NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical Technologies Evaluation Programme

Sponsor submission of evidence: April 20, 2015

Evaluation title: HeartFlow FFR_{CT} for the computation of fractional flow reserve from coronary CT angiography

Sponsor: HeartFlow

Date sections A and B submitted: March 19, 2015

Date section C submitted: April 20, 2015

April 2015

Contents

Instructions for sponsors

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the Medical Technologies Evaluation Programme process for developing NICE medical technologies guidance. Use of the submission template is mandatory.

The purpose of the submission is for the sponsor to collate, analyse and present all relevant evidence that supports the case for adoption of the technology into the NHS in England, within the scope defined by NICE. Failure to comply with the submission template and instructions could mean that the NICE cannot issue recommendations on use of the technology.

The submission should be completed after reading the 'Medical Technologies Evaluation Programme Methods guide' and the 'Medical Technologies Evaluation Programme Process guide' available at www.nice.org.uk/mt. After submission to, and acceptance by, NICE, the submission will be critically appraised by an External Assessment Centre appointed by NICE.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly. For further information on disclosure of information, submitting cost models and equality issues, users should see section 11 of this document 'Related procedures for evidence submission'.

The submission should be concise and informative. The main body of the submission should not exceed 100 pages (excluding the pages covered by the template and appendices). The submission should be sent to NICE electronically in Word or a compatible format, not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level

of detail requested, but that is considered to be relevant to the case for adoption. Appendices will not normally be presented to the Medical Technologies Advisory Committee when developing its recommendations. Any additional appendices should be clearly referenced in the body of the submission. Appendices should not be used for core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the economic evidence section with 'see appendix X'.

All studies and data included in the submission must be referenced. Identify studies by the first author or trial ID, rather than by relying on numerical referencing alone (for example, 'Trial 123/Jones et al.[126], rather than 'one trial[126]').Please use a recognised referencing style, such as Harvard or Vancouver.

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

If a submission is based on preliminary regulatory recommendations, the sponsor must advise NICE immediately of any variation between the preliminary and final approval.

Document key

Boxed text with a grey background provides specific and/or important guidance for that section. This should not be removed.

Information in highlighted black italic is to help the user complete the submission and may be deleted.

The user should enter text at the point marked 'Response' or in the tables as appropriate. 'Response' text may be deleted.

List of tables and figures

Glossary of terms

Term	Definition
AUC	Area under the curve of receiver operating characteristic
CABG	Coronary Artery Bypass Grafting
CAD	Coronary artery disease
CCTA	Coronary CT angiography
CI	Confidence interval
CMR	Cardiac magnetic resonance (synonymous with MRI)
DA	Diagnostic accuracy
DOR	Diagnostic odds ratio
DSCT	Dual-source computed tomography
DTU	Downstream Test Utilization
ECHO	Stress echocardiography
FFR	Fractional flow reserve
FFR_{CT}	Fractional flow reserve derived from CT
GPI	Glycoprotein IIb/IIIa inhibitors
ICA	Invasive Coronary Angiography
ICER	Incremental cost effectiveness ratio
MACE	Major Adverse Cardiovascular Events
MI	Myocardial infarction
MPS	Myocardial perfusion scintigraphy
MRI	Magnetic resonance imaging
NIT	Noninvasive Testing
NLR	Negative likelihood ratio
OMT	Optimal Medical Therapy
PCI	Percutaneous Coronary Intervention
PET	Positron emission tomography
PLR	Positive likelihood ratio
PTL	Pre-test likelihood
QCA	Quantitative Coronary Angiography
QOL	Quality of life
QALY	Quality adjusted life year
SD	Standard Deviation
SN	Sensitivity
SP	Specificity
SPECT	Single photon emission computed tomography
UDF	Updated Diamond Forrester Score
XT	Exercise stress test

Section C – Economic evidence

Section C requires sponsors to present economic evidence for their technology.

All statements should be evidence-based and directly relevant to the decision problem.

The approach to the de novo cost analysis expected to be appropriate for most technologies is cost-consequence analysis. Sponsors should read section 7 of the Medical Technologies Evaluation Programme Methods guide on cost-consequences analysis, available from www.nice.org.uk/mt

Sponsors are requested to submit section C with the full submission. For details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

8 Existing economic evaluations

8.1 Identification of studies

8.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in section 10, appendix 3.

The PubMed and Web of Science databases were used for the health economics literature search. PubMed was searched on March 26th, 2015 and the Web of Science was searched on March 31st, 2015. The searches were restricted to articles that have been published in English since 1985. The complete search strategies are listed below:

PubMed Search Strategy:

noninvasive fractional flow reserve or noninvasive FFR or coronary CT angiography or coronary computed tomography angiography or coronary angiography or nuclear myocardial perfusion or magnetic resonance perfusion or myocardial perfusion scintigraphy or SPECT or stress echocardiography or stress perfusion or stress myocardial perfusion or dobutamine stress

AND

obstructive CAD or stable CAD or stable coronary artery disease or suspected coronary artery disease

AND

QALY or quality adjusted life years or incremental cost effectiveness ratio or ICER or economic outcomes or economic analysis or cost savings or health care costs or health care spending or cost analysis

Web of Science Search Strategy:

“noninvasive fractional flow reserve” or “noninvasive FFR” or “coronary CT angiography” or “coronary computed tomography angiography” or “coronary angiography” or “nuclear myocardial perfusion” or “magnetic resonance perfusion” or “myocardial perfusion scintigraphy” or “SPECT” or “stress echocardiography” or “stress perfusion” or “stress myocardial perfusion” or “dobutamine stress”

AND

“obstructive CAD” or “stable CAD” or “stable coronary artery disease” or “suspected coronary artery disease”

AND

“QALY” or “quality adjusted life years” or “incremental cost effectiveness ratio” or “ICER” or “economic outcomes” or “economic analysis” or “cost savings” or “health care costs” or “health care spending” or “cost analysis”

8.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table C1 Selection criteria used for health economic studies

Inclusion criteria	
Population	People with stable chest pain with possible CAD with pre-test likelihood of 10 to 90%
Interventions	FFR_{CT}, CCTA, invasive coronary angiography, MPS with SPECT, stress ECHO, and stress MRI
Outcomes	Quality adjusted life years, incremental cost effectiveness ratio, cost savings, health care costs, health care spending, cost analysis
Study design	N/A
Language restrictions	English
Search dates	January 1985 to March 2015
Exclusion criteria	
Population	People with unstable chest pain or pre-test likelihood of <10% or >90%
Interventions	PET, CT perfusion, TAG
Outcomes	N/A
Study design	N/A
Language restrictions	Not English
Search dates	Prior to January 1985

8.1.3 Report the numbers of published studies included and excluded at each stage in an appropriate format.

Figure C1 PRISMA diagram for health economics studies

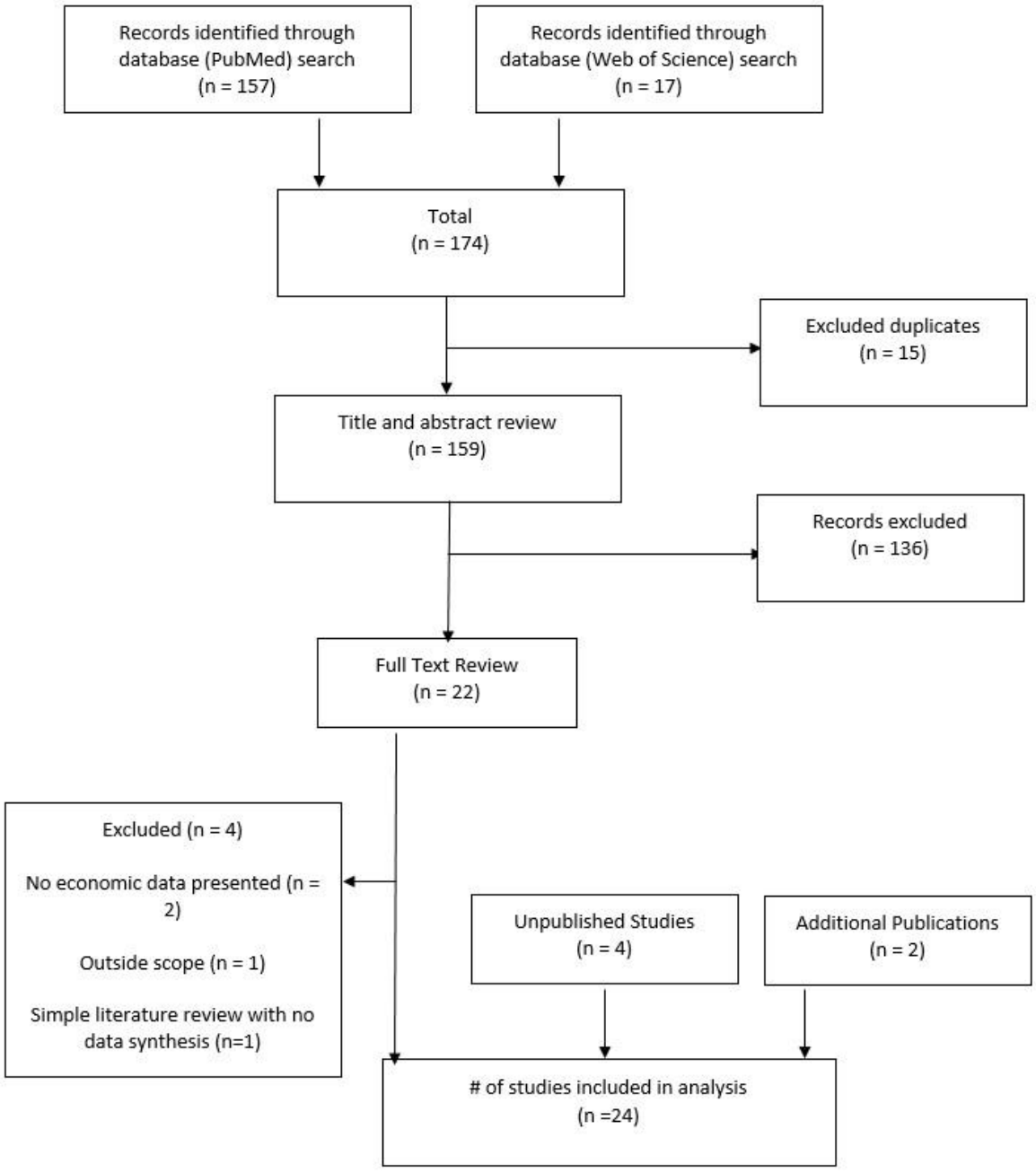


Table C2 Rationale behind exclusion of economics studies

Primary study reference	Study name (acronym)	Reason for exclusion
Zeb 2014	CCTA as a cost-effective test strategy: systematic review	Simple literature review that does not include a meta-analysis or other form of data synthesis.
Malago 2013	Role of MDCT coronary angiography in the clinical setting	There is no quantification of cost savings or cost-effectiveness in this publication.
Meyer 2012	Cost-effectiveness of CCTA vs SPECT	Simulation model of CCTA vs SPECT using MRI as the reference standard which is outside of the scope.
Marcassa 2008	Position statement on MPS	Publication is a position statement that aims to summarize the current SPECT/MPS guidelines and its clinical value alongside other diagnostic modalities; no economic data are presented.

8.2 Description of identified studies

8.2.1 Provide a brief review of each study, stating the methods, results and relevance to the scope. A suggested format is provided in table C2.

Table C3.1 Summary list of all evaluations involving costs – Published Studies

Study name (year)	Location of Study	Summary of model and comparators	Patient population	Costs	Patient outcomes	Results
[E1] Rajani 2015	UK	Cost model using UK NHS 2013 – 2014 Tariffs. Comparison between current NICE-proposed algorithm for pre-test likelihood (PTL) 0 – 100%, and one incorporating FFRct for pre-test likelihood 10% - 90%.	NA	DSE £292 ETT £172 CCTA £166 CAC £98 MR-contrast £213 MR-perfusion £279 MPS £249 ICA £1259 PCI • ≤2 stents £2742 • ≥3 stents £3262 Invasive FFR £3262 FFRct £888	Need for ICA: • 704/1000 for current NICE-proposed algorithm • 369/1000 for algorithm incorporating FFR_{CT} for pre-test likelihood 10% - 90% Need for PCI: • 446/1000 for current NICE-proposed algorithm • 229/1000 for algorithm incorporating FFR_{CT} for pre-test likelihood 10% - 90%	For algorithm incorporating FFR_{CT} for pre-test likelihood 10% - 90% vs. current NICE-proposed algorithm: Avg. immediate saving per patient presenting with chest pain: £200. This does not include downstream cost savings related to medical therapy post-PCI or treatment of complications.

[E2] Kimura 2015	Japan	Patient pathways considered: 1. Revascularization based on ICA alone 2. Revascularization based on ICA and FFR 3. ICA based on CCTA and Revascularization based on ICA 4. ICA based on CCTA and FFRct, revascularization based on ICA and FFRct	Patients from the HeartFlow NXT trial; Patients with suspected CAD referred for ICA Mean age : 64	Costs are in US $ CCTA 400 ICA and hospital stay 2,580 PCI – 1vessel 11,339 PCI – 2vessel 15,352 PCI – 3vessel 19,365 FFR 1,842 FFRct 2,000	Death or MI within 12 mo (%) Pathway: 1. 2.4 2. 1.9 3. 2.2 4. 1.9 Need for ICA (%) Pathway: 1. 100 2. 100 3. 75 4. 35	Initial treatment costs / patient ($US) Pathway: 1. 10,360 2. 7,222 3. 9,128 4. 7,222
[E3] Hlatky 2014	North America	Costs, clinical outcomes, and cost-effectiveness for CCTA vs SPECT vs PET	Patients with suspected CAD undergoing CCTA (n=590), PET (n=548), or SPECT (n=565)	Costs are in US $ 1) PET: 6,647 2) CCTA: 4,909 3) SPECT: 3,965	2 year mortality: 1) PET: 5.5% 2) SPECT: 1.6% 3) CCTA: 0.7%	ICER for CCTA vs. SPECT: 1) $11,700/LYA 2) 13% of bootstrap analyses favored SPECT PET: Higher costs and higher mortality than SPECT.
[E4] Hlatky 2013	U.S.	Patient pathways considered: 1. Revascularization based on ICA alone 2. Revascularization based on ICA and FFR 3. ICA based on CCTA and Revascularization based	Patients with suspected CAD referred for ICA Mean age : 62.7	Costs are in US $ Coronary CT angiography 351 Guide catheter 35 Guidewire 85 Contrast agent 69	Death or MI within 12 mo (%) Pathway: 1. 2.63 2. 1.96 3. 2.56	Initial treatment costs / patient ($US) Pathway: 1. 10,702

		on ICA 4. ICA based on CCTA and Revascularization based on FFR 5. ICA based on CCTA and FFRct, revascularization based on ICA and FFRct		GPI 71 ICA and hospital stay 3443 Pressure wire 650 Adenosine 102 Drug-eluting stent 2100 Balloon catheter 150 Clopidogrel 1200 CAD medication 1 year 500 PCI w/ complication 20 580 Angiography w/ complication 7146 FFRct 1500	4. 2.06 5. 2.31 Need for ICA (%) Pathway: 1. 100 2. 100 3. 84 4. 84 5. 51	2. 8,499 3. 9,635 4. 8,035 5. 7,674
[E5] Fearon 2013	US and Europe	Index hospitalization and follow up costs over 13 months. 1) PCI 2) Medical Therapy	888 patients with stable angina and FFR ≤ 0.80 Avg age: 64	Costs are in US $ PCI: 12,646 Medical Therapy: 9,763	Patient Utility improvement baseline – 1 month): PCI: 0.054 units Medical Therapy: 0.001 units	ICER: $36,000/QALY
[E6] Westwood 2013	Literature review and economic evaluation	Markov model. Next-generation CCTA scanners. • CCTA • ICA alone • CCTA + ICA	Difficult-to-Image patients with suspected CAD	CCTA: £5,808 ICA: £6,534 CCTA+ICA: £5,950	CCTA: 10.588 ICA: 10.597 CCTA+ICA: 10.590 (QALY)	ICER CCTA most attractive: ICA: £83,429 CCTA+ICA: £71,000
[E7] Nielsen (2012)	Denmark	Retrospective study of concurrent patients with exercise-stress test (XT) vs CCTA as initial diagnostic strategy	247 pts with XT vs 251 pts with CCTA; no difference in demographics or PTL; age (SD) =	Total costs per patient associated with medications, downstream test utilization, treatments, ambulatory visits and hospitalizations	During 12 month follow-up period there were 3 serious cardiac events (acute MI), all 3 in the XT group and each had a negative	Mean (SD) total costs per patient after 1 year were higher in the XT group compared to CCTA; €1777

