902	£124	£285
	69%	£332	£898	£122	£283
	70%	£332	£891	£118	£279
	71%	£333	£883	£115	£275
	72%	£333	£876	£111	£271

Table 17.8: Sensitivity analysis – sensitivity of ICA

**Cost savings by Dx sensitivity of ICA (SPECT model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Sensitivity of ICA	52%	£199	£269	-£231	<b>-£156</b>
	54%	£202	£273	-£242	<b>-£158</b>
	58%	£208	£280	-£264	<b>-£162</b>
	62%	£215	£288	-£286	<b>-£165</b>
	64%	£218	£292	-£296	<b>-£167</b>
	66%	£221	£296	-£308	<b>-£169</b>
	70%	£227	£303	-£331	<b>-£173</b>
	72%	£230	£307	-£342	<b>-£175</b>
	74%	£234	£311	-£353	<b>-£177</b>

**Cost savings by Dx sensitivity of ICA (MRI model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Sensitivity of ICA	52%	£262	£404	-£292	<b>-£130</b>
	54%	£265	£409	-£304	<b>-£131</b>
	58%	£273	£420	-£329	<b>-£135</b>
	62%	£280	£430	-£354	<b>-£139</b>
	64%	£283	£434	-£366	<b>-£140</b>
	66%	£287	£440	-£379	<b>-£142</b>
	70%	£294	£450	-£404	<b>-£146</b>
	72%	£298	£455	-£417	<b>-£147</b>
	74%	£302	£460	-£429	<b>-£149</b>

**Cost savings by Dx sensitivity of ICA (ECHO model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Sensitivity of ICA	52%	£310	£847	£141	<b>£265</b>
	54%	£313	£857	£138	<b>£269</b>
	58%	£321	£875	£132	<b>£276</b>
	62%	£329	£894	£126	<b>£282</b>
	64%	£332	£902	£124	<b>£285</b>
	66%	£337	£913	£121	<b>£289</b>
	70%	£344	£931	£115	<b>£296</b>
	72%	£348	£941	£112	<b>£299</b>
	74%	£352	£950	£109	<b>£303</b>

Table 17.9: Sensitivity analysis –specificity of ICA

**Cost savings by Dx specificity of ICA (SPECT model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Specificity ICA	76%	£197	£250	-£337	<b>-£203</b>
	77%	£200	£257	-£331	<b>-£198</b>
	79%	£206	£269	-£319	<b>-£187</b>
	81%	£212	£281	-£307	<b>-£177</b>
	83%	£218	£292	-£296	<b>-£167</b>
	85%	£224	£305	-£283	<b>-£155</b>
	86%	£227	£311	-£277	<b>-£150</b>
	87%	£231	£317	-£271	<b>-£145</b>
	88%	£234	£323	-£265	<b>-£139</b>

**Cost savings by Dx specificity of ICA (MRI model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Specificity ICA	76%	£268	£398	-£408	<b>-£174</b>
	77%	£270	£403	-£402	<b>-£169</b>
	79%	£275	£414	-£389	<b>-£159</b>
	81%	£279	£425	-£377	<b>-£149</b>
	83%	£283	£434	-£366	<b>-£140</b>
	85%	£288	£446	-£352	<b>-£129</b>
	86%	£290	£451	-£345	<b>-£124</b>
	87%	£293	£457	-£339	<b>-£120</b>
	88%	£295	£462	-£333	<b>-£115</b>

**Cost savings by Dx specificity of ICA (ECHO model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Dx Specificity ICA	76%	£320	£881	£92	<b>£263</b>
	77%	£322	£884	£96	<b>£266</b>
	79%	£326	£891	£106	<b>£273</b>
	81%	£329	£897	£115	<b>£279</b>
	83%	£332	£902	£124	<b>£285</b>
	85%	£336	£909	£134	<b>£293</b>
	86%	£338	£912	£139	<b>£296</b>
	87%	£340	£915	£144	<b>£300</b>
	88%	£341	£918	£148	<b>£303</b>

Table 17.10: Sensitivity analysis – angiography inappropriate proportion

**Cost savings by angio inappropriate proportion (SPECT model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Angio inappropriate	1%	£216	£292	-£320	-£176
	5%	£217	£292	-£311	-£173
	7%	£217	£292	-£306	-£171
	10%	£218	£292	-£296	-£167
	12%	£218	£292	-£289	-£164
	15%	£219	£292	-£277	-£159
	20%	£220	£292	-£252	-£150

**Cost savings by angio inappropriate proportion (MRI model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Angio inappropriate	1%	£279	£434	-£372	-£144
	5%	£281	£434	-£372	-£143
	7%	£282	£434	-£370	-£142
	10%	£283	£434	-£366	-£140
	12%	£284	£434	-£362	-£138
	15%	£286	£434	-£354	-£135
	20%	£289	£434	-£338	-£128

**Cost savings by angio inappropriate proportion (ECHO model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Angio inappropriate	1%	£326	£902	-£9	£235
	5%	£329	£902	£50	£257
	7%	£330	£902	£79	£268
	10%	£332	£902	£124	£285
	12%	£334	£902	£153	£297
	15%	£336	£902	£198	£314
	20%	£340	£902	£273	£343

Table 17.11: Sensitivity analysis – functional test uncertain proportion

**Cost savings by functional test uncertain proportion (SPECT model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Functional uncertain	1%	£218	£366	-£296	-£139
	5%	£218	£333	-£296	-£151
	7%	£218	£316	-£296	-£158
	10%	£218	£292	-£296	-£167
	12%	£218	£275	-£296	-£173
	15%	£218	£250	-£296	-£183
	20%	£218	£209	-£296	-£198

**Cost savings by functional test uncertain proportion (MRI model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Functional uncertain	1%	£283	£520	-£366	-£108
	5%	£283	£482	-£366	-£122
	7%	£283	£463	-£366	-£129
	10%	£283	£434	-£366	-£140
	12%	£283	£415	-£366	-£147
	15%	£283	£387	-£366	-£158
	20%	£283	£339	-£366	-£176

**Cost savings by functional test uncertain proportion (ECHO model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
Functional uncertain	1%	£332	£1,025	£124	£332
	5%	£332	£970	£124	£311
	7%	£332	£943	£124	£301
	10%	£332	£902	£124	£285
	12%	£332	£875	£124	£275
	15%	£332	£834	£124	£260
	20%	£332	£767	£124	£234