			56 (11); 52% men; 96% at low-intermediate PTL		test result. Mean (SD) radiation dose was higher for CCTA 9.0(3.7) compared to XT 2.1 (3.7) mSv (p<0.0001)	(3746) vs €1510 (3974) (p=0.03). Total costs were 14% lower in the CCTA group.
[E8] Min 2012	USA	Prospective, randomized trial of CCTA vs MPS with SPECT as initial diagnostic test for evaluation of stable angina	Pts with stable chest pain and suspected CAD. No diff in PTL (Framingham risk 18 vs 19); age lower in CCTA (55.9 vs 58.9, p=0.04); more men in CCTA (58% vs 43%, p=0.04)	Total costs for inpatient and outpatient services, medication costs, indirect costs to patient, costs of missed work and patient copay were included	No patient had MI or death with 98% FU at 55±34 days. CCTA and MPS had comparable improvement in angina-specific health. CCTA had improved medical management (aspirin and statin use, p=0.04 and p=0.03); similar rate of CAD related hospitalization and ICA use; CCTA had increased revascularization (8% vs 1%, p=0.03). CCTA had lower total radiation dose (7.4 vs 13.3 mSv, p<0.0001) with no difference in induced radiation	CCTA had lower total costs ($781 vs $1215, p<0.001) with no difference in induced costs.
[E9] Moschetti 2012	Germany, UK, Switzer	Subgroup analysis of European CMR registry of 11,040 consecutive pts with	717 consecutive patients with	Diagnostic costs were evaluated using invoicing costs of each test performed; cost analysis performed	No patient outcomes reported	In public sectors of Germany, UK

	land and US	CMR – comparison of CMR vs ICA modeled as first test with evaluation of diagnostic costs from payer perspective	clinically suspected CAD who had CMR (21% positive, 73% neg, 6% uncertain) and who did not have ICA beforehand. Patient age not provided.	from a health payer perspective in Germany, UK, Swiss and US health care settings		and Switzerland, cost savings from the CMR-driven strategy were 50%, 25% and 23%, respectively vs outpatient ICA and 46%, 50% and 48% vs inpatient ICA. In the US CMR provided cost savings of 51% vs inpatient ICA, but CMR cost 8% more vs outpatient ICA.
[E10] Dorenkamp 2012	Germany	Cost and cost-effectiveness analysis of 90 consecutive patients undergoing dual source CT (DSCT) and ICA	Patients without history of CAD referred for ICA, with equivocal or uninterpretable stress tests and intermed PTL for CAD (Morise 9-15).	Total costs included direct costs, induced costs and costs of complications. Effectiveness defined as accuracy of diagnosis of CAD. Cost-effectiveness of each test evaluated with mathematical model based on Bayes theorem	No clinical outcomes reported. Per patient diagnostic accuracy of DSCT for >50% stenosis by ICA: sensitivity 95%, specificity 90%, PPV 74%, NPV 99%	Direct costs for DSCT €98.60 and for ICA €317.75. Cost-effectiveness grew hyperbolically with increasing prevalence of CAD. Disease prevalence in this cohort was 24% and cost for one pt correctly diagnosed was €970 for DSCT and €1354 for ICA. For prevalence of

						49% DSCT and ICA were equally cost-effective €633. Above this threshold, ICA is more cost-effective
[E11] Cheezum 2011	USA	Retrospective comparison of MPS and CCTA with respect to posttest resource utilization and total direct costs among symptomatic patients without known CAD	241 symptomatic pts without known CAD undergoing MPS compared to 252 age and sex-matched pts undergoing CCTA during same time period. Average age 53±10 years; 44% women; No difference in PTL of CAD – 83% intermediate risk	Total direct measurable costs from payer perspective including cost of cardiac testing, clinic visits, inpatient and outpatient payments	No difference in the low rates of MACE between CCTA and MPS (0.4% vs 0.9%, ns). During follow up of 30±7 months, no difference between CCTA and MPS in per-patient posttest evaluation or testing (24.6% vs 27.7%, ns); CCTA had lower utilization rate of ICA (3.3% vs 8.1%, p=0.02) and nonsignificant trend toward reduced downstream cardiac testing (11.5% vs 17.0%, p=0.08)	Including evaluation of significant incidental findings (7.1% in CCTA), mean direct costs were significantly lower using CCTA $808 vs $1005 for MPS, (p<0.001)
[E12] Pilz 2011	Germany	Retrospective analysis of pts in CMR registry to a matched “gatekeeper” cohort of CMR pts at low risk, to determine rate of	218 pts with intermediate risk for CAD (Morise score 13.85)	Cost analysis from payer perspective using data on cost of ICA and CMR and the portion of averted cardiac caths	CMR reduced utilization of cardiac cath by 62.4%	CMR as a gatekeeper to cath reduced per-patient costs by a

		deferral of cath based on CMR and economic effects of change in practice	matched to 218 a "gatekeeper" cohort (Morise score 14.2). Age 63.2 vs 62.9; Male 56% vs 55%.			mean of €90. Per patient savings range from €323 in patient at lowest risk of CAD to €58 in patients at high risk, but not in the highest risk stratum.
[E13] Min 2010	NA	Decision analysis comparing 5 pathways: 1. CCTA only 2. CCTA first, SPECT 3. SPECT only 4. SPECT first, CCTA 5. ICA	Individuals with chest pain without known CAD in the ACCURACY trial; Base case: 55-year old man with 30% risk of obstructive CAD	Costs for imaging tests and downstream clinical events were based on Medicare reimbursement rates	For near-term costs per correct diagnosis, a CCTA-first strategy was the least expensive, followed by CCTA only (incremental cost-effectiveness ratio [ICER] = $17,516	For long-term cost-effectiveness, a CCTA only strategy showed favorable ICER of $20-429 per QALY relative to least expensive CCTA-first strategy. Both SPECT only and SPECT-first strategies were more costly and less effective than either CCTA strategy.
[E14] Ladapo 2009	United States	8 diagnostic strategies were modeled to assess patient outcomes (therapy for CAD, non-fatal MI, all-cause mortality, stroke), health care costs, and cost-effectiveness:	Men and women between the ages of 45 and 65 who presented with chest pain	Lifetime costs were modeled separately for each strategy for men and women. Strategy (1) led to costs of $35,500 for men and $18,210 for women, (2) $33,870 for men and $17,040 for women, (3) $35,720 and $18,280, (4) $33,970 and $17,880, (5) $34,510 and	There was little difference in health outcomes across the diagnostic strategies. Performing CCTA alone or with XT	All diagnostic strategies yielded similar health outcomes but performing CCTA- with or without XT or

		(1) CCTA followed by XT (2) XT followed by CCTA (3) CCTA alone (4) XT alone (5) stress echocardiography alone (6) SPECT alone (7) ICA (8) no diagnostic testing	syndrome and were suspected of having CAD.	$17,600, (6) $35,670 and $18,820, (7) $37,340 and $18,200, and (8) $27,580 and $14,680.	or performing SPECT alone marginally minimized the lifetime prevalence of adverse events and maximized longevity and quality-adjusted life expectancy. No strategy emerged as markedly superior to others.	performing SPECT-minimized adverse events and maximized longevity and QALYs. CCTA raised overall costs and when performed with stress testing its incremental cost-effectiveness ratio ranged from $26,200/QALY in men to $35,000/QALY in women.
[E15] Genders 2009	United Kingdom, United States, and the Netherlands	A Markov model that analyzed the cost-effectiveness of CCTA performed as a triage test prior to conventional ICA from the perspective of the patient, physician, hospital, health care system, and society. Recommendations from the UK, the US, and the Netherlands were used for the analyses.	Patients with suspected CAD who presented with chest pain suggestive of angina. These patients have been referred for ICA based on their history or functional test results.	From the hospital/health care perspective, CCTA helps reduce health care costs (according to UK/US recommendations) regardless of pre-test likelihood of CAD, and lowers all costs, including production losses, at a PTL of less than 87-92%. Analysis performed from a societal perspective (using a willingness to pay threshold of €80,000/QALY) suggest that CCTA is cost-effective when the PTL is lower than 44% in men and 37% in women.	The Markov model calculations from the patient/physician perspective maximizes life-years in 60-year old men and women at a PTL of CAD of less than 38% and 24%, respectively. QALYs are maximized at a PTL of less than 17% and 11% for men and women, respectively.	The optimal diagnostic strategy depends on optimization criteria, PTL of CAD, and test characteristics. Analysis suggests that CCTA performed as a triage test prior to ICA is cost-effective in men with a PTL of CAD less than 44% and in women with less than 37%.

						Above this level, conventional ICA remains the most cost-effective strategy. To maximize patient outcomes, a lower threshold applies and to lower costs, a higher threshold should be used.
[E16] Sharples 2007	Papworth Hospital NHS Foundation Trust, UK	Systematic review of economic evaluations of diagnostic strategies for CAD and a randomised controlled trial that looked at outcomes of 4 different diagnostic tests: (1) ICA (control) (2) SPECT (3) MRI (4) stress echo	Patients with suspected or known CAD and an XT result that required non-urgent ICA. 898 patients were randomised to ICA (n=222), SPECT (n=224), MRI (n=226), and stress echo (n=226). No significant differences between the groups at baseline.	Mean total additional costs over 18 months compared with ICA were £415 for SPECT, £426 for MRI, and £821 for stress echo with very little difference in QALYs.	Eighteen months post-randomisation: exercise time and cost-effectiveness (diagnosis, treatment, and follow-up costs) compared with ICA. Comparing SPECT and stress echo with ICA, a clinically significant difference in total exercise time can be ruled out. The MRI group had significantly shorter mean total exercise time of 35 seconds.	Between 20 and 25% of patients can avoid invasive testing using functional testing as a gateway to ICA, without substantial effects on outcomes. The SPECT strategy was as useful as ICA in identifying patients who should undergo revascularization and the additional cost was not significant. MRI had the largest

						number of test failures and had the least practical use in screening patients with suspected CAD, although it had similar outcomes to stress echo and is still an evolving technology. Stress echo patients had a 10% test failure rate, significantly shorter exercise time, and a greater number of adverse events, leading to significantly higher costs.
[E17] Mowatt 2004	UK	The authors conducted a systematic literature review of clinical and economic data and also created a decision tree model (Markov) to model the management of patients with suspected CAD. The strategies considered in the model were: (1) XT followed by SPECT (if +) followed	The literature search included adults with suspected or diagnosed CAD with the exception of pregnant women.	For the base case analysis , the results for costs and QALYs for the different strategies were: (1) £5190 yielding 12.473 QALYs (2) £5395 yielding 12.481 QALYs (3) £5529 yielding 12.497 QALYs (4) £5929 yielding 12.506 QALYs	At the baseline prevalence of 10.5%, SPECT–ICA was cost-effective whereas ICA, although generating more QALYs, did so at a relatively high incremental cost per QALY (£42,225). At 30% prevalence	SPECT is more sensitive than XT for the detection of CAD. SPECT provides independent and incremental information in predicting cardiac events in patients over

		by ICA (if +) (2) XT followed by ICA (if +) (3) SPECT followed by ICA (if +) (4) ICA alone	Subgroup analysis was planned on patients with previous MI and women.		rates, whereas SPECT–ICA was cost-effective, the ICA strategy produced more QALYs at a relatively low incremental cost-effectiveness ratio (£7331). At higher prevalence rates (50 and 85%), the SPECT–ICA strategy was extendedly dominated by the stress ECG–ICA and ICA strategies. In other words, over a defined range, if some patients received stress ECG–ICA with the rest receiving ICA, the costs would be lower and the QALYs higher than if SPECT–ICA alone was used.	and above that provided by XT and ICA. For the diagnosis of CAD in a low to medium-risk population, SPECT based strategies compared with those that rely on XT are likely to be associated with additional benefits which may be considered affordable.
[E18] Lee 2002	Korea	Three strategies by which to diagnose CAD were compared for their cost-effectiveness when considering the prognostic value of false-negative results:	Not explicitly stated in the publication – inferred to be all patients in Korea who	Costs of each pathway were not explicitly reported in the publication. Data on cost/ΔQALY were reported for each pathway as explained in the 'patient outcomes' column.	The myocardial SPECT followed by ICA strategy was the most cost-effective in patients with a PTL of CAD of	In view of the low event rate of negative SPECT, the more expensive myocardial SPECT

		(1) stress myocardial SPECT followed by ICA (2) exercise stress echocardiography followed by ICA (3) dobutamine stress echocardiography followed by ICA.	present for evaluation of possible CAD		0.3 or greater. The dobutamine echocardiography followed by ICA strategy was the most cost-effective in patients with a PTL of 0.2 or lower. The cost-effectiveness of exercise echocardiography was dubious because of the high nondiagnostic rate with inadequate exercise.	strategy (1) was more cost-effective than the cheaper stress echocardiography strategy (3).
[E19] Shreibati 2011	United States	Retrospective, observational cohort study comparing downstream utilization and spending associated with stress testing and anatomical (CCTA) cardiac testing	Patients enrolled in Medicare who were 66 years or older and received non-emergent, non-invasive testing for CAD	Costs in the 180 days post testing was higher for CCTA ($29719) than for MPS ($27884) or Stress Echo ($20371) or Exercise EKG ($17355).	Compared with stress MPS, CCTA was associated with an increased likelihood of subsequent ICA (22.9% vs. 12.1%), PCI (7.8% vs. 3.4%), and CABG (3.7% vs. 1.3%). CCTA was associated with a similar likelihood of all-cause mortality (1.05% vs. 1.28%) and a slightly lower likelihood of	Medicare beneficiaries who underwent CCTA in a nonacute setting were more likely to undergo subsequent invasive cardiac procedures, have higher costs in the following 180 days, and had similar outcomes compared with those who

					hospitalization for acute MI (0.19% vs. 0.43%).	underwent stress testing.
[E20] Genders 2015	UK, US, and Netherlands	Microsimulation model to evaluate cost-effectiveness of 5 diagnostic strategies: (1) no imaging (2) CCTA (3) cardiac stress imaging (CSI) (4) CCTA+CSI (5) ICA	60 year old patients with stable chest pain and a low-intermediate PTL of CAD. Base case: patients who were eligible for cardiac imaging and had a 30% PTL of CAD	Lifetime costs, QALYs and incremental cost-effectiveness ratios based on evidence from the literature and expert opinion with analysis from the perspective of UK, US, and Netherlands	Mean radiation exposure was low for stress Echo and MRI (6-9 mSv), intermediate for CCTA (11-14mSv) and high for SPECT (15-18 mSv). Risk of MACE was dependent on disease severity. Estimated QALYs were similar across strategies. Initial use of CCTA rather than CSI consistently increased effectiveness.	In US and Netherlands maximal QALY and cost-effectiveness was using CCTA first with CSI if >50% stenosis found and then ICA. For UK men, preferred strategy was OMT with no ICA if CCTA found only moderate CAD or CSI induced only mild ischemia. For UK women, optimal strategy was stress Echo with ICA if mild or moderate ischemia was induced. Results were sensitive to changes in PTL of CAD and assumptions about FP results. CCTA was a cost-effective triage

						for 60 y.o. patients with non-acute chest pain and low-intermediate PTL of CAD.