Table 17.12: Sensitivity analysis – CCTA uncertain proportion

**Cost savings by CCTA uncertain proportion (SPECT model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
CCTA uncertain	1%	£246	£289	-£291	<b>-£159</b>
	5%	£234	£290	-£293	<b>-£162</b>
	7%	£227	£291	-£295	<b>-£164</b>
	10%	£218	£292	-£296	<b>-£167</b>
	12%	£211	£292	-£297	<b>-£169</b>
	15%	£202	£293	-£299	<b>-£171</b>
	20%	£186	£294	-£302	<b>-£176</b>

**Cost savings by CCTA uncertain proportion (MRI model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
CCTA uncertain	1%	£308	£446	-£367	<b>-£130</b>
	5%	£297	£441	-£366	<b>-£134</b>
	7%	£292	£438	-£366	<b>-£137</b>
	10%	£283	£434	-£366	<b>-£140</b>
	12%	£278	£432	-£365	<b>-£142</b>
	15%	£269	£428	-£365	<b>-£146</b>
	20%	£255	£421	-£364	<b>-£152</b>

**Cost savings by CCTA uncertain proportion (ECHO model)**

		Disease Burden			All
		10-29%	30-60%	61-90%	
CCTA uncertain	1%	£357	£961	£160	<b>£327</b>
	5%	£346	£935	£144	<b>£309</b>
	7%	£341	£922	£136	<b>£299</b>
	10%	£332	£902	£124	<b>£285</b>
	12%	£327	£889	£116	<b>£276</b>
	15%	£319	£870	£104	<b>£262</b>
	20%	£305	£837	£84	<b>£239</b>

#### **4.6 Conclusions on the economic evidence**

Addressing the issues with the cost model submitted by the sponsor, the EAC re-estimated the cost savings of adapted NICE guideline using  $FFR_{CT}$  compared to the NICE recommended guidelines. The sponsor had considered SPECT as the preferred functional imaging technique in their submitted model. Since other functional imaging techniques such as MRI and ECHO are also used in the UK, the EAC estimated the cost model using different functional imaging techniques. When SPECT and MRI are used for functional imaging, the technology offers cost savings but not when ECHO is used. The EAC in its systematic review of economic evidence found one published study using the NICE pathway using data from one single-centre experience (Rajani et al 2015). The results of the EAC's cost-savings estimation is consistent with the findings of that study. The price of the technology is a major cost driver.

#### **Impact on the cost difference between the technology and comparator of additional clinical and economic analyses undertaken by the External Assessment Centre**

The cost model submitted by the sponsor reports a cost-saving of £159 when patient based accuracy (and SPECT as functional imaging) estimates are used. With the EAC's patient based estimates, the cost-saving for the SPECT model is £167. The cost-saving is lower (£151) when vessel based estimates are used.

### **5 Conclusions**

The EAC considers that the sponsor's systematic review was comprehensive; however, the majority of studies included by the sponsor did not fit the scope set by NICE and should have been excluded from the review. This reduced the available evidence submitted by the sponsor substantially.

The sponsor's interpretation of the available evidence was reasonable, and provided a fair assessment of the strengths and weaknesses. However, following the aforementioned exclusion of the majority of the sponsor's included studies; most of the outcomes were disregarded. The most robust data regarding the diagnostic accuracy and efficacy of  $FFR_{CT}$  is provided by 1 published (Norgaard et al. 2014) and 1 unpublished study (PLATFORM), respectively. The sponsor submitted preliminary unpublished evidence (90 days follow-up) from a post-market, prospective, controlled, sequential cohort, multicentre, study (PLATFORM). They show that among patients referred originally for ICA, 65% less underwent ICA in the group receiving CCTA and  $FFR_{CT}$  compared to the group undergoing standard management. In addition, MACE rates were similar between the 2 groups. The study was

powered for both these outcomes at 90 days. However, it is noted that according to experts' opinion 90 days follow-up is too short to adequately capture MACE and this should be considered a limitation of the study design. Finally, the recently published PROMISE study (Douglas et al. 2015) has shown that there is no statistically significant difference between the rate of primary end-point events occurring between a diagnostic pathway that utilises CCTA vs. functional-testing. This provides further evidence on the utilisation of a diagnostic pathway based on CCTA.

The sponsor performed a comprehensive and thorough meta-analysis of diagnostic accuracy studies. However, the inclusion criteria for selecting these studies were focused on eliminating the bias related to the reference test. As a result, most of the studies included in the meta-analysis were outside the scope. The EAC repeated the systematic review and performed a new meta-analysis. The meta-analysis of the comparators to invasive FFR was carried out by the EAC to provide estimates on diagnostic accuracy with 95% confidence intervals. The pooled estimates of sensitivity and specificity were the parameters required for the economic modelling and were provided for the CCTA (6 studies) and MRI (2 studies). For each of the other comparators, data from only 1 study was available.

Compared with the gold standard of invasive FFR,  $FFR_{CT}$  had a sensitivity of 86.1% (95% CI 76.5% - 92.8%) and a specificity of 78.9% (72.1% - 84.7%). Compared with CCTA,  $FFR_{CT}$  had lower sensitivity but higher specificity for patient-based analysis. For the vessel-based analysis (based on four CCTA studies),  $FFR_{CT}$  had a similar sensitivity and higher specificity. Compared with ECHO,  $FFR_{CT}$  had higher sensitivity but lower specificity for patient-based analysis. Vessel-based analysis was not available for ECHO. Compared with ICA,  $FFR_{CT}$  had higher sensitivity and a similar specificity for patient-based analysis. For the vessel-based analysis,  $FFR_{CT}$  also had a higher sensitivity and a similar specificity. Compared with MRI,  $FFR_{CT}$  had a similar sensitivity and a lower specificity. For vessel-based analysis,  $FFR_{CT}$  also had a similar sensitivity and a lower specificity. Compared with SPECT,  $FFR_{CT}$  had higher sensitivity and specificity for patient-based analysis. Vessel-based analysis was not available for SPECT.

The EAC notes that caution must be taken when interpreting the results of the meta-analyses, as no adjustment was made for confounding variables such as patient characteristics. This is due to the lack of detailed information available in the included studies. In addition, since some of the studies included by the EAC did not measure invasive FFR in all the vessels, irrespective of degree of coronary stenosis, it is possible that the sensitivity and specificity values reported in the primary studies, especially at the vessel level, could have been affected.

The major difference between the sponsor's and EAC's estimation of cost-savings is that the sponsor used patient based accuracy, whereas the EAC used vessel based accuracy estimates. The results show that the technology is cost saving when SPECT or MRI is used as the functional imaging technique in the NICE recommended pathway. The technology is however cost-incurring when ECHO is used for functional imaging.

## **6 Implications for research**

Although plenty of literature exists comparing the diagnostic accuracy of  $FFR_{CT}$  with CCTA and ICA, there are no studies comparing  $FFR_{CT}$  with non-invasive functional imaging in a population with intermediate pre-test likelihood of CAD. Therefore the EAC would recommend that further primary research to this end is carried out.

Another source of uncertainty during the evaluation of  $FFR_{CT}$  was the lack of an explicit requirement for the diagnostic accuracy and clinical outcomes studies to investigate a population with an intermediate pre-test likelihood of CAD. Since the intermediate pre-test likelihood population is further subdivided into 3 sub-pathways (10-29%, 30-60%, and 61-90%) these studies should include as part of their study design the collection of data that allows subgroup analysis based on the sub-pathways to be performed.

Finally, future studies including invasive FFR measurements as the reference standard should require these measurements to be performed in all major coronary arteries rather than based on a cut-off of degree of stenosis or clinicians judgement.

## References

Abbara, S., A. Arbab-Zadeh, T. Q. Callister, et al. (2009). "SCCT guidelines for performance of coronary computed tomographic angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee." *J Cardiovasc Comput Tomogr* 3(3): 190-204.

Abdool, M., R. Ashrafi, M. Davies, et al. (2014). "A UK cardiac centre experience of low-risk, stable chest pain patients with calcium score of zero." *British Journal of Cardiology* 21(78).

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 Formulary*, 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.

Cho, H. O., C. W. Nam, Y. K. Cho, et al. (2014). "Characteristics of function-anatomy mismatch in patients with coronary artery disease." *Korean Circulation Journal* 44(6): 394-99.

Choi, J. H., B. K. Koo, Y. E. Yoon, et al. (2012). "Diagnostic performance of intracoronary gradient-based methods by coronary computed tomography angiography for the evaluation of physiologically significant coronary artery stenoses: a validation study with fractional flow reserve." *European heart journal cardiovascular Imaging* 13(12): 1001-7.

Costa, M. A., S. Shoemaker, H. Futamatsu, et al. (2007). "Quantitative magnetic resonance perfusion imaging detects anatomic and physiologic coronary artery disease as measured by coronary angiography and fractional flow reserve." *Journal of the American College of Cardiology* 50(6): 514-22.

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.

De Bruyne, B., T. Baudhuin, J. A. Melin, et al. (1994). "Coronary flow reserve calculated from pressure measurements in humans. Validation with positron emission tomography." *Circulation* 89(3): 1013-22.

De Bruyne, B., N. H. Pijls, J. Bartunek, et al. (2001). "Fractional flow reserve in patients with prior myocardial infarction." *Circulation* 104(2): 157-62.

De Bruyne, B., N. H. J. Pijls, B. Kalesan, et al. (2012). "Fractional Flow Reserve–Guided PCI versus Medical Therapy in Stable Coronary Disease." *New England Journal of Medicine* 367(11): 991-1001.

De Cecco, C. N., A. Varga-Szemes, F. G. Meinel, et al. (2015). "Beyond Stenosis Detection: Computed Tomography Approaches for Determining the Functional Relevance of Coronary Artery Disease." *Radiologic Clinics of North America* 53(2): 317-34.

Desai, R. R. and S. Jha (2013). "Diagnostic performance of cardiac stress perfusion mri in the detection of coronary artery disease using fractional flow reserve as the reference standard: A meta-Analysis." *American Journal of Roentgenology* 201(2): W245-W52.

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.

DOH (2013). "National tariff payment system 2014/15."

DOH (2014). NHS reference cost 2013-2014, Department of Health.

Douglas, P. S. (1997). "Is noninvasive testing for coronary artery disease accurate?" *Circulation* 95(2): 299-302.

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

Fihn, S. D., J. M. Gardin, J. Abrams, et al. (2012). "2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons." *Journal of the American College of Cardiology* 60(24): e44-e164.

Gardner MJ (1992). "Confidence Interval Analysis (CIA), version 1.2." British Medical Journal.

Gaur, S., S. Achenbach, J. Leipsic, et al. (2013). "Rationale and design of the HeartFlowNXT (HeartFlow analysis of coronary blood flow using CT angiography: NeXt sTeps) study." *Journal of Cardiovascular Computed Tomography* 7(5): 279-88.

Gaur S, J. J., Bøtker HE, Gormsen LC, Christiansen EH, Kalsoft AK, Lassen JF, Nørgaard BL (2015). Non-Invasive Fractional Flow Reserve Derived From Coronary Computed Tomography Angiography: Experiences From Real-World Clinical Practice.

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.

Hacker, M., J. Rieber, R. Schmid, et al. (2005). "Comparison of Tc-99m sestamibi SPECT with fractional flow reserve in patients with intermediate coronary artery stenoses." *Journal of Nuclear Cardiology* 12(6): 645-54.

Jensen, J. M., M. Voss, V. B. Hansen, et al. (2012). "Risk stratification of patients suspected of coronary artery disease: comparison of five different models." *Atherosclerosis* 220(2): 557-62.

Jung, P. H., J. Rieber, S. Stork, et al. (2008). "Effect of contrast application on interpretability and diagnostic value of dobutamine stress echocardiography in patients with intermediate coronary lesions: Comparison with myocardial fractional flow reserve." *European Heart Journal* 29(20): 2536-43.

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.

Kamiya, K., M. Sakakibara, N. Asakawa, et al. (2014). "Cardiac magnetic resonance performs better in the detection of functionally significant coronary artery Stenosis compared to single-photon emission computed Tomography and Dobutamine stress echocardiography." *Circulation Journal* 78(10): 2468-76.

Kang, S. J., J. M. Ahn, S. Han, et al. (2013). "Sex differences in the visual-functional mismatch between coronary angiography or intravascular ultrasound versus fractional flow reserve." *Jacc: Cardiovascular Interventions* 6(6): 562-8.

Ko, B. S., J. D. Cameron, I. T. Meredith, et al. (2012). "Computed tomography stress myocardial perfusion imaging in patients considered for revascularization: A comparison with fractional flow reserve." *European Heart Journal* 33(1): 67-77.