Table C3.2 Summary list of all evaluations involving costs – Unpublished Studies

Study name (year)	Location of Study	Summary of model and comparators	Patient population	Costs	Patient outcomes	Results
[E21] PLATFORM	UK, France, Germany, Austria, Denmark, and Italy	Multicentre prospective controlled study comparing clinical outcomes, resource utilization, and QOL following standard practice-guided treatment (Cohort 1) versus FFR_{CT} guided treatment (Cohort 2). Cohorts 1A and 2A are patients referred for NIT for evaluation of suspected CAD. Cohorts 1B and 2B are patients referred for ICA.	Patients at intermediate likelihood of obstructive CAD (UDF score 20% - 80%)	All costs were assigned from Medicare values or NHS 2014 tariffs and the described method of analysis was performed under the direction of Mark Hlatky, MD. CCTA £136 MPI £220 ICA £1,241 PCI ≤2 vessels £2,704 PCI >2 vessels £3,216 CABG £20,424 FFR_{CT} £0	The primary outcome of PLATFORM was the rate of ICA without obstructive CAD. Patients in Cohort 1B had a rate of 75% while patients in Cohort 2B had a rate of 11%. Patients in Cohort 1B had an ICA rate of 100% while patients in Cohort 2B had a rate of 35%. Secondary outcomes looked at MACE defined as all cause death, non-fatal MI, and unplanned hospitalization for acute coronary syndrome. The rates were low and the two cohorts were not statistically different.	The PLATFORM trial demonstrated a significant difference in average cost per patient when diagnostic and treatment plans included FFR_{CT}. Average per-patient costs were: Cohort 1: £3916 Cohort 2: £2584 Cohort 1A: £1101 Cohort 2A: £1176 Cohort 1B: £5429 Cohort 2B: £3351 Cohort 2 (FFR_{CT} guided treatment) also experienced a statistically significantly greater increase in QOL between baseline and 90 days, as measured by their SAQ and EQ5FL scores. For Cohort 1 the increase in SAQ compared to baseline was 14.0 and for Cohort 2 was 18.3. Cohort 1

						experienced an increase in their EQ5DL score of 0.04 and Cohort 2 experienced an increase of 0.07.
[E22] Federspiel	United States	Procedure codes used to identify patients undergoing ICA. Expenditures in year proceeding ICA compared to expenditures in year following ICA.	31,156 Medicare patients undergoing ICA or with stable CAD in 2010.	Costs derived from Medicare 5% Standard Analytic Files including Carrier, Inpatient, Outpatient, and Denominator Files for 2009-11.	No patient outcomes reported	Mean allowed charges in the year preceding ICA were $8,855 and $20,047 in the year following ICA. For those patients who survived the year following ICA without PCI, CABG, valve surgery, MI or additional invasive or non-invasive coronary testing, mean allowed charges in the year preceding ICA were $7,823 and $10,083 in the year following ICA, an increase of 29%. Paper concludes that referral to ICA is associated with a significant increase in Medicare expenditures, even in patients who do not undergo subsequent cardiac procedures or noninvasive testing.
[E23] Papafaklis	Greece	Decision tree model that simulates	Patients with suspected CAD	Costs are in US $	Patient outcomes were not specifically modeled.	Projected costs per patient for the first

		outcomes and costs of two separate clinical strategies: 1) Initial assessment with FFR_{CT} and patients with FFR_{CT} proceeding to ICA and FFR-guided PCI 2) Initial assessment with ICA followed by FFR-guided PCI		1. ICA (without PCI): $3,350 2. FFR-guided PCI: $12,079 3. FFR_{CT}: $1,000 4. Acute MI care: $5,640 5. Chronic MI care: $2,100	However, the cost of initial management and 1-year clinical outcomes were included in the analysis.	year following assessment of suspected CAD were: 1) FFR_{CT} strategy - $7,318 when using data from the DeFACTO study and $4,866 when using data from the NXT study (refined FFR_{CT} technology). 2) ICA strategy - $7,714
[E24] PROMISE cost-effectiveness	United States	Patients randomly assigned to strategy of initial anatomical testing with the use of CCTA or to functional testing (XT, MPI, or stress echocardiography)	10,003 patients with symptoms suggestive of CAD. Mean age of patients was 60.8±8.3 years. 52.7% were women.	Costs were calculated using estimates for initial diagnostic test technical fees using resource-based cost accounting methods. Hospital based facility costs came from UB 04 forms. MD professional fee estimates taken from Medicare Fee Schedule.	Over median follow-up period of 25 months, a primary end-point event (death, myocardial infarction, hospitalization for unstable angina, or major procedural complication) occurred in 3.3% of the CCTA group and in 3.0% of the functional-imaging testing group (P=0.75).	There was no significant difference in cost between the two arms. Analysis concludes that increased use of CCTA may improve some aspects of care without causing a major new economic burden on the health care system.

8.2.2 Provide a complete quality assessment for each health economic study identified. A suggested format is shown in table C3.

Table C4.1 Quality assessment of Rajani 2015

Study name [E1] Comparative efficacy testing – Fractional flow reserve by coronary computed tomography for the evaluation of patients with stable chest pain		
Study design	Retrospective analysis and cost-consequences model	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	

12. Were the methods used to value health states and other benefits stated?	N/A	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	N/A	
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	No	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	N/A	
27. Was the approach to sensitivity analysis described?	No	
28. Was the choice of variables for sensitivity analysis justified?	No	

29. Were the ranges over which the parameters were varied stated?	N/A	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	N/A	
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	

Table C4.2 Quality assessment of Kimura 2015

Study name [E2] Cost analysis of non-invasive fractional flow reserve derived from coronary computed tomographic angiography in Japan		
Study design	Retrospective cost consequences model	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	

7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	Yes	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	

22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	N/A	
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	No	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	N/A	
27. Was the approach to sensitivity analysis described?	N/A	
28. Was the choice of variables for sensitivity analysis justified?	N/A	
29. Were the ranges over which the parameters were varied stated?	N/A	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	N/A	
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	

Table C4.3 Quality assessment of Hlatky 2014

Study name: [E3] Economic outcomes in studies of myocardial perfusion and anatomy imaging: The SPARC study		
Study design	Prospective Observational Registry	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**

1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	N/A	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	

16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	N/A	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	N/A	
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	No	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	

33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	

Table C4.4 Quality assessment of Hlatky 2013

Study name [E4] Projected Costs and Consequences of Computed Tomography-Determined Fractional Flow Reserve		
Study design	Retrospective cost consequences model	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	

10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	No	

26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	

Table C4.5 Quality assessment of Fearon 2013

Study name [E5] Cost-Effectiveness of Percutaneous Coronary Intervention in Patients with Stable Coronary Artery Disease and Abnormal Fractional Flow Reserve		
Study design	Prospective Randomized Trial	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	

4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	

19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	Yes	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	

Table C4.6 Quality assessment of Westwood 2013

Study name [E6] A systematic review and economic evaluation of new-generation computed tomography scanners for imaging in coronary artery disease and congenital heart disease: Somatom Definition Flash, Aquilion ONE, Brilliance iCT and Discovery CT750 HD		
Study design	Literature review and economic evaluation	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	

13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	No	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?		
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	Yes	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	

30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	

Table C4.7 Quality assessment of Nielsen 2012

Study name [E7] Effects on costs of frontline diagnostic evaluation in patients suspected of angina: coronary computed tomography angiography vs. conventional ischaemia testing		
Study design	Retrospective, 2 center study	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	

8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	No	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	N/A	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	N/A	
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	

24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	No	
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	

Table C4.8 Quality assessment of Min 2012

Study name [E8] Coronary CT angiography versus myocardial perfusion imaging for near-term quality of life, cost and radiation exposure: A prospective multicenter randomized pilot trial		
Study design	Randomized, controlled trial	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	

2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	No	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	No	

17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	No	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	N/A	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	N/A	
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	No	
28. Was the choice of variables for sensitivity analysis justified?	N/A	
29. Were the ranges over which the parameters were varied stated?	N/A	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	N/A	
31. Was an incremental analysis reported?	N/A	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	

35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	

Table C4.9 Quality assessment of Moschetti 2012

Study name [E9] Cost evaluation of cardiovascular magnetic resonance versus coronary angiography for the diagnostic work-up of coronary artery disease: Application of the European Cardiovascular Magnetic Resonance registry data to the German, United Kingdom, Swiss, and United States health care systems		
Study design	Retrospective economic modeling study	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	Specific for each country

11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	N/A	
13. Were the details of the subjects from whom valuations were obtained given?	N/A	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	No	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	No	

28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	No	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	No	
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	

Table C4.10 Quality assessment of Dorenkamp 2011

Study name [E10] Direct costs and cost-effectiveness of dual-source computed tomography and invasive coronary angiography in patients with an intermediate pretest likelihood for coronary artery disease		
Study design	Single center modeling study	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	No	
5. Were the alternatives being compared clearly described?	Yes	

6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	N/A	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	

21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives	N/A	
compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)		
31. Was an incremental analysis reported?	N/A	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	

Table C4.11 Quality assessment of Cheezum 2011

Study name [E11] Cardiac CT angiography compared with myocardial perfusion stress testing on downstream resource utilization

Study design	Retrospective single center study	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	N/A	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	No	

15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	N/A	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	N/A	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	N/A	
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	N/A	
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	No	
28. Was the choice of variables for sensitivity analysis justified?	N/A	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	No	
31. Was an incremental analysis reported?	No	

32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	

Table C4.12 Quality assessment of Pilz 2010

Study name [E12] Adenosine-stress cardiac magnetic resonance imaging in suspected coronary artery disease: a net cost analysis and reimbursement implications		
Study design	Retrospective economic modeling study	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	

10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	N/A	
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	No	
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	No	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	N/A	

26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	No	
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	

Table C4.13 Quality assessment of Min 2010

Study name [E13] Cost-effectiveness of Coronary CT Angiography versus Myocardial Perfusion SPECT for Evaluation of Patients with Chest Pain and No Known Coronary Artery Disease		
Study design	Decision analysis and economic modeling study	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	

4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	No	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	Yes	appendix
17. Were the methods for the estimation of quantities and unit costs described?	Yes	appendix
18. Were currency and price data recorded?	Yes	

19. Were details of price adjustments for inflation or currency conversion given?	Yes	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	Yes	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	

Table C4.14 Quality assessment of Ladapo 2009

Study name [E14] Clinical outcomes and cost-effectiveness of CCTA in the evaluation of patients with chest pain		
Study design	Computer simulation model	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	The comparative effectiveness of CCTA on patient outcomes and healthcare costs is unknown.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	The authors used a diverse range of management approaches but acknowledge that these represent only a subset of algorithms used in practice.
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	Test characteristics for CCTA and stress EKG, echocardiography, and SPECT were derived from meta-analyses. The authors pooled diagnostic accuracy estimates with a random effects model.
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	

13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	N/A	Productivity changes were not included
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	Yes	Quantities for each diagnostic strategy were not reported separately
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	Yes	All costs were converted to 2005 US dollars with the medical care component of the Consumer Price Index.
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
22. Was the time horizon of cost and benefits stated?	Yes	The model looked at a lifetime horizon
23. Was the discount rate stated?	Yes	3.0%
24. Was the choice of rate justified?	Yes	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	1-way sensitivity analysis on key parameters
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	

30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	Costs were presented both as total costs and separated into cardiac care and averse event costs
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	Authors did include a nondiagnostic exam rate for CCTA but not for other forms of stress testing – this may lead to an overestimation of the efficiency of this modality.
36. Were generalisability issues addressed?	Yes	Authors state their results are comparable to other studies examining the effectiveness of CCTA. They also state that large randomized controlled trials are needed.

Table C4.15 Quality assessment of Genders 2009

Study name [E15] CT Coronary Angiography in Patients Suspected of Having CAD: decision making from various perspectives in the face of uncertainty		
Study design	Decision analysis and economic modeling study	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	Determine the cost-effectiveness of CCTA performed as a triage test prior to conventional ICA.
2. Was the economic importance of the research question stated?	Yes	CCTA's effect on patient outcomes and cost-effectiveness has not been determined.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	No	No alternatives were considered
5. Were the alternatives being compared clearly described?	N/A	No alternative patient pathways were modeled or compared.
6. Was the form of economic evaluation stated?	Yes	

7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	All variables were entered in the model as distributions. The range was used in the sensitivity analysis.
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	Health states were modeled for whether a patient was alive or dead and whether a cardiovascular event occurred
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	Yes	
15. Was the relevance of productivity changes to the study question discussed?	Yes	
16. Were quantities of resources reported separately from their unit cost?	No	No quantities of resources used were reported
17. Were the methods for the estimation of quantities and unit costs described?	No	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	Yes	All costs were converted to year 2007 rates, given Dutch consumer price indices, and reported in Euros.
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	

22. Was the time horizon of cost and benefits stated?	Yes	Markov model (cycle length, 1 year) was used to model long term outcomes
23. Was the discount rate stated?	Yes	The discount rate was different in each analysis
24. Was the choice of rate justified?	Yes	Selected according to UK recommendations
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	N/A	No statistical analysis were performed
27. Was the approach to sensitivity analysis described?	Yes	One and two way sensitivity analyses were performed in addition to a probabilistic analysis
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	Varying the SN of CCTA changed the optimum pre-test likelihood of CAD threshold at which QALYs and cost-effectiveness was maximized. The threshold was not sensitive to changes across other parameter inputs.
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	Authors did not consider other noninvasive tests besides CCTA but rather considered only patients referred for ICA for whom either the history or functional test results suggested the presence of CAD.
36. Were generalisability issues addressed?	No	

Table C4.16 Quality assessment of Sharples 2007

Study name [E16] Cost-effectiveness of functional cardiac testing in the diagnosis and management of coronary artery disease: a randomized controlled trial. The CECaT trial		
Study design	Literature review and single-centre randomised controlled trial	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	A NHS perspective was adopted for the economic analysis.
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	The results were summarised under a series of pairwise comparisons.
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	N/A	

13. Were the details of the subjects from whom valuations were obtained given?	N/A	
14. Were productivity changes (if included) reported separately?	N/A	Not included
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	Yes	Detailed tables are presented with quantities
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Costs were based on 2005-6 prices from the finance department of the hospital
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	N/A	
20. Were details of any model used given?	N/A	No model used
21. Was there a justification for the choice of model used and the key parameters on which it was based?	N/A	
22. Was the time horizon of cost and benefits stated?	Yes	18-months of follow-up
23. Was the discount rate stated?	Yes	Discount rate of 3.5% was pplied to all costs incurred between 12 and 18 months
24. Was the choice of rate justified?	Yes	Department of Health guidelines
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	

30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	N/A	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	Authors note that this was a single-centre study and that there was significant breach of trial protocol.
36. Were generalisability issues addressed?	Yes	Authors note the need for wider availability of these diagnostic tests.

Table C4.17 Quality assessment of Mowatt 2004

Study name [E17] Systematic Review of the effectiveness and cost-effectiveness, and economic evaluation, of myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction		
Study design	Decision analysis and economic modeling study	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	Assess the effectiveness and cost-effectiveness of SPECT MPS for the diagnosis and management of angina and MI.
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	

7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	Multiple studies
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	QUADAS was used for quality assessment. Diagnostic performance indexes were extracted and recalculated for both SPECT and stress EKG. No attempt was made to synthesise the economic studies.
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	N/A	Not included
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	N/A	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	The costs were taken from the literature.
18. Were currency and price data recorded?	Yes	Costs for the treatments were described in 2001-02 pounds sterling
19. Were details of price adjustments for inflation or currency conversion given?	Yes	
20. Were details of any model used given?	Yes	The model layout was given in the appendix.
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	It was developed in consultation with clinicians and in consideration of the existing economic literature.

22. Was the time horizon of cost and benefits stated?	Yes	In the base-case analysis a horizon of 25 years was used. Shorter time horizons were explored in the sensitivity analysis.
23. Was the discount rate stated?	Yes	Annual discount rates of 6 and 1.5% were used for costs and outcomes,
24. Was the choice of rate justified?	Yes	In accordance with NICE guidelines.
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	Extensive reporting in the appendix and discussed in the text.
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	All of the studies were prognostic and may be biased. 34 of the studies took place in the US 12 were set in Europe and therefore may not be generalisable to the UK.

Table C4.18 Quality assessment of Lee 2002

Study name [E18] Comparison of the cost-effectiveness of stress myocardial SPECT and stress echocardiography in suspected coronary artery disease considering the prognostic value of false-negative results		
Study design	Diagnostic pathway model	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	Authors wanted to examine the impact of the different prognostic value of false negative from SPECT and stress echocardiography tests
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	No	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Literature review of the prognostic value of negative SPECT results was described
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes/No	Sources for SN/SP values were clearly stated but sources for nondiagnostic rate of tests were not clearly explained
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	No	It is inferred that authors used the range of values presented in literature for their sensitivity analysis
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	

13. Were the details of the subjects from whom valuations were obtained given?	Yes	0 (death) to 1 (perfect health) were the modeled health states
14. Were productivity changes (if included) reported separately?	N/A	Productivity changes were not included
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	No	No quantities were reported
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Test costs and the costs of treating complications were obtained from Korean insurance data.
18. Were currency and price data recorded?	Yes	All costs were presented in US dollars.
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	Outline of the model was presented
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
22. Was the time horizon of cost and benefits stated?	Yes	Time horizon is stated but not clear
23. Was the discount rate stated?	Yes	Discount rate of 5% was used.
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	Ranges were extracted from the literature
29. Were the ranges over which the parameters were varied stated?	Yes	

30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	Authors state that the study was undertaken to emphasize the importance of the prognostic value of cases of negative or false-negative results in terms of the cost-effectiveness of the studied strategies.
36. Were generalisability issues addressed?	No	

Table C4.19 Quality assessment of Shreibati 2011

Study name [E19] Association of Coronary CT Angiography or Stress Testing with Subsequent Utilization and Spending among Medicare Beneficiaries		
Study design	Retrospective, observational cohort study	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	The number of CCTA procedures among Medicare beneficiaries has increased steadily
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	

7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	N/A	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	N/A	
13. Were the details of the subjects from whom valuations were obtained given?	N/A	
14. Were productivity changes (if included) reported separately?	No	Patients' level of symptoms and QOL were not captured in this study
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Quantities were based on actual claims data, not on estimates
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	N/A	Time horizon of the study was 180-days following the index test
20. Were details of any model used given?	N/A	Study based on actual Medicare claims data
21. Was there a justification for the choice of model used and the key parameters on which it was based?	N/A	

22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	N/A	Time horizon of the study was 180-days following the index test
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	Yes	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	Sensitivity analysis was not performed in the usual sense because the study is based on actual claim data and costs
28. Was the choice of variables for sensitivity analysis justified?	N/A	
29. Were the ranges over which the parameters were varied stated?	Yes	One analysis capped 180-day spending at $200,000 to assess sensitivity to outliers
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	N/A	
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	Total spending and CAD-related spending were reported separately
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	Study did not include long-term follow up needed to assess the effect of CCTA on subsequent cardiac events and did not look at QOL
36. Were generalisability issues addressed?	Yes	Results are likely representative of individuals older than 65 years but the findings should not be extended to CCTA performed on patients in the emergency room

Table C4.20 Quality assessment of Genders 2015

Study name [E20] The Optimal Imaging Strategy for Patients with Stable Chest Pain; A cost-effectiveness Analysis		
Study design	Microsimulation transition-state model	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	N/A	

14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	N/A	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	Yes	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	

31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	

Table C4.21 Quality assessment of PLATFORM – unpublished

Study name [E21] The PLATFORM Study: Prospective Longitudinal Trial of FFR_{CT}: Outcome and Resource Impacts		
Study design	Multicentre prospective post-market sequential cohort study	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	N/A	No estimates were used as results are from actual patient data

9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	N/A	
13. Were the details of the subjects from whom valuations were obtained given?	N/A	
14. Were productivity changes (if included) reported separately?	N/A	Productivity changes were not reported
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	N/A	
20. Were details of any model used given?	N/A	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	N/A	
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	N/A	

25. Was an explanation given if cost or benefits were not discounted?	No	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	N/A	No sensitivity analysis was performed as results are from actual patient data
28. Was the choice of variables for sensitivity analysis justified?	N/A	
29. Were the ranges over which the parameters were varied stated?	N/A	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	N/A	
31. Was an incremental analysis reported?	N/A	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	

Table C4.22 Quality assessment of Federspiel – unpublished

Study name [E22] Health care utilization preceding and following coronary angiogram among Medicare beneficiaries		
Study design	Retrospective economic modeling study	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	

3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	N/A	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	N/A	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	No	

18. Were currency and price data recorded?	N/A	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	No	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	No	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	N/A	
27. Was the approach to sensitivity analysis described?	N/A	
28. Was the choice of variables for sensitivity analysis justified?	N/A	
29. Were the ranges over which the parameters were varied stated?	N/A	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	No	
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	

36. Were generalisability issues addressed?	Yes	

Table C4.23 Quality assessment of Papafaklis – unpublished

Study name [E23] Projected Cost of Computed Tomography-Derived Fraction Flow Reserve in Suspected Coronary Artery Disease: Effect of Enhanced Image Quality and Technology Refinements		
Study design	Decision Tree Model	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	Two sources of effectiveness were cited and the model was run with data from both studies.
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	

12. Were the methods used to value health states and other benefits stated?	N/A	
13. Were the details of the subjects from whom valuations were obtained given?	N/A	
14. Were productivity changes (if included) reported separately?	N/A	Productivity changes were not included
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	N/A	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
22. Was the time horizon of cost and benefits stated?	Yes	Study was based on initial management and 1-year clinical outcomes
23. Was the discount rate stated?	N/A	1-year horizon so discount rate is not needed
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	Sensitivity analysis was run only for SN and SP of FFR_{CT}
28. Was the choice of variables for sensitivity analysis justified?	Yes	The one variable in the sensitivity analysis was explained

29. Were the ranges over which the parameters were varied stated?	Yes	Data from two studies of FFR_{CT} technology was used
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	No	
36. Were generalisability issues addressed?	No	

Table C4.24 Quality assessment of PROMISE cost-effectiveness – unpublished

Study name: [E24] PROMISE – Economic Outcomes (2015)		
Study design:	Multi-centre, Randomised	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	

7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	No	
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	No	
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	N/A	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	N/A	

22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	No	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	N/A	
28. Was the choice of variables for sensitivity analysis justified?	N/A	
29. Were the ranges over which the parameters were varied stated?	N/A	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	No	
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	

9 De novo cost analysis

Section 9 requires the sponsor to provide information on the de novo cost analysis.

The de novo cost analysis developed should be relevant to the scope.

All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.

Note that NICE cites the price of the product used in the model in the Medical Technology guidance.

9.1 Description of the de novo cost analysis

9.1.1 Provide the rationale for undertaking further cost analysis in relation to the scope.

To date, while there have been several publications on the cost consequences of patient care including FFR_{CT}, including one in the UK, none has used the NICE guideline on stable chest pain (CG95) as the comparator or otherwise matches the specific scope. The de novo cost analysis allows us to estimate the economic impact of using FFR_{CT} in the UK within the scope.

Patients

9.1.2 What patient group(s) is (are) included in the cost analysis?

As outlined in the scope, the patient population included in the cost analysis includes people with stable chest pain who require investigation for possible coronary artery disease and have a pre-test likelihood between 10% and 90%.

Technology and comparator

9.1.3 Provide a justification if the comparator used in the cost analysis is different from the scope.

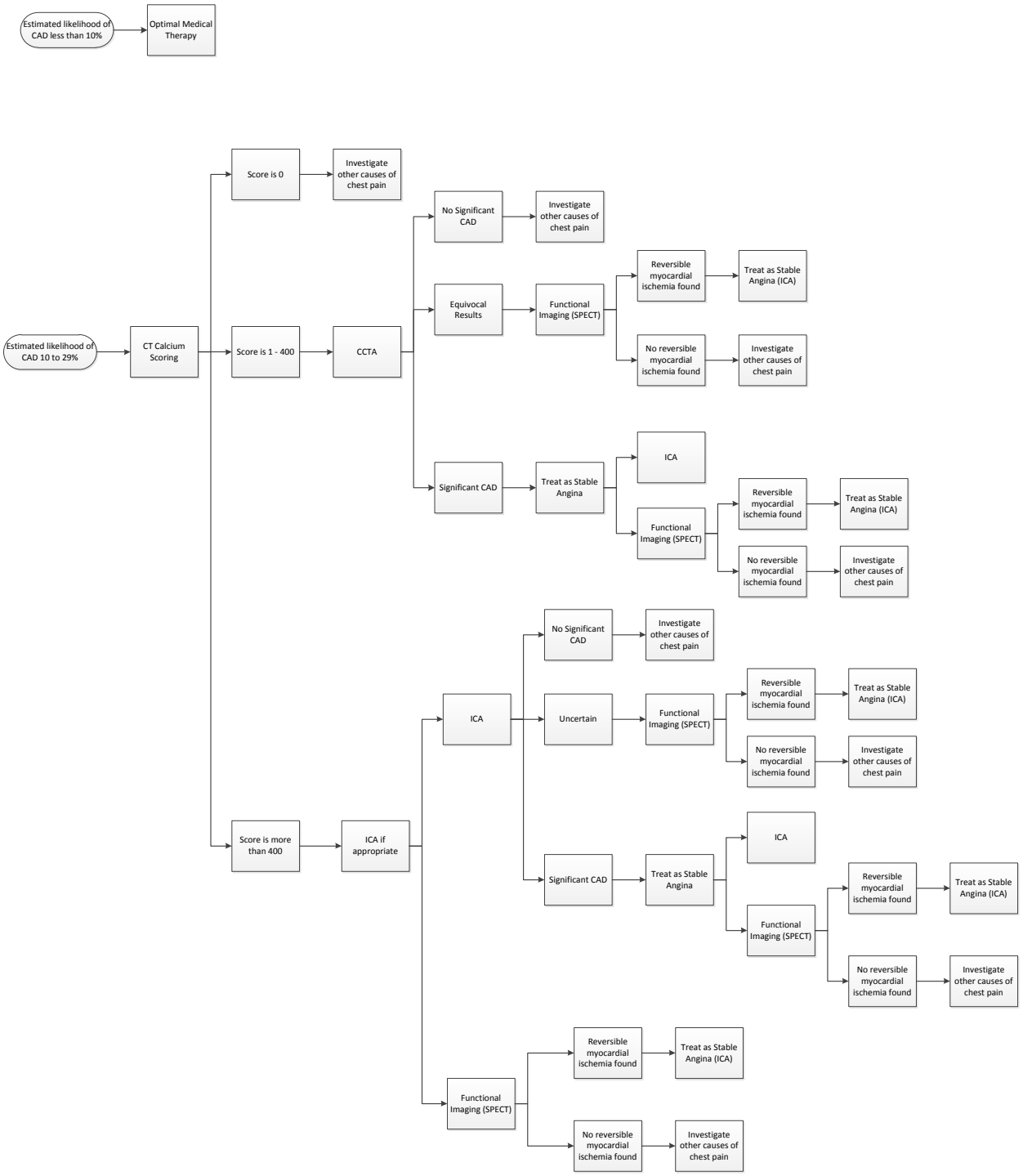
Not applicable.

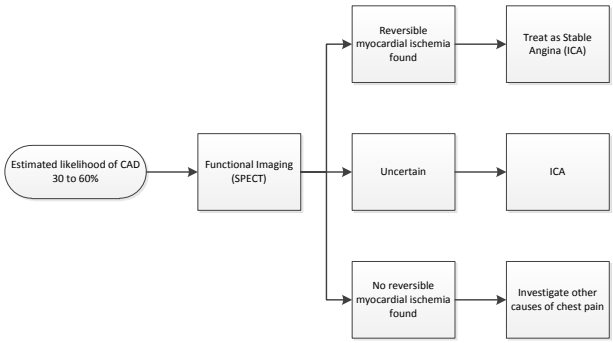
Model structure

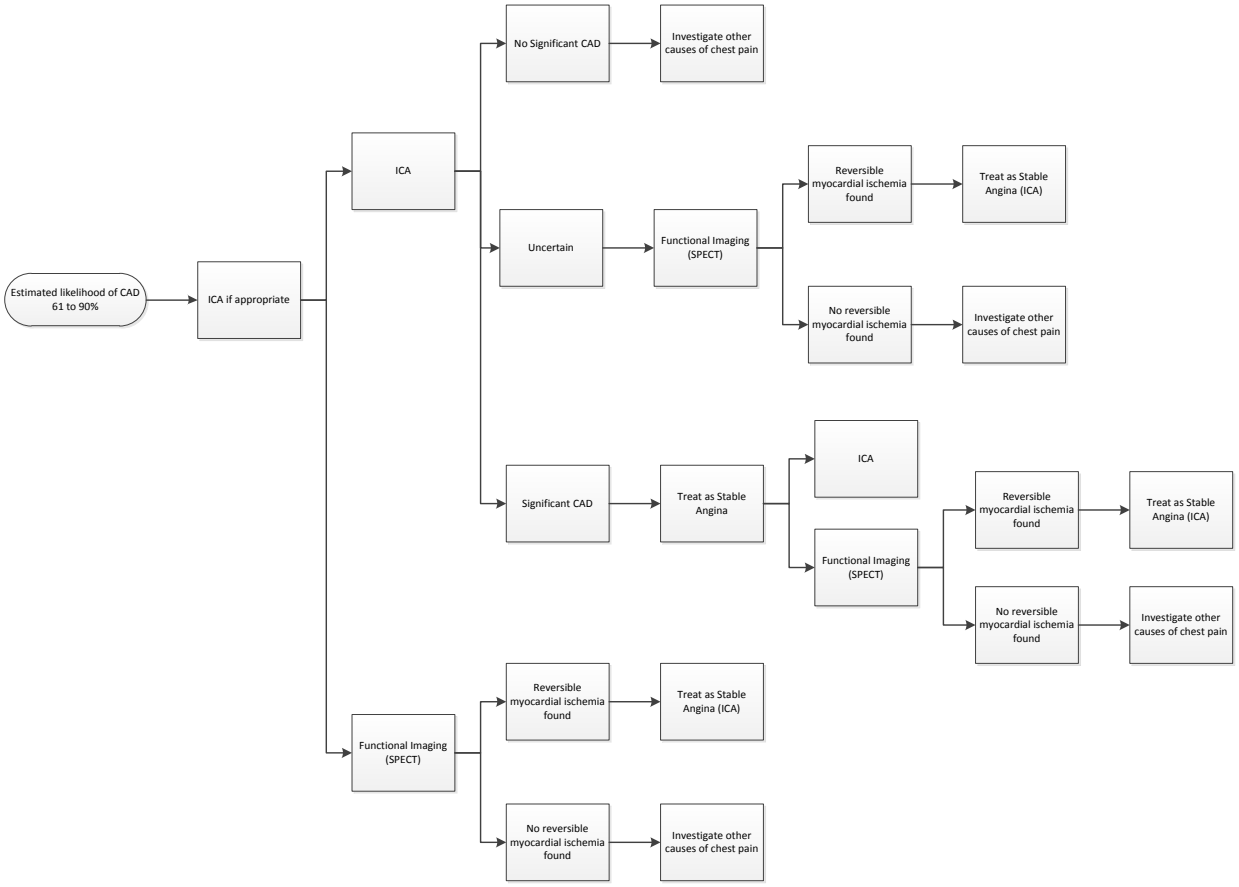
9.1.4 Provide a diagram of the model structure you have chosen.

The cost effectiveness model is based on the NICE guideline on stable chest pain pathway (CG95) (see diagram in section 3.3). It is proposed that HeartFlow's noninvasive FFR_{CT} 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%. Below we have provided flow charts used in the economic model. The first (Figure C2.1) describes the NICE guidelines for patients with stable chest pain and the second (Figure C.2.2) incorporates the use of FFR_{CT} as described above.