Ko, B. S., D. T. Wong, J. D. Cameron, et al. (2014). "320-row CT coronary angiography predicts freedom from revascularisation and acts as a gatekeeper to defer invasive angiography in stable coronary artery disease: a fractional flow reserve-correlated study." *European Radiology* 24(3): 738-47.

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.

Levine, G. N., E. R. Bates, J. C. Blankenship, et al. (2011). "2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions." *Circulation* 124(23): e574-e651.

Li, M., T. Zhou, L. F. Yang, et al. (2014). "Diagnostic accuracy of myocardial magnetic resonance perfusion to diagnose ischemic stenosis with fractional flow reserve as reference: systematic review and meta-analysis." *Jacc: Cardiovascular Imaging* 7(11): 1098-105.

Li, S., X. Tang, L. Peng, et al. (2015). "The diagnostic performance of CT-derived fractional flow reserve for evaluation of myocardial ischaemia confirmed by invasive fractional flow reserve: a meta-analysis." *Clin Radiol* 70(5): 476-86.

Libby, P. and P. Theroux (2005). "Pathophysiology of Coronary Artery Disease." *Circulation* 111(25): 3481-88.

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.

Min, J. K., D. S. Berman, M. J. Budoff, et al. (2011). "Rationale and design of the DeFACTO (Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography) study." *Journal of Cardiovascular Computed Tomography* 5(5): 301-09.

Min, J. K., S. Koduru, A. M. Dunning, et al. (2012a). "Coronary CT angiography versus myocardial perfusion imaging for near-term quality of life, cost and radiation exposure: A prospective multicenter randomized pilot trial." *Journal of Cardiovascular Computed Tomography* 6(4): 274-83.

Min, J. K., J. Leipsic, M. J. Pencina, et al. (2012b). "Diagnostic accuracy of fractional flow reserve from anatomic CT angiography." *JAMA* 308(12): 1237-45.

Min, J. K., L. J. Shaw, D. S. Berman, et al. (2008). "Costs and Clinical Outcomes in Individuals Without Known Coronary Artery Disease Undergoing Coronary Computed Tomographic Angiography from an Analysis of Medicare Category III Transaction Codes." *The American Journal of Cardiology* 102(6): 672-78.

Montalescot, G., U. Sechtem, S. Achenbach, et al. (2013). 2013 ESC guidelines on the management of stable coronary artery disease.

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).

Nielsen, L. H., N. Ortner, B. L. Nørgaard, et al. (2014). The diagnostic accuracy and outcomes after coronary computed tomography angiography vs. conventional functional testing in patients with stable angina pectoris: a systematic review and meta-analysis.

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.

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.

Paetsch, I., C. Jahnke, E. Fleck, et al. (2005). Current clinical applications of stress wall motion analysis with cardiac magnetic resonance imaging.

Park, S. J., S. J. Kang, J. M. Ahn, et al. (2012). "Visual-functional mismatch between coronary angiography and fractional flow reserve." *JACC: Cardiovascular Interventions* 5(10): 1029-36.

Pijls, N. H. and J. W. Sels (2012). "Functional measurement of coronary stenosis." *J Am Coll Cardiol* 59(12): 1045-57.

Pijls, N. H., B. Van Gelder, P. Van der Voort, et al. (1995). "Fractional flow reserve. A useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow." *Circulation* 92(11): 3183-93.

Pijls, N. H. J., B. De Bruyne, K. Peels, et al. (1996). "Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses." *New England Journal of Medicine* 334(26): 1703-08.

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.

Pryor, D. B., L. Shaw, C. B. McCants, et al. (1993). "Value of the History and Physical in Identifying Patients at Increased Risk for Coronary Artery Disease." *Annals of Internal Medicine* 118(2): 81-90.

Ragosta, M., A. H. Bishop, L. C. Lipson, et al. (2007). "Comparison between angiography and fractional flow reserve versus single-photon emission computed tomographic myocardial perfusion imaging for determining lesion significance in patients with multivessel coronary disease." *American Journal of Cardiology* 99(7): 896-902.

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.

Rieber, J., P. Jung, I. Erhard, et al. (2004). "Comparison of pressure measurement, dobutamine contrast stress echocardiography and SPECT for the evaluation of intermediate coronary stenoses. The COMPRESS trial." *International Journal of Cardiovascular Interventions* 6(3-4): 142-7.

Rossi, A., S. L. Papadopoulou, F. Pugliese, et al. (2014). "Quantitative computed tomographic coronary angiography: Does it predict functionally significant coronary stenoses?" *Circulation: Cardiovascular Imaging* 7(1): 43-51.

Rozanski, A., G. A. Diamond, D. Berman, et al. (1983). "The declining specificity of exercise radionuclide ventriculography." *New England Journal of Medicine* 309(9): 518-22.

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.

Sahiner, I., U. O. Akdemir, S. A. Kocaman, et al. (2013). "Quantitative evaluation improves specificity of myocardial perfusion SPECT in the assessment of functionally significant intermediate coronary artery stenoses: a comparative study with fractional flow reserve measurements." *Annals of Nuclear Medicine* 27(2): 132-9.

Schoenhagen, P., K. M. Ziada, D. G. Vince, et al. (2001). "Arterial remodeling and coronary artery disease: the concept of "dilated" versus "obstructive" coronary atherosclerosis." *J Am Coll Cardiol* 38(2): 297-306.

Serruys, P. W., C. Girasis, S.-L. Papadopoulou, et al. (2012). "Non-invasive fractional flow reserve: scientific basis, methods and perspectives." *EuroIntervention* 8(4): 511-19.

StataCorp (2013). *Stata Statistical Software: Release 13*, StataCorp LP.

Stuijzand, 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.

Takx, R. A. P., B. A. Blomberg, H. E. Aidi, et al. (2015). "Diagnostic Accuracy of Stress Myocardial Perfusion Imaging Compared to Invasive Coronary Angiography With Fractional Flow Reserve Meta-Analysis." *Circulation: Cardiovascular Imaging* 8(1).

Taylor, A. J., M. Cerqueira, J. M. Hodgson, et al. (2010). "ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 Appropriate Use Criteria for Cardiac Computed Tomography." *Journal of Cardiovascular Computed Tomography* 4(6): 407.e1-07.e33.