Figure C2.1 Flow Chart of current NICE stable chest pain pathway used for economic model




Estimated likelihood of CAD 30 to 60%
Functional Imaging (SPECT)
Reversible myocardial ischemia found
Uncertain
No reversible myocardial ischemia found
Treat as Stable Angina (ICA)
ICA
Investigate other causes of chest pain


Estimated likelihood of CAD 61 to 90%
ICA if appropriate
ICA
No Significant CAD
Investigate other causes of chest pain
Uncertain
Functional Imaging (SPECT)
Reversible myocardial ischemia found
Treat as Stable Angina (ICA)
No reversible myocardial ischemia found
Investigate other causes of chest pain
Significant CAD
Treat as Stable Angina
ICA
Functional Imaging (SPECT)
Reversible myocardial ischemia found
Treat as Stable Angina (ICA)
No reversible myocardial ischemia found
Investigate other causes of chest pain
Functional Imaging (SPECT)
Reversible myocardial ischemia found
Treat as Stable Angina (ICA)
No reversible myocardial ischemia found
Investigate other causes of chest pain

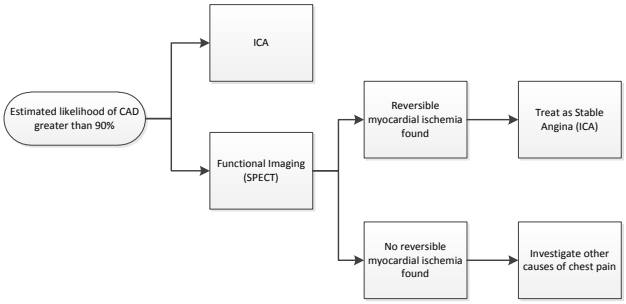
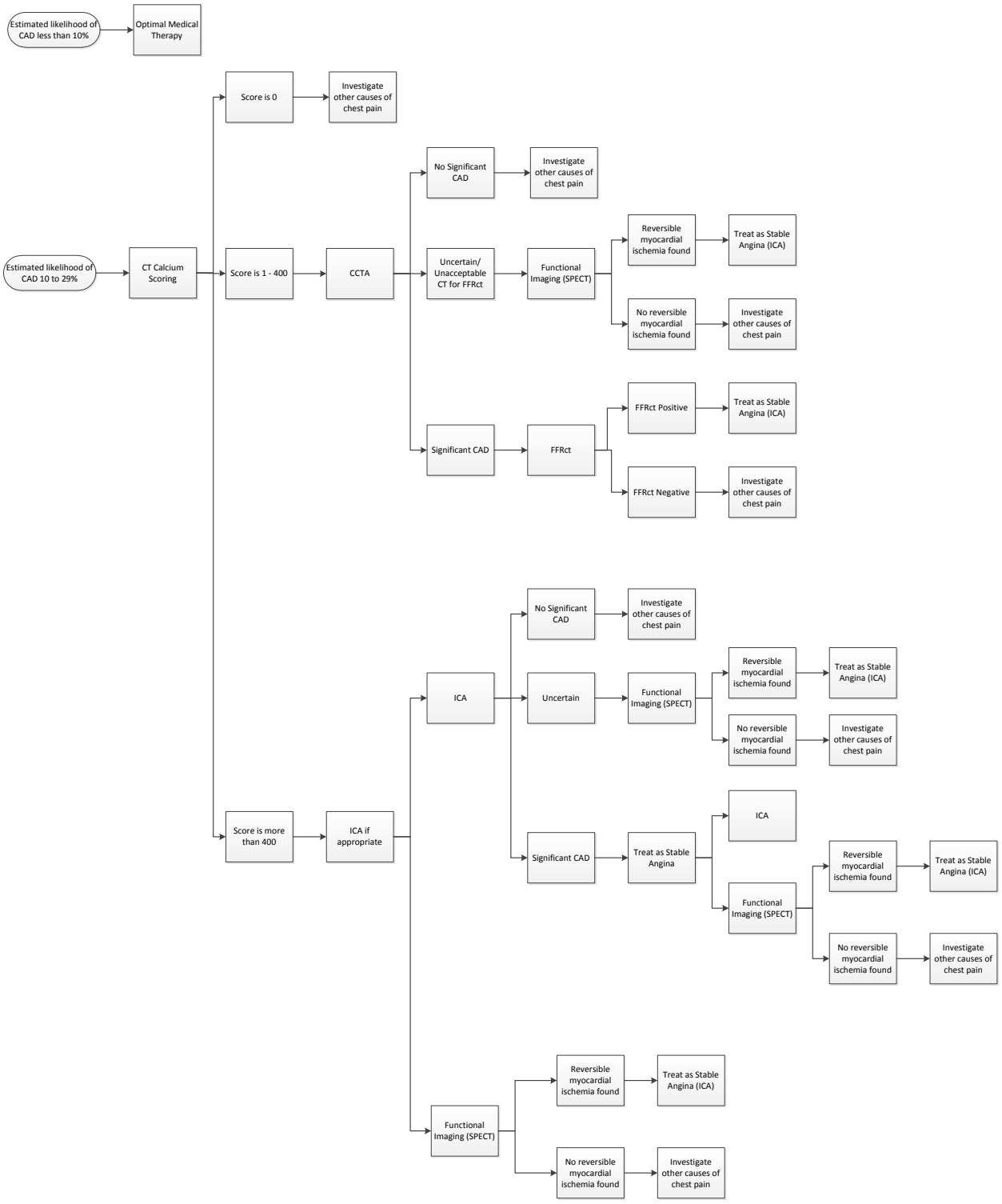
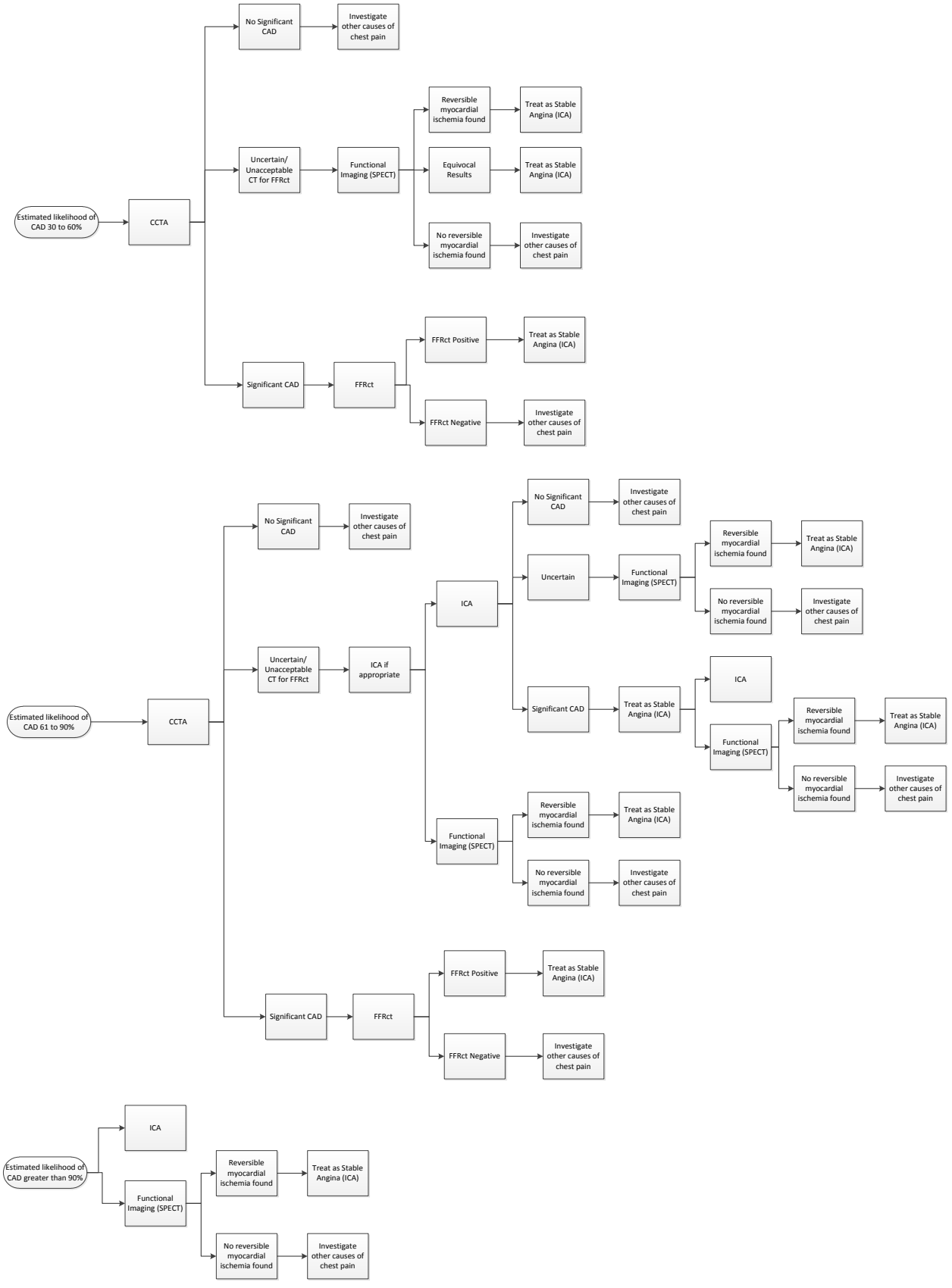

Estimated likelihood of CAD greater than 90%
ICA
Functional Imaging (SPECT)
Reversible myocardial ischemia found
Treat as Stable Angina (ICA)
No reversible myocardial ischemia found
Investigate other causes of chest pain

Figure C2.2 Flow Chart of proposed FFR_{CT} pathway used for economic model




Estimated likelihood of CAD 30 to 60%
CCTA
No Significant CAD
Investigate other causes of chest pain
Uncertain/ Unacceptable CT for FFRct
Functional Imaging (SPECT)
Reversible myocardial ischemia found
Treat as Stable Angina (ICA)
Equivocal Results
Treat as Stable Angina (ICA)
No reversible myocardial ischemia found
Investigate other causes of chest pain
Significant CAD
FFRct
FFRct Positive
Treat as Stable Angina (ICA)
FFRct Negative
Investigate other causes of chest pain
Estimated likelihood of CAD 61 to 90%
CCTA
No Significant CAD
Investigate other causes of chest pain
Uncertain/ Unacceptable CT for FFRct
ICA if appropriate
ICA
No Significant CAD
Investigate other causes of chest pain
Uncertain
Functional Imaging (SPECT)
Reversible myocardial ischemia found
Treat as Stable Angina (ICA)
No reversible myocardial ischemia found
Investigate other causes of chest pain
Significant CAD
Treat as Stable Angina (ICA)
ICA
Functional Imaging (SPECT)
Reversible myocardial ischemia found
Treat as Stable Angina (ICA)
No reversible myocardial ischemia found
Investigate other causes of chest pain
Functional Imaging (SPECT)
Reversible myocardial ischemia found
Treat as Stable Angina (ICA)
No reversible myocardial ischemia found
Investigate other causes of chest pain
Significant CAD
FFRct
FFRct Positive
Treat as Stable Angina (ICA)
FFRct Negative
Investigate other causes of chest pain
Estimated likelihood of CAD greater than 90%
ICA
Functional Imaging (SPECT)
Reversible myocardial ischemia found
Treat as Stable Angina (ICA)
No reversible myocardial ischemia found
Investigate other causes of chest pain

9.1.5 Justify the chosen structure in line with the clinical pathway of care identified in response to question 3.3.

The model is based on the clinical pathway identified in response to question 3.3. The model is divided into two scenarios. The first scenario calculates the cost of treating patients by using the existing NICE Clinical Guideline #95 for patients with stable chest pain. The second scenario calculates the cost of treating the same patient population while incorporating FFR_{CT} technology as described above. The overall costs are then compared between the two scenarios.

9.1.6 Provide a list of all assumptions in the cost model and a justification for each assumption.

The following sensitivity and specificity measurements were used in the model.

Table C5.1 Model assumptions – test accuracy

	Sens	Spec	Source
SPECT	76%	38%	Melikian, JACC CV Int 2010
Stress Echo	48%	73%	Jung, EHJ 2008
CCTA	94%	48%	Meijboom, JACC, 2008
ICA	69%	67%	Meijboom, JACC 2008
FFR_{CT}	86%	79%	Nørgaard, JACC, 2014

In table C5.2 below, the Payment by Results 2014-15 tariff for the relevant activity is used as a proxy for cost. In respect of hospitals, tariff is based—albeit imperfectly—on average costs reported for the relevant HRGs by hospitals to the Department of Health. Tariff represents a 'real' cost to NHS commissioners[1]. This is consistent with the approach adopted for NICE in costing CG95 (Costing Report for CG95, NICE, July 2011).

Table C5.2 Model assumptions - costs

Test	Cost	Source
CCTA	£136	Payment by Results 2014-15 tariff for HRG RA14Z
FFRct	£888	List price HeartFlow
SPECT (MPI)	£220	Payment by Results 2014-15 tariff for HRG RA37Z

[1] https://www.nice.org.uk/guidance/cg95/resources/cg95-chest-pain-of-recent-onset-costing-report2

ICA	£1,241	Payment by Results 2014-15 tariff for HRG EA36A
PCI ≤ 2 vessels	£2,704	Payment by Results 2014-15 tariff for HRG EA31Z
PCI >2 vessels	£3,216	Payment by Results 2014-15 tariff for HRG EA49Z

9.1.7 Define what the model's health states are intended to capture.

The model captures and quantifies the change in the rate of death and myocardial infarction (MI) at one year. It also quantifies the number of ICA and PCI procedures avoided through the use of FFR_{CT}.

9.1.8 Describe any key features of the cost model not previously reported. A suggested format is presented below.

Table C6 Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	From date of test to 1 year following procedure	This model enables the quantification of cost consequences of incorporating FFR_{CT} into the treatment pathway at the time of treatment as well as the one-year follow-on cost consequences.	
Discount of 3.5% for costs	3.5% p.a. discount	This is the HM Treasury figure recommended by NICE in the current Medical Technologies Evaluation Programme Process Guide. The model does not currently include costs beyond time of treatment.	
Perspective (NHS/PSS)	NHS	No PSS figures are available. Although not highly relevant in this case, improved health outcomes will, if anything, decrease PSS costs, decreasing the ICER	
Cycle length	Single cycle, one year	Consistent with the relevant clinical pathway and available clinical trial data	
NHS, National Health Service; PSS, Personal Social Services			

9.2 Clinical parameters and variables

9.2.1 Describe how the data from the clinical evidence were used in the cost analysis.

SN and SP values were found in the literature and used to model the likelihood of a patient correctly or incorrectly testing positively (functionally important CAD present) or negatively (no functionally important CAD present) upon receiving the respective diagnostic test. The reference source used for each diagnostic test is listed in Table C5.1 in section 9.1.6.

In the course of the literature search we came upon two alternative sources that were candidates for the SN and SP values of SPECT. In [A3] Zhou 2014 the author notes that at the per-patient level the SN and SP of SPECT were 77% and 77%[2], respectively. The other possible source was the third-party meta-analysis which we presented in section 7.8. This unpublished study reports a SN and SP for SPECT at the patient level of 74% and 75%, respectively. However, upon further analysis of the publications that compromise both of these papers, two common outliers were found; a 2005 study by Marcus Hacker[3] and a 2004 study by Johannes Rieber[4]. Following detailed review of the methods and conclusions of these two papers we discovered evidence that caused us to doubt the validity of their results and therefore exclude these SN and SP values from our model. For the Johannes Rieber study we note that the clinicians were not blinded and the results were not core lab adjudicated. In the Marcus Hacker study we found that two different and non-standard SPECT methods (the summed stress score and summed difference score; SSSr and SDSr in the paper) were used and that ROC curves were used to identify a threshold and then SN and SP values were reported from that threshold, rather than prospectively validated in a separate validation cohort. Without such prospective validation, the method is invalid for establishing diagnostic performance vis a vis a cut point. Finally, these two papers are from the same group of investigators and it is not entirely clear from the manuscripts that they represent completely different cohorts of patients. Also included

[2] Zhou, T. (2014). "SPECT myocardial perfusion versus fractional flow reserve for evaluation of functional ischemia: A meta analysis." European Journal of Radiology **83**: 951-956.

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

[4] Rieber J, Jung P, Erhard I e. a. (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: 142-7.

in both the [A3] Zhou 2014 and third-party meta-analysis is a paper by Melikian that reports a SN and SP of SPECT of 76% and 38%, respectively[5]. This paper meets other quality guidelines, is widely quoted in recent literature[6], and therefore it serves as the source for our base-case analysis.

Similarly, there were two alternative sources that were candidates for the SN and SP values of ICA in comparison to invasive FFR. In [A1] Christou 2007, the author notes that at the per-patient level the SN and SP of ICA were 78% and 51%[7], respectively. The unpublished, third-party analysis reports values of 69% for SN and 67% for SP. In previous economic modeling exercises we have utilized a study by Meijboom et al which reports SN and SP values of 69% and 67%[8], respectively. With confirmation from the third-party analysis, we have chosen these values to form our analysis.

For FFR_{CT} the literature search in [A5] Li 2014 reported SN and SP values of 89% and 71%[9], respectively and the third party analysis reported values of 90% and 71%. For the model we have chosen to use SN and SP values of 86% and 79%, respectively, for our base-case analysis which reflect our most recent validation study, published by Norgaard et al[10]. The results reported in this study reflect substantial refinements in FFR_{CT} technology and physiological modeling along with an increased focus on CT image quality and adherence to official recommendations for CCTA acquisition which have improved automated image processing and enabled more accurate identification of lumen boundaries. This latest version of the technology is the current clinically marketed version of our software and is exactly the version being reviewed by NICE. Two additional prior studies included in [A5] Li 2014 and the third party analysis reflected performance of prior, now outdated, versions of our technology, and some

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[5] Melikian, N. e. a. (2010). "Fractional Flow Reserve and Myocardial Perfusion Imaging in Patients with Angiographic Multivessel Coronary Artery Disease." JACC: Cardiovascular Interventions. **3**(3): 307-314.

[6] Nørgaard, B. B. e. a. (2015). "Fractional flow reserve derived from coronary CT angiography in stable coronary artery disease: a new standard in non-invasive testing?" European Radiology [Epub ahead of print]

[7] Zhou, T. (2014). "SPECT myocardial perfusion versus fractional flow reserve for evaluation of functional ischemia: A meta analysis." European Journal of Radiology **83**: 951-956.

[8] Meijboom, W.B. e. a. (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 American College of Cardiology **52**(8): 636-643.

[9] Li, S. (2015). "The diagnostic performance of CT-derived fractional flow reserve for evaluation of myocardial ischaemia confirmed by invasive fractional flow reserve: a meta-analysis." Clinical Radiology online publication January 23, 2015; dx.doi.org/10.1016/j.crad.2014.12.013.

[10] Nørgaard B.L. 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)." J Am Coll Cardiol 63(12):1145-55

subjects from these earlier two studies were used in development of the current version, so we have excluded these earlier studies from the present analysis.

Alternative sources of SN and SP values of each of the discussed diagnostic tests will appear in the sensitivity analysis performed on the economic model as presented in section 9.4.

9.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

The primary endpoint follow-up period for the first prospective outcomes based clinical study of FFR_{CT}, PLATFORM, is 90 days and those results are included in this application. Prolonged follow-up beyond 90 days is currently in process. Clinical outcome estimates in the DeNovo model presented here are based on one year death and MI rates from studies of observed FFR-positive (i.e. “appropriate”) and FFR-negative (i.e. “inappropriate”) revascularization, as published in the literature.

Economic outcomes are based on costs incurred during the index management of new-onset stable chest pain. While we recognize that there likely will be ongoing economic benefits associated with improved clinical outcomes, and fewer unnecessary invasive procedures, we conservatively have chosen not to include these in the model. Such clinical outcomes would include 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. A more detailed evaluation of these additional costs and cost savings can be found in section 9.3.10.

9.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

The patient pathway at each stage is determined by the SN and SP of the

diagnostic test performed at that stage. More details on the accuracy of these tests and the respective references can be found on Table C5.1in Section 9.1.6.

9.2.4 Were adverse events such as those described in section 7.7 included in the cost analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

FFR_{CT} is a diagnostic test with no direct adverse events other than the misdiagnosis of patients. These misdiagnoses (false positives and false negatives) are tracked in the model for both the pathway following current NICE guidelines and the proposed pathway using CCTA and FFR_{CT}. The accuracy of the diagnoses in each pathway and resultant appropriateness of procedures drive the one-year death and MI rate. The model suggests that utilization of CCTA and FFR_{CT} would result in lower death and MI rates and thus provide patient benefit and lower subsequent costs. These subsequent cost savings are not captured in the model. Doing so would further increase the cost-effectiveness of FFR_{CT}.

9.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

In researching appropriate model inputs and parameters we sought guidance from cardiology and health economic experts. HeartFlow identified and collaborated with three experts: Dr. Mark Hlatky, Dr. Ronak Rajani, and Dr. Mark Charny.

Dr. Hlatky is a professor of health research and policy and medicine at Stanford University. Dr. Hlatky has done significant research and published extensively on the cost consequences of diagnosing patients with suspected CAD. Dr. Hlatky receives sponsored research support from HeartFlow.

Dr. Ronak Rajani is a consultant cardiologist in heart failure and cardiac imaging at Guy's and St. Thomas' NHS Foundation Trust. He is also the cardiology lead for CCTA, research and development. He has published numerous manuscripts in the field of cardiac imaging. Dr. Rajani does not have any conflicts of interest regarding

HeartFlow.

Dr. Mark Charny is a managing director of Translucency, a healthcare consulting firm. His previous experience includes work on cost-effectiveness studies in the NHS. He has also worked on clinical effectiveness and guidelines in the Department of Health. Dr. Charny has published widely in peer-reviewed medical literature. Dr. Charny serves as a consultant for HeartFlow.

These experts provided guidance on the appropriate model design and build. Dr. Hlatky provided guidance on the initial model parameters. Before the initiation of the NICE review process in 2014, Dr. Rajani provided initial UK site-specific data on procedure volumes, patient pathways, and outcomes, resulting in a peer-reviewed publication[11]. Since beginning the NICE review in the autumn of 2014, he has not served as an expert advisor to HeartFlow. Dr. Charny contributed to the model design, provided NHS cost weights, and validated some model assumptions. The actual modelling of patient flow (portion of patients that test positive or negative for each test) was derived from diagnostic accuracy measurements as published in the literature.

- *the criteria for selecting the experts*

HeartFlow solicited input in three areas:

1) Cardiovascular test utilization health economic analysis. Prof. Hlatky is a foremost authority in this area.
2) Cardiac imaging, particularly CCTA, in the UK. Dr. Rajani is a foremost authority in this area.
3) NICE and NHS assessments. Dr. Charny is has deep experience in these areas.

- *the number of experts approached*

We approached the three individuals mentioned above.

- *the number of experts who participated*

Only these three individuals participated. Dr. Rajani did not participate after the NICE process commenced in autumn, 2014.

- *declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought*

Prof. Hlatky receives research support from HeartFlow in the form of a sponsored research agreement to Stanford University.

[11] Rajani, R. e. a. (2015). "Comparative Efficacy Testing - Fractional Flow Reserve by Coronary Computed Tomography for the Evaluation of Patients with Stable Chest Pain." International Journal of Cardiology **183**: 173-177.

Dr. Charny is a paid consultant to HeartFlow.

- *the background information provided and its consistency with the totality of the evidence provided in the submission*

All information provided was internally consistent and consistent with literature.

- *the method(s) used to collect and collate the opinions*

Each of the three experts was engaged individually by HeartFlow. There was no dialogue between the experts related to this application.

- *the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)*

Information was gathered by in-person, email, and telephone communications.

9.2.6 Summarise all the variables included in the cost analysis. Provide cross-references to other parts of the submission. A suggested format is provided in table C5 below.

Table C7 Model assumptions and references

Variable	**Base-case value**	Reference*
Price		
SPECT	£220	HRG: RA37Z
CT	£136	HRG: RA14Z
Calcium Score	£77	HRG RA08Z
FFR_{CT}	£888	List Price
Angiograpy	£1,241	HRG: EA36A
PCI ≤ 2 stents	£2,704	HRG: EA31Z
PCI > 2 stents	£3,216	HRG: EA49Z
Sensitivity and Specificity		
SN FFR_{CT}	86%	Nørgaard JACC 2014
SP FFR_{CT}	79%	Nørgaard JACC 2014
SN SPECT	76%	Melikian JACC CV Int. 2010
SP SPECT	38%	Melikian JACC CV Int. 2010
SN CCTA	94%	Meijboom JACC 2008

SP CCTA	48%	Meijboom JACC 2008
SN ICA	69%	Meijboom JACC 2008
SP ICA	67%	Meijboom JACC 2008
Disease Burden		
10-29% Prob of Disease	18.6%	Rajani, R. Intl J Cardio 2015
30-60% Prob of Disease	28.4%	Rajani, R. Intl J Cardio 2015
61-90% Prob of Disease	27.7%	Rajani, R. Intl J Cardio 2015

** Full references in bibliography at end of submission*

9.3 Resource identification, measurement and valuation

NHS costs

9.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

The following Healthcare Resource Group (HRG) codes are currently used:

Table C8.1 Applicaable Healthcare Resource Group (HRG) Codes

Variable	**Base-case value**	Reference
Price		
SPECT	£220	HRG: RA37Z
CT	£136	HRG: RA14Z
Calcium Score	£77	HRG RA08Z
FFR_{CT}	£888	List Price
Angiograpy	£1,241	HRG: EA36A
PCI ≤ 2 stents	£2,704	HRG: EA31Z
PCI > 2 stents	£3,216	HRG: EA49Z

9.3.2 State the Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS) codes for the operations, procedures and interventions relevant to the use of the technology for the clinical management of the condition.

The information below covers a range of situations which might apply to a patient of interest to HeartFlow. The tables below list OPCS codes for procedures and interventions of relevance to this submission. The table below also shows the mapping of these OPCS codes to HRGs (mapping in the table proceeds from right to left)

Table C8.2 2014/15 mapping of relevant OPCS procedure codes to 5-character HRGs

OPCS procedure code	Procedure code description	If no other conditions shown or apply, maps to	Maps to	if condition below applies	Maps to	if condition below applies
K483	Open angioplasty of coronary artery	EA14Z	EA16Z	EA_EP_RFA_PCI_PACE	EA51Z	EA_valve
K484	Exploration of coronary artery	EA14Z	EA16Z	EA_EP_RFA_PCI_PACE	EA51Z	EA_valve
K488	Other specified other open operations on coronary artery	EA14Z	EA16Z	EA_EP_RFA_PCI_PACE	EA51Z	EA_valve
K489	Unspecified other open operations on coronary artery	UZ06Z[12]				
K491	Percutaneous transluminal balloon angioplasty of one coronary artery	EA31Z	EA49Z	EA_rotablation	EA49Z	EA_ivus
K492	Percutaneous transluminal balloon angioplasty of multiple coronary arteries	EA31Z	EA49Z	EA_rotablation	EA49Z	EA_ivus
K493	Percutaneous transluminal balloon angioplasty of bypass graft of coronary artery	EA31Z	EA49Z	EA_rotablation	EA49Z	EA_ivus
K494	Percutaneous transluminal cutting balloon angioplasty of coronary artery	EA31Z	EA49Z	EA_rotablation	EA49Z	EA_ivus
K498	Other specified transluminal balloon angioplasty of coronary artery	EA31Z	EA49Z	EA_rotablation	EA49Z	EA_ivus
K499	Unspecified transluminal balloon angioplasty of coronary artery	EA31Z	EA49Z	EA_rotablation	EA49Z	EA_ivus
K501	Percutaneous transluminal laser coronary angioplasty	EA31Z	EA49Z	EA_rotablation	EA49Z	EA_ivus
K502	Percutaneous transluminal coronary thrombolysis using streptokinase	EA35Z				
K503	Percutaneous transluminal injection of therapeutic substance into coronary artery NEC	EA35Z				
K504	Percutaneous transluminal atherectomy of coronary artery	EA35Z				
K508	Other specified other therapeutic transluminal operations on coronary artery	EA35Z				
K509	Unspecified other therapeutic transluminal operations on coronary artery	EA35Z				
K511	Percutaneous transluminal angioscopy	EA35Z				
K512	Intravascular ultrasound of coronary artery	EA35Z				

[12] UZ06Z is 'data invalid for grouping'. A hospital receives no reimbursement for a stay (spell) coded to UZ06Z.

K518	Other specified diagnostic transluminal operations on coronary artery	EA35Z				
K519	Unspecified diagnostic transluminal operations on coronary artery	EA35Z				
K634	Coronary arteriography using two catheters	EA36A*				
K635	Coronary arteriography using single catheter	EA36A*				
K636	Coronary arteriography NEC	EA36A*				
K638	Other specified contrast radiology of heart	EA36A*				
K639	Unspecified contrast radiology of heart	EA36A*				
K751	Percutaneous transluminal balloon angioplasty and insertion of 1-2 drug-eluting stents into coronary artery	EA31Z	EA49Z	EA_rotablation	EA49Z	EA_ivus
K752	Percutaneous transluminal balloon angioplasty and insertion of 3 or more drug-eluting stents into coronary artery	EA49Z				
K753	Percutaneous transluminal balloon angioplasty and insertion of 1-2 stents into coronary artery	EA31Z	EA49Z	EA_rotablation	EA49Z	EA_ivus
K754	Percutaneous transluminal balloon angioplasty and insertion of 3 or more stents into coronary artery NEC	EA49Z				
K758	Other specified percutaneous transluminal balloon angioplasty and insertion of stent into coronary artery	EA31Z	EA49Z	EA_rotablation	EA49Z	EA_ivus
K759	Unspecified percutaneous transluminal balloon angioplasty and insertion of stent into coronary artery	EA31Z	EA49Z	EA_rotablation	EA49Z	EA_ivus

K585	Transluminal intracardiac echocardiography	EA36A
K631	Angiocardiography of combination of right and left side of heart	EA36A
K632	Angiocardiography of right side of heart NEC	EA36A
K633	Angiocardiography of left side of heart NEC	EA36A
K634	Coronary arteriography using two catheters	EA36A
K635	Coronary arteriography using single catheter	EA36A
K636	Coronary arteriography NEC	EA36A
K638	Other specified contrast radiology of heart	EA36A
K639	Unspecified contrast radiology of heart	EA36A
K651	Catheterisation of combination of right and left side of heart NEC	EA36A
K652	Catheterisation of right side of heart NEC	EA36A
K653	Catheterisation of left side of heart NEC	EA36A
K658	Other specified catheterisation of heart	EA36A

K659	Unspecified catheterisation of heart	EA36A
L133	Arteriography of pulmonary artery	EA36A
U205	Stress echocardiography	EA45
U212	Computed tomography NEC	RA08Z or RA14Z
U214	Single photon emission computed tomography NEC	RA37Z

* assumes that the patient is aged ≥ 19 years.