- Tonino, P. A. L., B. De Bruyne, N. H. J. Pijls, et al. (2009). "Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention." *New England Journal of Medicine* 360(3): 213-24.
- Whitaker J, W. A., Alfakih K, (2014). "A survey on the implementation of the NICE guidelines on chest pain of recent onset " *Br J Cardiol* 21: 118-19.
- Whiting, P. F., A. W. Rutjes, M. E. Westwood, et al. (2011). "QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies." *Ann Intern Med* 155(8): 529-36.
- Windecker, S., P. Kolh, F. Alfonso, et al. (2014). 2014 ESC/EACTS Guidelines on myocardial revascularization.
- Wong, D. T., B. S. Ko, J. D. Cameron, et al. (2014). "Comparison of diagnostic accuracy of combined assessment using adenosine stress computed tomography perfusion + computed tomography angiography with transluminal attenuation gradient + computed tomography angiography against invasive fractional flow reserve." *Journal of the American College of Cardiology* 63(18): 1904-12.
- Zamora, J., V. Abraira, A. Muriel, et al. (2006). "Meta-DiSc: a software for meta-analysis of test accuracy data." *BMC Medical Research Methodology* 6: 31-31.
- Zhou, T., L. F. Yang, J. L. Zhai, et al. (2014). "SPECT myocardial perfusion versus fractional flow reserve for evaluation of functional ischemia: A meta analysis." *European Journal of Radiology* 83(6): 951-56.

## **Appendix**

### **Appendix 1 – Summary of key points from sponsor-excluded published studies**

**Table 12: Summary of study design, interventions and comparator for sponsor included diagnostic accuracy studies.**

Included by EAC or Sponsor	EAC reference [sponsor reference]	Outcomes	Population	Intervention	Comparator	Reference test
EAC excluded Sponsor included	Christou 2007	Meta-analysis	Unselected population with CAD (asymptomatic, stable angina, unstable angina, early after myocardial infarction, after PCI, other)	No	QCA	Invasive FFR
EAC excluded Sponsor included	M. Li 2014	Meta-analysis	Unselected population with CAD not further defined	No	MRI	Invasive FFR
EAC excluded Sponsor included	Zhou 2014	Meta-analysis	Unselected population with CAD, patients undergoing percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG), or prior heart transplantation were excluded.	No	SPECT	Invasive FFR
EAC excluded Sponsor included	Takx 2015	Meta-analysis	Patients with suspected or known CAD	No	SPECT, ECHO, MRI, PET, and CCTA	Invasive FFR
EAC excluded Sponsor	S. Li 2014	Meta-analysis	Patients with clinically suspected or known CAD	FFRCT	CCTA	Invasive FFR

included						
EAC included Sponsor excluded	Danad 2013	Primary study	Patients being evaluated for CAD (with a predominantly intermediate pre-test likelihood for CAD)	No	CCTA	FFR
EAC excluded Sponsor included	Meijboom, 2008	Primary study	Patients with stable CAD (angina pectoris)	No	CCTA, ICA	FFR
EAC included Sponsor excluded	Kajander 2010	Primary study	Patients with an intermediate (30% to 70%) pre-test likelihood of CAD	No	CCTA	FFR
EAC excluded Sponsor included	Koo, 2011	Primary study	Patients with suspected or known CAD.	FFRCT	CCTA	FFR
EAC excluded Sponsor included	Choi, 2012	Primary study	Patients who were found to have $\geq 50\%$ diameter stenosis (DS) in a major coronary artery.	No	CCTA	FFR
EAC excluded Sponsor included	Ko, 2012	Primary study	Patients undergoing cardiac catheterisation for a suspected diagnosis of CAD.	No	CCTA	FFR
EAC excluded Sponsor included	Ko, 2014	Primary study	Patients with suspected angina who were referred for non-urgent ICA from an outpatient clinic setting.	No	CCTA, ICA	FFR

EAC included Sponsor excluded	Neglia 2015	Primary study	Patients with an intermediate probability of CAD	No	CCTA, SPECT, ECHO	FFR
EAC included Sponsor included	Norgaard, 2014	Primary study	Patients scheduled to undergo clinically indicated ICA for suspected CAD.	FFRCT	CCTA, ICA	FFR
EAC excluded Sponsor included	Rossi, 2014	Primary study	Patients with stable angina who underwent both CCTA and ICA and a subsequent measurement of FFR	No	CCTA	FFR
EAC included Sponsor included	Stuijzand, 2014	Primary study	Patients with intermediate probability of CAD.	No	CCTA	FFR
EAC excluded Sponsor included	Wong, 2014	Primary study	Patients with known CAD who were considered for revascularisation, and symptomatic patients with suspected CAD awaiting ICA.	No	CCTA	FFR
EAC excluded Sponsor included	Rieber, 2004	Primary study	Patients with suspected CAD.	No	ECHO, SPECT	FFR
EAC excluded Sponsor	Jung, 2008	Primary study	Patients with an intermediate coronary stenosis.	No	ECHO	FFR

included						
EAC excluded Sponsor included	Kamiya, 2014	Primary study	Patients who had at least 1 angiographic stenosis $\geq 50\%$ on ICA.	No	ECHO, MRI, SPECT	FFR
EAC excluded Sponsor included	Park, 2012	Primary study	Patients with COPD who underwent ICA due to angina.	No	ICA	FFR
EAC excluded Sponsor included	Kang, 2013	Primary study	Patient who had undergone angiographic, IVUS, and invasive physiological assessment before intervention.	No	ICA	FFR
EAC excluded Sponsor included	Cho, 2014	Primary study	Patients who underwent ICA an invasive physiological evaluation using a pressure wire before intervention. All patients had at least one target vessel with $>30\%$ stenosis diameter measured by ICA analysis.	No	ICA	FFR
EAC excluded Sponsor included	Costa, 2007	Primary study	Patients with suspected CAD.	No	MRI	FFR
EAC included	Bernhardt, 2012	Primary study	Patients with stable CAD.	No	MRI	FFR

Sponsor included						
EAC excluded Sponsor included	Hacker, 2005	Primary study	Patients with stable CAD.	No	SPECT	FFR
EAC excluded Sponsor included	Ragosta, 2007	Primary study	Patients with multivessel CAD.	No	SPECT	FFR
EAC excluded Sponsor included	Melikian, 2010	Primary study	Patients with angiographic 2- or 3-vessel CAD.	No	SPECT	FFR
EAC excluded Sponsor included	Sahiner, 2013	Primary study	Patients with suspected CAD.	No	SPECT	FFR
EAC excluded Sponsor included	NXT Calcium	Primary study sub-analysis of the NXT trial	Patients studied with FFR and ICA for the same coronary lesions regardless of clinical setting (asymptomatic, stable angina, unstable angina, early after MI, post PCI)	FFRCT	ICA	FFR

**Table 13: Summary of study design, interventions and comparator for sponsor included clinical outcomes studies.**

Included by EAC or Sponsor	Study	Outcomes	Population	Comparator (s)
EAC excluded Sponsor included	Gaur 2014	FFRCT reproducibility	Patients with known or suspected CAD	FFRCT
EAC included Sponsor excluded	Cheezum 2011 (Cheezum et al. 2011)	Clinical outcomes	Patients without known CAD who underwent 64-slice CCTA for possible angina.	CCTA
EAC excluded Sponsor excluded	Dominici 2013	Clinical outcomes	Patients with stable, unstable angina and silent ischaemia.	Coronary artery catheterisation
EAC excluded Sponsor excluded	Imamura 2009	Clinical outcomes	Patients without prior cardiac events, who were then stratified by pre-test probability of CAD.	SPECT
EAC excluded Sponsor included	Patel 2010	Clinical outcomes	Patients without known CAD who were undergoing elective cardiac catheterisation	elective cardiac catheterization
EAC excluded Sponsor included	Patel 2014	Clinical outcomes	Patients without known CAD who were undergoing elective cardiac catheterisation	ECHO SPECT MRI (Stress testing with CMR)

				CCTA
EAC included Sponsor excluded	Sahinarslan 2013	Clinical outcomes	Patients who presented with stable angina pectoris, and had not previously undergone ICA or CCTA.	CCTA ICA
EAC excluded Sponsor included	Stergiopoulos 2014	Clinical outcomes	Meta-analysis	ECHO
EAC excluded Sponsor included	Tandon 2012	Clinical outcomes	Patients with suspected CAD without history of revascularisation or cardiac transplantation	CCTA SPECT
EAC excluded Sponsor included	Porter 2013	Clinical outcomes	Patients with intermediate to high pre-test probability for CAD	ECHO
EAC excluded Sponsor included	Lipinski 2013	Clinical outcomes	Meta-analysis	MRI
EAC included Sponsor included	Hachamovitch 2012	Clinical outcomes	Patients without previous CAD with an intermediate to high CAD likelihood	SPECT CCTA
EAC included Sponsor excluded	Min 2008	Clinical outcomes	Patients without known CAD	CCTA SPECT

EAC excluded Sponsor included	Min 2011	Clinical outcomes	Patients without known CAD undergoing CCTA	CCTA
EAC included Sponsor included	Min 2012	Clinical outcomes	Patients presenting with stable chest pain and suspected CAD.	CCTA SPECT
EAC excluded Sponsor excluded	Mouden 2013	Clinical outcomes	Patients suspected of having CAD but in whom it was unconfirmed and who had a low to intermediate pre-test likelihood for CAD	CCTA SPECT
EAC included Sponsor excluded	Mouden 2014	Clinical outcomes	Patients without a history of coronary disease with suspected stable angina	SPECT
EAC excluded Sponsor excluded	Nielsen 2014	Clinical outcomes	Meta-analysis	CCTA SPECT
EAC excluded Sponsor included	Newby 2015	Clinical outcomes	Patients aged 18–75 years and referred by a primary-care physician to a dedicated cardiology chest pain clinic with stable suspected angina due to coronary heart disease were eligible for inclusion.	CCTA
EAC included Sponsor excluded	Ovrehus 2011	Clinical outcomes	Patients with suspected stable angina pectoris and a low to intermediate pre-test likelihood of CAD.	CCTA
EAC	Douglas 2015	Clinical	Patients with intermediate pre-test likelihood of obstructive	CCTA

included Sponsor included		outcomes	CAD	ECHO
EAC excluded Sponsor included	Tonino 2009	Clinical outcomes	Patients with multivessel disease (at least two vessels with stenosis > 50%) indicated for PCI	Invasive FFR, ICA
EAC excluded Sponsor included	De Bruyne 2014	Clinical outcomes	Patients with stable CAD involving up to 3 vessels (as determined on angiography) that was suitable with PCI.	FFR-guided PCI
EAC excluded Sponsor included	Frohlich 2014	Clinical outcomes	Patients undergoing elective or urgent PCI	FFR-Guided vs Angiography- Guided PCI
EAC excluded Sponsor included	Curzen 2014	Clinical outcomes	Patients with stable cardiac-sounding CP who had been listed by their supervising cardiologist on clinical grounds for diagnostic CA	ICA or invasive FFR
EAC excluded Sponsor included	Park 2013	Clinical outcomes	Patients who had at least one coronary lesion with a visually estimated diameter stenosis of 0.50% in a vessel and in whom PCI was indicated clinically.	FFR-guided PCI
EAC excluded Sponsor included	RIPCARD FFRCT	Clinical outcomes	200 consecutive patients enrolled in the HeartFlow NXT study. Patients with stable Chest Pain undergoing CCTA and referred for ICA.	FFRCT
EAC excluded	Real World Usage	Clinical outcomes	Consecutive patients with atypical angina and intermediate range (40-70%) stenosis by coronary CCTA	FFRCT

Sponsor included				
------------------	--	--	--	--

## Appendix 2 – EAC systematic review search terminology

### Diagnostic accuracy

Embase 1980 to 2015; Searched on 31<sup>th</sup> March 2015

1. heartflow.mp.
2. non-invasive.mp.
3. noninvasive.mp.
4. 2 or 3
5. fractional flow reserve/ or FFR.mp.
6. 4 and 5
7. CT-based FFR.mp.
8. FFRct.mp.
9. computed tomographic angiography/ or coronary CT angiography.mp.
10. CCTA.mp.
11. coronary angiography.mp. or angiocardiology/
12. nuclear myocardial perfusion.mp.
13. SPECT.mp. or single photon emission computer tomography/
14. cardiac.mp. or cardiac imaging/
15. 13 and 14
16. myocardial perfusion scintigraphy.mp.
17. MRI.mp.
18. magnetic resonance imaging.mp. or nuclear magnetic resonance imaging/
19. 17 or 18
20. heart perfusion/ or heart muscle perfusion/ or perfusion.mp. or perfusion/
21. stress.mp. or stress/
22. 19 and 20 and 21
23. stress echocardiography.mp. or stress echocardiography/
24. myocardial perfusion imaging.mp. or myocardial perfusion imaging/
25. stress perfusion.mp.
26. dobutamine/ or dobutamine stress.mp.
27. fractional flow reserve.mp. or fractional flow reserve/
28. fractional flow reserve/ or FFR.mp.
29. 27 or 28
30. 1 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 15 or 16 or 22 or 23 or 24 or 25 or 26
31. diagnostic accuracy.mp. or diagnosis/ or diagnostic accuracy/
32. sensitivity.mp. or "sensitivity and specificity"/
33. roc curve/ or receiver operating characteristic/ or area under the curve/ or ROC.mp.
34. prognosis/ or prognosis.mp.
35. predictive value/ or predictive validity/ or predictive.mp.
36. 31 or 32 or 33 or 34 or 35
37. 29 and 30 and 36
38. limit 37 to (english language and yr="1995 -Current")

**Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present; Searched on 31<sup>th</sup> March 2015**

1. heartflow.mp.
2. non-invasive.mp.
3. noninvasive.mp.
4. 2 or 3
5. FFR.mp.
6. 4 and 5
7. CT-based FFR.mp.
8. FFRct.mp.
9. fractional flow reserve.mp. or Fractional Flow Reserve, Myocardial/
10. 4 and 9
11. coronary CT angiography.mp.
12. CCTA.mp.
13. coronary angiography.mp. or Coronary Angiography/
14. nuclear myocardial perfusion.mp.
15. cardiac SPECT.mp.
16. myocardial perfusion scintigraphy.mp.
17. magnetic resonance perfusion.mp.
18. Magnetic Resonance Imaging/ or MRI.mp.
19. 17 or 18
20. perfusion.mp.
21. stress.mp.
22. 19 and 20 and 21
23. stress echocardiography.mp. or Echocardiography, Stress/
24. Myocardial Perfusion Imaging/ or stress myocardial perfusion.mp.
25. stress perfusion.mp.
26. Dobutamine/ or dobutamine stress.mp.
27. fractional flow reserve.mp. or Fractional Flow Reserve, Myocardial/
28. FFR.mp.
29. 27 or 28
30. "Sensitivity and Specificity"/ or diagnostic accuracy.mp.
31. ROC Curve/ or ROC.mp.
32. prognosis.mp. or Prognosis/
33. "Predictive Value of Tests"/ or predictive.mp.
34. 30 or 31 or 32 or 33
35. 1 or 6 or 7 or 8 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 22 or 23 or 24 or 25 or 26
36. 29 and 34 and 35
37. limit 36 to (english language and yr="1995 -Current")

## Clinical outcomes

Embase 1980 to 2015; Searched on 8<sup>th</sup> April 2015

1. heartflow.mp.
2. non-invasive.mp.
3. noninvasive.mp.
4. 2 or 3
5. fractional flow reserve/ or FFR.mp.
6. 4 and 5
7. CT-based FFR.mp.
8. FFRct.mp.
9. computed tomographic angiography/ or coronary CT angiography.mp.
10. CCTA.mp.
11. coronary angiography.mp. or angiocardiography/
12. nuclear myocardial perfusion.mp.
13. SPECT.mp. or single photon emission computer tomography/
14. cardiac.mp. or cardiac imaging/
15. 13 and 14
16. myocardial perfusion scintigraphy.mp.
17. MRI.mp.
18. magnetic resonance imaging.mp. or nuclear magnetic resonance imaging/
19. 17 or 18
20. heart perfusion/ or heart muscle perfusion/ or perfusion.mp. or perfusion/
21. stress.mp. or stress/
22. 19 and 20 and 21
23. stress echocardiography.mp. or stress echocardiography/
24. myocardial perfusion imaging.mp. or myocardial perfusion imaging/
25. stress perfusion.mp.
26. dobutamine/ or dobutamine stress.mp.
27. fractional flow reserve.mp. or fractional flow reserve/
28. FFR.mp.
29. treatment outcome.mp. or treatment outcome/
30. Percutaneous Coronary Intervention.mp. or percutaneous coronary intervention/
31. Major adverse cardiac event.mp.
32. coronary stent/ or Stent.mp. or stent/
33. Myocardial Infarction.mp.
34. balloon angioplasty.mp. or percutaneous transluminal angioplasty/
35. PCI.mp.
36. coronary artery bypass.mp. or coronary artery bypass graft/
37. coronary artery bypass surgery/ or CABG.mp.
38. radiation/ or radiation dose/ or radiation.mp.
39. heart catheterization/ or cardiac catheterization rate\$.mp.
40. ICA rate\$.mp.
41. heart muscle revascularization/ or revascularization/ or revascularization.mp.
42. cardiovascular mortality/ or mortality/ or mortality.mp.

43. death/ or death.mp. or heart death/
44. acute heart infarction/ or heart infarction/ or myocardial infraction.mp.
45. MI.mp.
46. quality of life.mp. or "quality of life"/
47. test utilization.mp.
48. 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47
49. stable coronary artery disease.mp.
50. stable CAD.mp.
51. stable angina.mp. or stable angina pectoris/
52. 49 or 50 or 51
53. 1 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 15 or 16 or 22 or 23 or 24 or 25 or 26 or 27 or 28
54. 48 and 52 and 53
55. limit 54 to (english language and yr="2005 -Current")

**Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present; Searched on 8<sup>th</sup> April 2015**

1. heartflow.mp.
2. noninvasive.mp.
3. non-invasive.mp.
4. 2 or 3
5. fractional flow reserve.mp. or Fractional Flow Reserve, Myocardial/
6. 4 and 5
7. CT-based FFR.mp.
8. FFRct.mp.
9. coronary CT angiography.mp.
10. CCTA.mp.
11. coronary angiography.mp. or Coronary Angiography/
12. nuclear myocardial perfusion.mp.
13. SPECT.mp. or Tomography, Emission-Computed, Single-Photon/
14. Cardiac Imaging Techniques/ or cardiac.mp.
15. 13 and 14
16. Magnetic Resonance Imaging/ or MRI.mp.
17. Myocardial Perfusion Imaging/ or Perfusion Imaging/ or Perfusion/ or perfusion.mp.
18. stress.mp.
19. 16 and 17 and 18
20. stress echocardiography.mp. or Echocardiography, Stress/
21. myocardial perfusion imaging.mp. or Myocardial Perfusion Imaging/
22. dobutamine.mp. or Dobutamine/
23. fractional flow reserve.mp. or Fractional Flow Reserve, Myocardial/
24. FFR.mp.
25. 23 or 24
26. 1 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 15 or 19 or 20 or 21 or 22 or 25
27. treatment outcome.mp. or Treatment Outcome/
28. percutaneous coronary intervention.mp. or Percutaneous Coronary

Intervention/
29. major adverse cardiac event.mp.
30. stent.mp. or Stents/
31. myocardial infarction.mp. or Myocardial Infarction/
32. balloon angioplasty.mp. or Angioplasty, Balloon/
33. PCI.mp.
34. coronary artery bypass.mp. or Coronary Artery Bypass/
35. CABG.mp.
36. Radiation, Ionizing/ or radiation.mp.
37. heart catheterization.mp. or Cardiac Catheterization/
38. ICA rate\$.mp.
39. Myocardial Revascularization/ or revascularization.mp.
40. mortality.mp. or Mortality/
41. Death/ or Death, Sudden, Cardiac/ or death.mp.
42. heart infarction.mp.
43. MI.mp.
44. quality of life.mp. or "Quality of Life"/
45. test utilization.mp.
46. 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45
47. stable coronary artery disease.mp.
48. stable CAD.mp.
49. stable angina.mp. or Angina, Stable/
50. 47 or 48 or 49
51. 26 and 46 and 50
52. limit 51 to (english language and yr="2005 -Current")

## Health Economics

### Embase 1980 to 2015 Week 17

1	heartflow.mp.	8
2	non-invasive.mp.	97258
3	noninvasive.mp.	85081
4	2 or 3	167582
5	fractional flow reserve/ or FFR.mp.	3260
6	4 and 5	425
7	CT-based FFR.mp.	2
8	FFRct.mp.	52
9	computed tomographic angiography/ or coronary CT angiography.mp.	26865
10	CCTA.mp.	1660

11	coronary angiography.mp. or angiocardiology/	86102
12	nuclear myocardial perfusion.mp.	117
13	SPECT.mp. or single photon emission computer tomography/	54002
14	cardiac.mp. or cardiac imaging/	634237
15	13 and 14	6775
16	myocardial perfusion scintigraphy.mp.	1401
17	MRI.mp.	252966
18	magnetic resonance imaging.mp. or nuclear magnetic resonance imaging/	575207
19	17 or 18	599086
20	heart perfusion/ or heart muscle perfusion/ or perfusion.mp. or perfusion/	211546
21	stress.mp. or stress/	805474
22	19 and 20 and 21	1516
23	stress echocardiography.mp. or stress echocardiography/	7251
24	myocardial perfusion imaging.mp. or myocardial perfusion imaging/	7230
25	stress perfusion.mp.	856
26	dobutamine/ or dobutamine stress.mp.	19953
27	fractional flow reserve.mp. or fractional flow reserve/	2657
28	fractional flow reserve/ or FFR.mp.	3260
29	1 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 15 or 16 or 22 or 23 or 24 or 25 or 26 or 27 or 28	141621
30	(econom\$ or cost\$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1046144
31	29 and 30	4639
32	limit 31 to (English language and yr="2005 -Current")	2970
33	(CAD or coronary artery disease).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	198517

34	32 and 33	1168
----	-----------	------

**Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present; Searched on 27 April 2015**

1	heartflow.mp.	4
2	non-invasive.mp.	51699
3	noninvasive.mp.	68386
4	2 or 3	118442
5	fractional flow reserve/ or FFR.mp.	1727
6	4 and 5	197
7	CT-based FFR.mp.	2
8	FFRct.mp.	25
9	fractional flow reserve.mp. or Fractional Flow Reserve, Myocardial/	1388
10	4 and 9	215
11	coronary CT angiography.mp.	983
12	CCTA.mp.	695
13	coronary angiography.mp. or Coronary Angiography/	60298
14	nuclear myocardial perfusion.mp.	61
15	cardiac SPECT.mp.	255
16	myocardial perfusion scintigraphy.mp.	869
17	magnetic resonance perfusion.mp.	223
18	Magnetic Resonance Imaging/ or MRI.mp.	348850
19	17 or 18	348938
20	perfusion.mp.	161772
21	stress.mp.	615651
22	19 and 20 and 21	583
23	stress echocardiography.mp. or Echocardiography, Stress/	4238
24	Myocardial Perfusion Imaging/ or stress myocardial perfusion.mp.	2814
25	stress perfusion.mp.	456
26	Dobutamine/ or dobutamine stress.mp.	6554

27	fractional flow reserve.mp. or Fractional Flow Reserve, Myocardial/	1388
28	FFR.mp.	1308
29	1 or 6 or 7 or 8 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 22 or 23 or 24 or 25 or 26 or 27 or 28	71956
30	(economic\$ or cost\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	636928
31	29 and 30	1783
32	(CAD or coronary artery disease).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	95101
33	31 and 32	763
34	limit 33 to (English language and yr="2005 -Current")	406

### **ECONLIT (27 April 2015)**

(fractional flow reserve) OR (ffr OR ffrct) AND (coronary artery disease OR cad) AND (cost\* OR economic\*) (0)

### **Cochrane Databases—CDSR, DARE, HTA, NHS EED**

- #1 fractional flow reserve or ffr (221)
- #2 ffrct (2)
- #3 non-invasive (3716)
- #4 noninvasive (3629)
- #5 #3 or #4 (7036)
- #6 #5 and #1 (19)
- #7 CT-based ffr (1)
- #8 (computed tomographic angiography) or (coronary CT angiography) (845)
- #9 CCTA (56)
- #10 coronary angiography or angiocardiology (6183)
- #11 nuclear myocardial perfusion (378)
- #12 SPECT or (single photon emission computer tomography) (1312)
- #13 MRI or (magnetic resonance imaging) (11590)
- #14 (heart perfusion) or (heart muscle perfusion) (2392)
- #15 stress (26512)
- #16 #13 and #14 and #15 (38)
- #17 myocardial perfusion imaging (898)
- #18 stress echocardiography (755)
- #19 stress perfusion (726)

- #20 dobutamine or dobutamine stress (979)
- #21 #1 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #16 or #17 or #18 or #19 or #20 (9561)
- #22 economic\* or cost\* (69499)
- #23 #21 and #22 (1163)
- #24 coronary artery disease or cad (12728)
- #25 #23 and #24 (354)
- #26 Publication Year from 2005 to 2015 (115)