Table C8.3 Meaning of conditions in table C8.2

EA_EP_RFA_PCI_PC_PACE	Requires an additional procedure from list EA_EP_RFA_PCI_PACE, indicating EP, RFA, percutaneous coronary intervention or pacing, in any position
EA_ivus	Requires an additional procedure from list EA_IVUS, indicating intravenous ultrasound or use of pressure wire, in any position
EA_rotablation	Requires an additional procedure (OPCS K504), indicating percutaneous transluminal atherectomy of coronary artery (rotablation), in any position
EA_valve	Requires an additional procedure from list EA_Valve, indicating valve replacement, in any position

Table C8.4: Procedures included in Table C8.2

Condition	OPCS procedure code	Procedure code description
EA_EP_RFA_PCI_PACE	K491	Percutaneous transluminal balloon angioplasty of one coronary artery
	K492	Percutaneous transluminal balloon angioplasty of multiple coronary arteries
	K493	Percutaneous transluminal balloon angioplasty of bypass graft of coronary artery
	K498	Other specified transluminal balloon angioplasty of coronary artery
	K499	Unspecified transluminal balloon angioplasty of coronary artery
	K501	Percutaneous transluminal laser coronary angioplasty
	K502	Percutaneous transluminal coronary thrombolysis using streptokinase
	K503	Percutaneous transluminal injection of therapeutic substance into coronary artery NEC
	K508	Other specified other therapeutic transluminal operations on coronary artery
	K509	Unspecified other therapeutic transluminal operations on coronary artery
	K521	Open ablation of atrioventricular node
	K571	Percutaneous transluminal ablation of atrioventricular node
	K572	Percutaneous transluminal ablation of conducting system of heart NEC
	K581	Percutaneous transluminal mapping of conducting system of heart NEC
	K582	Percutaneous transluminal electrophysiological studies on conducting system of heart
	K601	Implantation of intravenous cardiac pacemaker system NEC

	K603	Renewal of intravenous cardiac pacemaker system
	K605	Implantation of intravenous single chamber cardiac pacemaker system
	K606	Implantation of intravenous dual chamber cardiac pacemaker system
	K607	Implantation of intravenous biventricular cardiac pacemaker system
	K608	Other specified cardiac pacemaker system introduced through vein
	K609	Unspecified cardiac pacemaker system introduced through vein
	K611	Implantation of cardiac pacemaker system NEC
	K613	Renewal of cardiac pacemaker system NEC
	K615	Implantation of single chamber cardiac pacemaker system
	K616	Implantation of dual chamber cardiac pacemaker system
	K617	Implantation of biventricular cardiac pacemaker system
	K618	Other specified other cardiac pacemaker system
	K619	Unspecified other cardiac pacemaker system
	K641	Percutaneous radiofrequency ablation of epicardium
	K753	Percutaneous transluminal balloon angioplasty and insertion of 1-2 stents into coronary artery
	K754	Percutaneous transluminal balloon angioplasty and insertion of 3 or more stents into coronary artery NEC
EA_IVUS	Y442	Monitoring of pressure in organ NOC
	Y532	Approach to organ under ultrasonic control
EA_rotablation	K504	Percutaneous transluminal atherectomy of coronary artery
EA_Valve	K251	Allograft replacement of mitral valve
	K252	Xenograft replacement of mitral valve
	K253	Prosthetic replacement of mitral valve
	K254	Replacement of mitral valve NEC
	K255	Mitral valve repair NEC
	K258	Other specified plastic repair of mitral valve
	K259	Unspecified plastic repair of mitral valve
	K261	Allograft replacement of aortic valve
	K262	Xenograft replacement of aortic valve
	K263	Prosthetic replacement of aortic valve
	K264	Replacement of aortic valve NEC
	K265	Aortic valve repair NEC
	K268	Other specified plastic repair of aortic valve
	K269	Unspecified plastic repair of aortic valve
	K271	Allograft replacement of tricuspid valve
	K272	Xenograft replacement of tricuspid valve
	K273	Prosthetic replacement of tricuspid valve
	K274	Replacement of tricuspid valve NEC
	K275	Repositioning of tricuspid valve
	K276	Tricuspid valve repair NEC
	K278	Other specified plastic repair of tricuspid valve
	K279	Unspecified plastic repair of tricuspid valve

	K281	Allograft replacement of pulmonary valve
	K282	Xenograft replacement of pulmonary valve
	K283	Prosthetic replacement of pulmonary valve
	K284	Replacement of pulmonary valve NEC
	K285	Pulmonary valve repair NEC
	K288	Other specified plastic repair of pulmonary valve
	K289	Unspecified plastic repair of pulmonary valve
	K291	Allograft replacement of valve of heart NEC
	K292	Xenograft replacement of valve of heart NEC
	K293	Prosthetic replacement of valve of heart NEC
	K294	Replacement of valve of heart NEC
	K295	Repair of valve of heart NEC
	K296	Truncal valve repair
	K297	Replacement of truncal valve
	K298	Other specified plastic repair of unspecified valve of heart
	K299	Unspecified plastic repair of unspecified valve of heart
	K301	Revision of plastic repair of mitral valve
	K302	Revision of plastic repair of aortic valve
	K303	Revision of plastic repair of tricuspid valve
	K304	Revision of plastic repair of pulmonary valve
	K305	Revision of plastic repair of truncal valve
	K308	Other specified revision of plastic repair of valve of heart
	K309	Unspecified revision of plastic repair of valve of heart
	K311	Open mitral valvotomy
	K312	Open aortic valvotomy
	K313	Open tricuspid valvotomy
	K314	Open pulmonary valvotomy
	K315	Open truncal valvotomy
	K318	Other specified open incision of valve of heart
	K319	Unspecified open incision of valve of heart

Resource identification, measurement and valuation studies

9.3.3 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.

The model uses the Payment by Results 2014-15 tariff for the relevant activity as a proxy for cost, as in the Costing Report for CG95[13] . In respect of hospitals, tariff is based—albeit imperfectly—on average costs reported for the relevant HRGs by hospitals to the Department of Health. Tariff represents a 'real' cost to NHS commissioners.

13 https://www.nice.org.uk/guidance/cg95/resources/cg95-chest-pain-of-recent-onset-costing-report2

9.3.4 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model[2].

In assessing the applicability of the resources used in the De Novo model, HeartFlow approached and collaborated with three cardiology and health economic experts: Dr. Mark Hlatky, Dr. Ronak Rajani (prior too initiation of the NICE review process in autumn, 2014, and Dr. Mark Charny.

We had several in person and telephone conferences. We also exchanged information via email. Early on we worked closely with Dr. Hlatky in the design of the model. Dr. Rajani provided UK site specific data on procedure volumes, patient pathways, and outcomes. Dr. Charny guided the model design and validated model assumptions including cost weights.

Technology and comparators' costs

9.3.5 Provide the list price for the technology.

The list price of the technology is £888.

9.3.6 If the list price is not used in the de novo cost model, provide the alternative price and a justification.

Not applicable. The list price is used in the model.

9.3.7 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost model. A suggested format is provided in tables C6 and C7. Table C7 should only be completed when the most relevant UK comparator for the cost analysis refers to another technology.

The costs of initial diagnostic tests are listed in the tables below. Although the initial diagnostic test cost may be higher when CCTA and then FFR_{CT} are utilized in an individual, the average treatment costs for the population are lower across the range of PTL included in the scope. This is a result of improved diagnostic accuracy, lower rate of invasive procedures, and no need for FFR_{CT} in many

patients where CCTA alone is sufficient to rule out CAD.

Table C9 Costs per treatment/patient associated with the technology in the cost model

Variable	Base-case value	Reference
Price		
SPECT	£220	HRG: RA37Z
CT	£136	HRG: RA14Z
Calcium Score	£77	HRG RA08Z
FFR_{CT}	£888	List Price
Angiograpy	£1,241	HRG: EA36A
PCI ≤ 2 stents	£2,704	HRG: EA31Z
PCI > 2 stents	£3,216	HRG: EA49Z

Health-state costs

9.3.8 If the cost model presents health states, the costs related to each health state should be presented in table C8. The health states should refer to the states in section 9.1.7. Provide a rationale for the choice of values used in the cost model.

The model does not present health states. Sensitivity analysis takes into consideration different disease burdens and is presented in Section 9.5.6.

Adverse-event costs

9.3.9 Complete table C9 with details of the costs associated with each adverse event referred to in 9.2.4 included in the cost model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

Adverse events are not included in the cost analysis. While the model indicates that the adoption of HeartFlow would result in a lower adverse event rate (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) and thus lower subsequent costs, we have not included such cost savings in the analysis. The ICER calculated by the model is therefore conservative.

Miscellaneous costs

9.3.10 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

Additional costs/savings not included in the model:

- Death and MI – The model projects a decrease in rate of one-year death and MI with use of CCTA and FFR_{CT}. This improvement is achieved through more accurate diagnoses of patients with suspected CAD, and use of invasive procedures only in those with the most to gain.
- Vascular access site complications – It is estimated that 2.8% of interventions result in major entry site complications[14]. The use of FFR_{CT} could reduce the number of interventions and thus major entry site complications.
- Coronary artery perforation / dissection – ICA, invasive FFR, and PCI procedures involve the introduction of guidewires, catheters, and other tools into the heart and vascular structure. These tools can injure the coronary arteries leading to an increased risk of death or MI as well as added costs. By properly and non-invasively diagnosing patients with FFR_{CT} technology the number of patients sent to ICA would be reduced and PCIs would be more often avoided in those with negative FFR.
- Radiation – Functional imaging tests such as SPECT and invasive procedures such as ICA and PCI require significant radiation. It has been estimated that the use of HeartFlow in place of SPECT would result in a 17 mSv reduction in average radiation exposure per patient.[15] There may be downstream costs related to radiation exposure and cancer risk.
- Contrast – Imaging techniques and procedures including CCTA, ICA, and PCI require the use of contrast media. Some patients may be allergic to

[14] Young, K e. a. (2014). "Trends in Major Entry Site Complications from Percutaneous Coronary Intervention (from the Dynamic Registry)." AM J Cardiol. **113**(4): 626-30.

[15] Bilbey e.a. (2015). "Potential Impact of Noninvasive FFRCT on Radiation Dose Exposure and Downstream Clinical Event Rate", ACC Poster Presentation.

contrast media and in patients with reduced kidney function there is a risk of further nephrotoxicity. FFR_{CT} has the potential to reduce the amount of contrast media patients receive on average, and therefore reduce the costs of treatment for these conditions.

- CABG and PCI procedures – The model and clinical studies including PLATFORM and FFR_{CT} RIPCORD suggest that the utilization of FFR_{CT} may decrease the number of patients who require CABG or PCI procedures. The treatment for some patients will be reclassified to a less invasive procedure (either CABG to PCI, or PCI to OMT) which will lower the likelihood of complications and reduce costs. Conversely, patients will also be identified in whom more invasive treatments are required (OMT to PCI or CABG, or PCI to CABG).

9.3.11 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

The use of FFR_{CT} technology may result in reduced need to utilize some currently used diagnostic tests (SPECT, stress echo, MRI, XT, and ICA). Although the use of tests may decrease, there will likely remain a need for these facilities, as they are used for a variety of medical purposes (not just CAD diagnosis or treatment) as well as for patients in whom CCTA is contraindicated. The reduction in such tests may reduce and defer the expense of new or replacement facilities which would otherwise be required.

We have not attempted to quantify these savings as the replacement needs and pricing of capital equipment varies greatly and depends on site-specific needs and local market conditions.

9.4 Approach to sensitivity analysis

Section 9.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

9.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost analysis.

We conducted sensitivity analysis on the following variables:

- Cost of FFR_{CT}
- Accuracy (SN and SP) of diagnostic tests
- Disease prevalence in presenting population

9.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

A deterministic sensitivity analysis was undertaken.

9.4.3 Complete table C10.1, C10.2 and/or C10.3 as appropriate to summarise the variables used in the sensitivity analysis.

Table C10 Variables used in one-way scenario-based deterministic sensitivity analysis

Variable	Base-case value	Range of values
Price		
FFR_{CT}	£888	£700 – 1,300
Sensitivity and Specificity		
SN FFR_{CT}	86%	71 – 100%
SP FFR_{CT}	79%	64 – 94%
SN SPECT	76%	56 – 91%
SP SPECT	34%	23 – 87%
SN CCTA	94%	72 – 100%
SP CCTA	48%	33 – 88%
SN ICA	69%	54 – 86%
SP ICA	67%	40 – 82%

9.4.4 If any parameters or variables listed in section 9.2.6 were omitted from the sensitivity analysis, provide the rationale.

We did not perform sensitivity analysis on the costs of alternative diagnostic tests and interventions. We used published 2014-15 NHS Tariffs. These were not adjusted for Market Forces Factors, which are intended to compensate hospitals for unavoidably high local capital and labour costs.

9.5 Results of de novo cost analysis

Section 9.5 requires the sponsor to report the de novo cost analysis results. These should include the following:

- costs
- disaggregated results such as costs associated with treatment, costs associated with adverse events, and costs associated with follow- up/subsequent treatment
- a tabulation of the mean cost results
- results of the sensitivity analysis.

Base-case analysis

9.5.1 Report the total costs associated with use of the technology and the comparator(s) in the base-case analysis. A suggested format is presented in table C11.

Table C11.1 DeNovo model base-case results

	Average total cost per patient
NICE Recommended Guideline	**£2,239**
Adapted NICE Guideline using FFR_{CT}	**£2,080**
Difference	**-£159**

9.5.2 Report the total difference in costs between the technology and comparator(s).

When compared to current NICE-recommended guidelines (CG95), the use of a pathway of CCTA and (as needed) FFR_{CT}, results in average saving of £159 per patient presenting with new onset stable chest pain.

9.5.3 Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented in table C12.

Costs in the model are based on HRG codes as listed in response to question 9.3.7.

9.5.4 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented in table C13.

The model includes an analysis of cost per patient based on disease probability. In all cases the model compares the recommended NICE guidelines (CG95)[16] to a pathway where FFR_{CT} as described in question 9.1.4.

Table C11.2 Summary of costs by health state per patient

Prevalence of Disease	Cost Intervention: NICE Guideline	Cost Comparator: FFR_{CT}	Incremental cost/saving	% absolute increment
<10%	£0	£0	£0	9.6%
10-29%	£1,385	£1,361	-£25	18.6%
30-60%	£2,125	£2,095	-£30	28.4%
61-90%	£3,402	£2,875	-£527	27.7%
>90%	£2,769	£2,769	£0	15.7%
Total	**£2,239**	**£2,080**	**-£159**	**100.0%**

Table C11.3 Summary of 1-year MACE rate by health state per patient

Prevalence of Disease	Event Rate: NICE Guideline	Event Rate HeartFlow	Increment	% absolute increment
<10%	1.20%	1.20%	0.00%	9.6%
10-29%	1.63%	1.57%	-0.06%	18.6%
30-60%	2.53%	2.37%	-0.17%	28.4%
61-90%	3.20%	3.17%	-0.03%	27.7%
>90%	3.48%	3.48%	0.00%	15.7%
Overall	**2.57%**	**2.50%**	**-0.07%**	**100.0%**

[16] www.nice.org.uk/guidance/CG95

9.5.5 If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided in table C14.

Although the utilisation of CCTA and FFR_{CT} results in lower adverse events for all health states, we did not calculate costs of adverse events. A description of adverse events is provided in response to question 9.3.10.

Sensitivity analysis results

9.5.6 Present results of deterministic one-way sensitivity analysis of the variables described in table C10.1.

Table C12.1 Sensitivity Analysis results: price of FFR_{CT}

Cost Savings by Price of FFR_{CT}

Price HeartFlow	Disease Burden <10%	10-29%	30-60%	61-90%	>90%	All
£ 700	£0	-£106	-£150	-£669	£0	**-£248**
£ 800	£0	-£63	-£86	-£593	£0	**-£201**
£ 888	£0	-£25	-£30	-£527	£0	**-£159**
£ 1,000	£0	£24	£41	-£443	£0	**-£107**
£ 1,100	£0	£68	£105	-£368	£0	**-£59**
£ 1,200	£0	£111	£169	-£293	£0	**-£12**
£ 1,300	£0	£155	£233	-£218	£0	**£35**

Table C12.2 Sensitivity Analysis results: SN of FFR_{CT}

Cost Savings by Dx Sensitivity of FFR_{CT}

Dx Sensitivity FFR_{CT}	Disease Burden <10%	10-29%	30-60%	61-90%	>90%	All	Event Rate
71%	£0	-£69	-£205	-£827	£0	**-£300**	0.01%
76%	£0	-£54	-£146	-£727	£0	**-£253**	-0.02%
77%	£0	-£51	-£135	-£707	£0	**-£244**	-0.02%
81%	£0	-£39	-£88	-£627	£0	**-£206**	-0.04%
86%	£0	-£25	-£30	-£527	£0	**-£159**	-0.07%
91%	£0	-£10	£28	-£427	£0	**-£112**	-0.09%
96%	£0	£5	£86	-£327	£0	**-£65**	-0.12%
98%	£0	£11	£109	-£287	£0	**-£47**	-0.13%
100%	£0	£17	£132	-£247	£0	**-£28**	-0.14%

Table C12.3 Sensitivity Analysis results: SP of FFR_{CT}

Cost Savings by Dx Specificity of FFR_{CT}

Dx Specificity FFR_{CT}	Disease Burden <10%	10-29%	30-60%	61-90%	>90%	All	Event Rate
64%	£0	£73	£88	-£472	£0	**-£92**	-0.02%
65%	£0	£67	£80	-£476	£0	**-£97**	-0.03%
69%	£0	£41	£48	-£490	£0	**-£115**	-0.04%
74%	£0	£8	£9	-£509	£0	**-£137**	-0.05%
79%	£0	-£25	-£30	-£527	£0	**-£159**	-0.07%
84%	£0	-£57	-£70	-£546	£0	**-£182**	-0.08%
89%	£0	-£90	-£109	-£564	£0	**-£204**	-0.10%
94%	£0	-£122	-£148	-£583	£0	**-£226**	-0.11%

Table C12.4 Sensitivity Analysis results: SN of SPECT

Cost Savings by Dx Sensitivity of SPECT

Dx Sensitivity SPECT	Disease Burden <10%	10-29%	30-60%	61-90%	>90%	All	Event Rate
56%	£0	£1	£164	-£292	£0	**-£34**	-0.15%
61%	£0	-£6	£116	-£351	£0	**-£65**	-0.13%
66%	£0	-£12	£67	-£409	£0	**-£97**	-0.11%
71%	£0	-£18	£18	-£468	£0	**-£128**	-0.09%
76%	£0	-£25	-£30	-£527	£0	**-£159**	-0.07%
81%	£0	-£31	-£79	-£586	£0	**-£191**	-0.05%
86%	£0	-£37	-£128	-£645	£0	**-£222**	-0.02%
91%	£0	-£44	-£176	-£704	£0	**-£253**	0.00%

Table C12.5 Sensitivity Analysis results: SP of SPECT

Cost Savings by Dx Specificity of SPECT

Dx Specificity SPECT	Disease Burden <10%	10-29%	30-60%	61-90%	>90%	All	Event Rate
23%	£0	-£100	-£209	-£579	£0	**-£238**	-0.11%
28%	£0	-£75	-£149	-£561	£0	**-£212**	-0.10%
30%	£0	-£65	-£125	-£555	£0	**-£201**	-0.09%
33%	£0	-£50	-£90	-£544	£0	**-£186**	-0.08%
38%	£0	-£25	-£30	-£527	£0	**-£159**	-0.07%
43%	£0	£1	£29	-£510	£0	**-£133**	-0.05%
48%	£0	£26	£89	-£493	£0	**-£106**	-0.04%
53%	£0	£51	£148	-£476	£0	**-£80**	-0.02%
87%	£0	£223	£553	-£360	£0	**£99**	0.09%

Table C12.6 Sensitivity Analysis results: SN of CCTA

Cost Savings by Dx Sensitivity of CCTA

Dx Sensitivity of CCTA	Disease Burden <10%	10-29%	30-60%	61-90%	>90%	All	Event Rate
72%	£0	-£33	-£343	-£1,061	£0	**-£398**	0.02%
79%	£0	-£31	-£244	-£891	£0	**-£322**	0.00%
84%	£0	-£29	-£173	-£770	£0	**-£268**	-0.03%
89%	£0	-£27	-£101	-£649	£0	**-£213**	-0.05%
94%	£0	-£25	-£30	-£527	£0	**-£159**	-0.07%
98%	£0	-£23	£27	-£430	£0	**-£116**	-0.08%
99%	£0	-£23	£41	-£406	£0	**-£105**	-0.09%
100%	£0	-£22	£55	-£382	£0	**-£94**	-0.09%

Table C12.7 Sensitivity Analysis results: SP of CCTA

Cost Savings by Dx Specificity of CCTA

Dx Specificity CCTA	Disease Burden <10%	10-29%	30-60%	61-90%	>90%	All	Event Rate
33%	£0	-£79	£83	-£475	£0	**-£123**	-0.06%
34%	£0	-£76	£76	-£478	£0	**-£125**	-0.06%
38%	£0	-£61	£45	-£492	£0	**-£135**	-0.06%
43%	£0	-£43	£8	-£510	£0	**-£147**	-0.07%
48%	£0	-£25	-£30	-£527	£0	**-£159**	-0.07%
53%	£0	-£6	-£68	-£545	£0	**-£171**	-0.07%
58%	£0	£12	-£106	-£562	£0	**-£184**	-0.07%
63%	£0	£30	-£144	-£580	£0	**-£196**	-0.07%
88%	£0	£121	-£333	-£667	£0	**-£257**	-0.08%

Table C12.8 Sensitivity Analysis results: SN of ICA

Cost Savings by Dx Sensitivity of ICA

Dx Sensitivity of ICA	Disease Burden <10%	10-29%	30-60%	61-90%	>90%	All	Event Rate
54%	£0	-£31	-£37	-£425	£0	**-£134**	-0.07%
59%	£0	-£29	-£35	-£459	£0	**-£142**	-0.07%
64%	£0	-£27	-£32	-£493	£0	**-£151**	-0.07%
65%	£0	-£26	-£32	-£500	£0	**-£152**	-0.07%
69%	£0	-£25	-£30	-£527	£0	**-£159**	-0.07%
74%	£0	-£23	-£28	-£561	£0	**-£168**	-0.07%
79%	£0	-£20	-£26	-£595	£0	**-£176**	-0.07%
84%	£0	-£18	-£24	-£629	£0	**-£184**	-0.07%
86%	£0	-£17	-£23	-£643	£0	**-£188**	-0.07%

Table C12.9 Sensitivity Analysis results: SP of ICA

Cost Savings by Dx Specificity of ICA

Dx Specificity ICA	Disease Burden <10%	10-29%	30-60%	61-90%	>90%	All	Event Rate
40%	£0	-£188	-£250	-£704	£0	**-£301**	-0.16%
52%	£0	-£116	-£152	-£626	£0	**-£238**	-0.12%
57%	£0	-£85	-£112	-£593	£0	**-£212**	-0.10%
62%	£0	-£55	-£71	-£560	£0	**-£186**	-0.08%
67%	£0	-£25	-£30	-£527	£0	**-£159**	-0.07%
71%	£0	£0	£2	-£501	£0	**-£138**	-0.05%
72%	£0	£6	£10	-£494	£0	**-£133**	-0.05%
77%	£0	£36	£51	-£462	£0	**-£107**	-0.03%
82%	£0	£66	£92	-£429	£0	**-£80**	-0.02%

9.5.7 Present results of deterministic multi-way scenario sensitivity analysis described in table C10.2.

Table C12.10 Sensitivity Analysis results: Multi-way scenario SN and SP of FFR_{CT} and SPECT

Cost Savings by SN & SP of SPECT and SN & SP of FFR_{CT}

Dx SN & SP SPECT		Dx SN & SP FFR_{CT} Worst SN 71% SP 64%	Base SN 86% SP 79%	Best SN 100% SP 94%
Worst	SN 55% SP 23%	-£181	-£107	-£42
Base	SN 76% SP 38%	-£233	**-£159**	-£95
Best	SN 91% SP 87%	-£69	£5	£70

9.5.8 Present results of the probabilistic sensitivity analysis described in table C10.3.

We did not perform probabilistic sensitivity analysis.

9.5.9 What were the main findings of each of the sensitivity analyses?

Across a wide range of prices for FFR_{CT} as well as wide range of sensitivity and specificity values for each of the diagnostic tests (FFR_{CT}, CCTA, SPECT, ICA) included in the model, the use of FFR_{CT} resulted in overall cost savings.

We ran a sensitivity analysis on the price of FFR_{CT} and found the break-even point to be £1,226. Our list price of £888 results in an average savings per patient of £159. As would be expected, as the price of FFR_{CT} decreases the savings to the system increase, and vice versa.

For each of the diagnostic tests we ran sensitivity analyses with ranges up to 15% above and below the base SN and SP values. In addition we reported (highlighted in blue) the results of sensitivity analyses using the minimum and maximum values for the 95% confidence intervals as reported in papers referenced in the clinical section and discussed in section 9.2.1. In most all scenarios, the use of FFR_{CT} resulted in net cost savings. In only one scenario where we used a very high specificity of SPECT (87%, well outside of those observed and published in literature) did we find a result where net costs increased with the use of FFR_{CT}.

9.5.10 What are the key drivers of the cost results?

Key drivers of the cost results include the SN and SP of each test. The model demonstrates that when the SN of a test increases, the average cost of treating patients with CAD also tends to increase. This increase is a result of identifying and thus treating more patients with disease. Conversely as the SP of a given test increases, the cost average cost of treating a patient decreases as patients without disease are more accurately identified and unnecessary treatments are avoided. Although improved SN may cause costs to increase, we would also expect clinical outcomes to improve as those with disease are treated.

The price of FFR_{CT} is also a key driver. As would be expected, as the price of FFR_{CT} decreases, average cost savings per patient increase.

Miscellaneous results

9.5.11 Describe any additional results that have not been specifically requested in this template. If none, please state.

None

9.6 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 9.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

9.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1 and sections 3.2 and 7.4.4.

As stated in the scope, no subgroups were to be considered. In the model, patients with pre-test probability of CAD of <10% and >90% are not considered as FFR_{CT} candidates. Thus their pathway does not change from current NICE guidelines.

9.6.2 Define the characteristics of patients in the subgroup(s).

Not applicable.

9.6.3 Describe how the subgroups were included in the cost analysis.

Not applicable.

9.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 9.5.1 (base-case analysis).

Not applicable.

9.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

Not applicable.

9.7 Validation

9.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

Through the process of completing the literature search and building the health economic model we identified a variety of practice patterns. In addition to evaluating the impact of following NICE guidelines (CG95), we also ran scenarios that quantify the health and economic impacts of utilizing FFR_{CT} technology in place of a particular diagnostic test. These scenarios assume that one of two simple pathways is followed:

- Scenario 1: All patients receive SPECT. The decision to send the patient to angiography is based on the results of the SPECT test.
- Scenario 2: All patients receive CCTA and then FFR_{CT} if the CT shows obstructive disease. The decision to send the patient to angiography is based on the results of the FFR_{CT} test.

Under the first scenario, where SPECT is used as the initial test, the model estimates that 69% of patients would receive ICA and 30% would receive PCI. The average cost per patient is £1,891. The estimated one year death and MI rate is 2.34%.

When the same patient population follows scenario 2, the model estimates that 29% of patients would receive an angiography and 17% would receive PCI. The average cost per patient is £1,529. The estimated one year death and MI rate is 2.03%. The model assumes an FFR_{CT} price of £888.

Table C13 Health Economics SPECT and CCTA – FFR_{CT} Pathways

	SPECT	CT - FFR_{CT}
ICA	69%	29%
PCI	30%	17%
Avg Cost / Patient	£1,891	£1,529
One Year Death & MI	2.34%	2.03%

9.8 Interpretation of economic evidence

9.8.1 Are the results from this cost analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

The results from the analysis are directionally consistent with the published literature. Currently there are four[17] [18] [19] [20]publications on the economics of FFR_{CT}. All publications suggest cost savings resulting from the incorporation of FFR_{CT}. The patient populations in each of these papers vary both in disease burden and stage at which the patients analyzed present; ranging from the presentation for a first diagnostic test to presentation for ICA. Average cost savings per patient range from £159 to £2,036 ($3,028). The prospective controlled PLATFORM study results, including two centers in the UK supplying 104 patients (18% of the study population overall), not yet published but noted in section 8, also show significant cost savings from the incorporation of FFR_{CT}.

[17] Hlatky, Clinical Cardiology (2013), "Projected Costs and Consequences of Compute Tomography-Determined Fractional Flow Reserve"
[18] Papafaklis, ACC Poster (2015), "Projected Cost of Computed Tomography-Derived Fractional Flow Reserve in Suspected Coronary Artery Disease: Effect of Enhanced Image Quality and Technology Refinements"
[19] Kimura, Cardiovasc Interv and Ther, (2014), "Cost analysis of non-invasive fractional flow reserve derived from coronary computed tomographic angiography in Japan"
[20] Rajani R, International Journal of Cardiology 183 (2015) 173-177, "Comparative efficacy testing – Fractional flow reserve by coronary computed tomography for the evaluation of patients with stable chest pain"

9.8.2 Is the cost analysis relevant to all groups of patients and NHS settings in England that could potentially use the technology as identified in the scope?

Yes. The cost analysis includes all patients identified within the scope: “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 technology relies on CCTA, facilities which are widely available across the UK.

9.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

The analysis has a number of strengths. The assumptions used in the economic analysis were drawn from a large patient population, and several studies, where diagnostic accuracies were evaluated. The results are consistent with the literature.

One weakness is that the use of FFR_{CT} in real world scenarios is limited. The SN and SP of FFR_{CT} are based on what was reported in HeartFlow’s most current clinical validation study. FFR_{CT} outcomes research is a single study, PLATFORM, which is a prospective controlled study conducted in Europe including two centres in the UK.

9.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Further analysis could be undertaken when there additional use of FFR_{CT} and associated data become available. We expect that longer term follow up data will provide insight into the potential for additional incremental savings.

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10 Appendices

10.3 Appendix 3: Search strategy for economic evidence (section 8.1.1)

The following information should be provided.

10.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

The PubMed and Web of Science databases were used for the health economics literature search.

10.3.2 The date on which the search was conducted.

PubMed was searched on March 26th, 2015 and the Web of Science was searched on March 31st, 2015.

10.3.3 The date span of the search.

The health economics literature search was restricted to articles published since 1985.

10.3.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example,MeSH) and the relationship between the search terms (for example, Boolean).

PubMed Search Strategy:
noninvasive fractional flow reserve or noninvasive FFR or coronary CT angiography or coronary computed tomography angiography or coronary angiography or nuclear myocardial perfusion or magnetic resonance perfusion or myocardial perfusion scintigraphy or SPECT or stress echocardiography or stress perfusion or stress myocardial perfusion or dobutamine stress

AND

obstructive CAD or stable CAD or stable coronary artery disease or suspected coronary artery disease

AND

QALY or quality adjusted life years or incremental cost effectiveness ratio or ICER or economic outcomes or economic analysis or cost savings or health care costs or health care spending or cost analysis

Web of Science Search Strategy:
"noninvasive fractional flow reserve" or "noninvasive FFR" or "coronary CT angiography" or "coronary computed tomography angiography" or "coronary angiography" or "nuclear myocardial perfusion" or "magnetic resonance perfusion" or "myocardial perfusion scintigraphy" or "SPECT" or "stress echocardiography" or "stress perfusion" or "stress myocardial perfusion" or "dobutamine stress"

AND

"obstructive CAD" or "stable CAD" or "stable coronary artery disease" or "suspected coronary artery disease"

AND

"QALY" or "quality adjusted life years" or "incremental cost effectiveness ratio" or "ICER" or "economic outcomes" or "economic analysis" or "cost savings" or "health care costs" or "health care spending" or "cost analysis"

10.3.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were performed.

11 Related procedures for evidence submission

11.1 Cost models

An electronic executable version of the cost model should be submitted to NICE with the full submission.

NICE accepts executable cost models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the External Assessment Centre, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the External Assessment Centre with temporary licences for the non-standard

software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing comments on the medical technology consultation document.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- a copy of the instructions for use, regulatory documentation and quality systems certificate have been submitted
- an executable electronic copy of the cost model has been submitted
- the checklist of confidential information provided by NICE has been completed and submitted.

- A PDF version of all studies (or other appropriate format for unpublished data, for example, a structured abstract) included in the submission have been submitted

11.2 Disclosure of information

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Medical Technologies Advisory Committee's decisions should be publicly available at the point of issuing the medical technology consultation document and medical technology guidance.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted

correctly. NICE is assured that information marked ‘academic in confidence’ can be presented and discussed during the public part of the Medical Technologies Advisory Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as ‘academic in confidence’.

Please therefore underline all confidential information, and highlight information that is submitted under ‘commercial in confidence’ in blue and information submitted under ‘academic in confidence’ in yellow.

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the External Assessment Centre and the Medical Technologies Advisory Committee. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

11.3 Equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the evaluation of the technology, and to reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the evaluation, or if there is information that could be included in the evidence presented to the Medical Technologies Advisory Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp