NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Medical technology guidance

SCOPE

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

1 Technology

1.1 Description of the technology

HeartFlow FFR_{CT} is a software medical device that computes fractional flow reserve (FFR) using standard coronary CT angiography (cCTA) images. Fractional flow reserve (FFR) is a pressure derived index of the maximal blood flow in a vessel with a stenosis expressed as a ratio of maximal blood flow in the same vessel in the absence of any stenosis.

Image data, from a 64-slice or above cCTA scan, is sent securely using software installed on the local clinical imaging system to the HeartFlow central processing centre in the USA. A HeartFlow case analyst uses CT images to create 3D computer models of the coronary arteries incorporating coronary flow characteristics. The results are presented in a report which is sent electronically to the referring clinician within 48 hours and includes 3D models of the coronary anatomy combined with functional information of the estimated FFR values (known as FFR_{CT} values). This information is designed to guide clinicians on management options for patients with coronary artery disease. HeartFlow FFR_{CT} is intended for use in patients with chest pain who need invasive or non-invasive investigation for suspected stable coronary artery disease to guide treatment.

1.2 Regulatory status

HeartFlow FFR_{CT} received a CE mark in July 2011 as 'medical software used for the assessment of coronary data'.

1.3 Claimed benefits

The benefits of HeartFlow FFR_{CT} to patients compared with current NHS care claimed by the sponsor are:

- analysis is performed using standard cCTA scans, without the need for additional imaging, radiation or medication.
- provides the same accuracy in excluding coronary artery disease as cCTA, while also characterizing the coronary arteries from both functional and anatomical perspectives, differentiating between ischaemic and non-ischaemic vessels in a manner which cCTA cannot.
- allows physicians to evaluate patients for anatomic coronary artery disease and accurately determine which coronary lesions are causal of myocardial ischemia, avoiding unnecessary invasive diagnostic or therapeutic procedures and the attendant risk of complications.
- lessens the predilection for revascularization in patients which can accompany the identification of anatomic stenosis by invasive coronary angiography (ICA) alone, by more accurately identifying if those stenoses are ischaemic.
- significantly improves the diagnostic accuracy for coronary artery disease compared to cCTA alone against the gold standard of invasive FFR, and provides both functional and anatomic assessment of coronary arteries.
- superior diagnostic performance compared to cCTA alone, or other non-invasive or invasive tests such as nuclear myocardial perfusion, magnetic resonance perfusion, stress-echocardiography, exercise treadmill testing, invasive angiography, or intravascular ultrasound, for the detection and exclusion of coronary artery lesions that cause ischaemia.

The benefits to the healthcare system claimed by the sponsor are:

- Reduction of downstream costs arising from inconclusive or inaccurate diagnostic tests.

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

1.4 Relevant diseases and conditions

HeartFlow FFR_{CT} is intended for use in patients with chest pain who require invasive or non-invasive investigation for suspected coronary artery disease.

Figures for 2006 showed that 6.5% of all adult men (aged 16 and over), and 4% of all adult females in England had coronary heart disease[1]. An audit carried out by the British Cardiovascular Intervention Society in 2012 found that 241,240 diagnostic angiography procedures and 92,445 percutaneous coronary intervention procedures took place in that year. 13,762 of these included FFR measurement (7630 during diagnostic angiography, 6132 during percutaneous coronary intervention)[2].

1.5 Current management

Chest pain of recent onset (NICE clinical guideline 95) recommends that in people presenting with stable chest pain without confirmed coronary artery disease, a diagnosis of stable angina should be based on clinical assessment alone or clinical assessment plus diagnostic testing (anatomic testing for coronary artery disease and/or functional testing for myocardial ischaemia).

[1] Coronary heart disease statistics 2012. British Heart Foundation: London.
[2] Ludman, P (2013) BCIS Audit Returns 2012: adult interventional procedures

The guideline recommends the risk stratification of patients using the Diamond Forrester criteria to give an estimated likelihood of coronary artery disease (table 1 in the guideline). This assessment is based on a combination of the clinical characteristics of the patient, the nature of the chest pain symptoms and the result of an electrocardiogram. The outcome is an estimation of the pre-test likelihood of coronary artery disease as a cause for the symptoms: patients are categorized as at less than 10% risk; 10% to 29%; 30% to 60%; 61% to 90% or greater than 90% risk. This risk stratification is used to guide the clinician on the need for further investigations, if any, and to identify which investigations are appropriate.

If people have features of typical angina based on clinical assessment, and their estimated pre-test likelihood of coronary artery disease is greater than 90%, angina can be assumed and managed as such. If the pre-test likelihood of coronary artery disease is less than 10%, no further testing may be necessary and alternative causes for chest pain can be considered.

For patients with intermediate levels of pre-test likelihood of coronary artery disease (10-90%), the NICE chest pain of recent onset guideline recommends further investigation as follows:

- if the estimated pre-test likelihood of coronary artery disease is 61-90%, invasive coronary angiography (ICA) should be offered as the first-line diagnostic investigation where coronary revascularization is being considered, and ICA is clinically appropriate and acceptable to the person.
- if the estimated pre-test likelihood of coronary artery disease is 61-90% and coronary revascularization is not being considered or ICA is not clinically appropriate or acceptable to the person, non-invasive functional imaging for myocardial ischaemia may be appropriate.
- if the estimated pre-test likelihood of coronary artery disease is 30-60%, non-invasive functional imaging for myocardial ischaemia should be offered
- if the estimated pre-test likelihood of coronary artery disease is 10-29%, CT coronary calcium scoring should be offered as the first line diagnostic investigation. If the calcium score is:

- zero, consider other causes of chest pain
- between 1 and 400, 64 slice or above coronary CT angiography (cCTA) should be offered
- greater than 400, ICA should be offered and, where this is not clinically appropriate or acceptable to the individual and revascularization is not being considered, non-invasive functional imaging should be offered.

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

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

- Myocardial perfusion scintigraphy with single photon emission computed tomography (MPS with SPECT), or
- Stress echocardiography, or
- First-pass contrast enhanced magnetic resonance (MR) perfusion, or
- MR imaging for stress induced wall motion abnormalities.

When the result of non-invasive functional imaging is inconclusive, the guideline recommends offering ICA. Appendix 1 shows the guideline pathway algorithm.

When ICA is undertaken to define the presence or absence and the severity of coronary stenosis, it may sometimes be necessary to combine this with the invasive measurement of FFR. This is undertaken when there is uncertainty about the functional significance of a coronary stenosis (40-70% severity) and involves the introduction of a fine pressure wire across the narrowing into the distal vessel. The pressure gradient across the stenosis is measured at baseline and again during maximal blood flow in the coronary vessel which is induced by injecting adenosine. Other guidelines (European Society of Cardiology, American College of Cardiology) state that with lesions with an

FFR of 0.80 (indicating 80% of normal blood flow) or less, functional significance is present and revascularization may be considered.

If ICA is undertaken without invasive FFR measurement and the angiogram is inconclusive, the NICE chest pain of recent onset guideline recommends non-invasive functional testing for imaging for myocardial ischaemia.

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

2 Reasons for developing guidance on HeartFlow FFR_{CT} for the computation of fractional flow reserve from coronary CT angiography

The Committee considered that HeartFlow FFR_{CT} may offer benefits to patients and the healthcare system when used in individuals with stable symptoms suspected of having coronary artery disease.

The Committee was advised that the ability of the HeartFlow FFR_{CT} to provide anatomical and functional assessment of the coronary arteries simultaneously means that it offers potential advantages over existing methods of investigation.

The Committee considered that a detailed description of the patient pathway and the place of HeartFlow FFR_{CT} in that pathway would be fundamental to an evaluation. In particular, clear understandings about patient selection and about the use of any other investigations of the coronary arteries, with their sequence in treatment, would be important in constructing a plausible value proposition.

The Committee noted that the data flows and subsequent processing involved were complex and that, were HeartFlow FFR_{CT} to be adopted routinely,

assurances on both compliance with data protection legislation and on production resilience would be needed.

3 Statement of the decision problem

	Scope issued by NICE
Population	People with stable chest pain who require investigation for possible coronary artery disease and have a pre-test likelihood of coronary artery disease in the range 10-90%.
Intervention	Heartflow FFR_{CT} applied to standard coronary CT angiography (cCTA) image data.
Comparator(s)	The comparator will vary depending on the pre-test likelihood of coronary artery disease and on whether coronary revascularization is being considered, in line with Chest pain of recent onset (NICE clinical guideline 95) and depending on local treatment pathways and infrastructure (see Appendix 1). Comparators will include: • cCTA imaging without FFR_{CT} estimation • invasive coronary angiography combined with invasive measurement of FFR using pressure wire studies • myocardial perfusion scintigraphy with single photon emission computed tomography (MPS with SPECT) • other functional imaging (such as stress echocardiography or MR techniques) For diagnostic accuracy, the reference standard is invasive FFR measurement.
Outcomes	The outcome measures to consider will include: • Sensitivity and specificity in determining functional significance of coronary artery disease • Positive and negative likelihood ratios and area-under-curve for measurement of FFR_{CT} versus invasive FFR measurement • Rates of undertaking diagnostic coronary angiography • Rates of revascularization by percutaneous coronary intervention and coronary artery bypass graft • Radiation exposure • Mortality • Invasive test related adverse events • Major adverse cardiac events (MACE) • Use of non-invasive functional tests • Quality of life • Device-related adverse events
Cost analysis	Costs will be considered from an NHS and personal social services perspective. Sensitivity analysis of costs will be considered for units with and without access to a cCTA system. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the

	technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of tests are needed.	
Subgroups to be considered	None	
Special considerations, including those related to equality	No special considerations related to equality.	
Special considerations, specifically related to equality issues		
	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristics?	No
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure MTAC will have relevant information to consider equality issues when developing guidance?	No

4 Related NICE guidance

Published

- Prasugrel with percutaneous coronary intervention for treating acute coronary syndromes (review of technology appraisal guidance 182). NICE technology appraisals, TA317, July 2014. Available from: http://www.nice.org.uk/guidance/TA317
- Endoscopic saphenous vein harvest for coronary artery bypass grafting. NICE interventional procedures guidance, IPG494, June 2014. Available from: http://www.nice.org.uk/guidance/IPG494
- Bioresorbable stent implantation for treating coronary artery disease. NICE interventional procedures guidance, IPG492, May 2014. Available from: http://www.nice.org.uk/guidance/IPG492
- MI – secondary prevention: Secondary prevention in primary and secondary care for patients following a myocardial infarction. NICE

guidelines [CG172] Published date: November 2013. Available from: http://www.nice.org.uk/guidance/CG172

- Lower limb peripheral arterial disease: diagnosis and management. NICE guidelines, CG147, August 2012. Available from: http://www.nice.org.uk/guidance/CG147
- Services for the prevention of cardiovascular disease. NICE commissioning guides, CMG45, May 2012. Available from: http://www.nice.org.uk/guidance/cmg45
- New generation cardiac CT scanners (Aquilion ONE, Brilliance iCT, Discovery CT750 HD and Somatom Definition Flash) for cardiac imaging in people with suspected or known coronary artery disease in whom imaging is difficult with earlier generation CT scanners. NICE diagnostics guidance, DG3, January 2012. Available from: http://www.nice.org.uk/guidance/DG3
- The VeriQ system for assessing graft flow during coronary artery bypass graft surgery. NICE medical technologies guidance, MTG8, November 2011. Available from: http://www.nice.org.uk/guidance/MTG8
- Ticagrelor for the treatment of acute coronary syndromes. NICE technology appraisals, TA236, October 2011. Available from: http://www.nice.org.uk/guidance/TA236
- Management of stable angina. NICE guidelines, CG126, July 2011. Available from: http://www.nice.org.uk/guidance/CG126
- Percutaneous laser coronary angioplasty. NICE interventional procedures guidance IPG378, January 2011. Available from: http://www.nice.org.uk/guidance/IPG378
- Off-pump coronary artery bypass grafting. NICE interventional procedures guidance, IPG377, January 2011. Available from: http://www.nice.org.uk/guidance/IPG377
- SeQuent Please balloon catheter for in-stent coronary restenosis. NICE medical technologies guidance, MTG1, December 2010. Available from: http://www.nice.org.uk/guidance/MTG1
- Chronic heart failure: Management of chronic heart failure in adults in primary and secondary care. NICE guidelines, CG108, August 2010. Available from: http://www.nice.org.uk/guidance/CG108

- Prevention of cardiovascular disease. NICE guidelines, PH25, June 2010. Available from: http://www.nice.org.uk/guidance/PH25
- Chest pain of recent onset: Assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. NICE guidelines, CG95, March 2010. Available from: http://www.nice.org.uk/guidance/CG95
- Drug-eluting stents for the treatment of coronary artery disease. NICE technology appraisals, TA152, July 2008. Available from: http://www.nice.org.uk/guidance/TA152
- Totally endoscopic robotically assisted coronary artery bypass grafting. NICE interventional procedures guidance, IPG128, June 2005. Available from: http://www.nice.org.uk/guidance/IPG128
- Intraoperative fluorescence angiography for the evaluation of coronary artery bypass graft patency. NICE interventional procedures guidance, IPG98, October 2004. Available from: http://www.nice.org.uk/guidance/ipg98
- Myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction. NICE technology appraisals, TA73, November 2003. Available from: http://www.nice.org.uk/guidance/TA73
- Guidance on the use of coronary artery stents. NICE technology appraisals, TA71, October 2003. Available from: http://www.nice.org.uk/guidance/TA71
- Guidance on the use of glycoprotein IIb/IIIa inhibitors in the treatment of acute coronary syndromes. NICE technology appraisals, TA47, September 2002. Available from: http://www.nice.org.uk/guidance/TA47

NICE advice

- Acute coronary syndromes (including myocardial infarction). NICE quality standards, QS68, September 2014. Available from: http://www.nice.org.uk/guidance/QS68
- Cardiovascular disease prevention. NICE Pathway, July 2014. Available from: http://pathways.nice.org.uk/pathways/cardiovascular-disease-prevention

- The PressureWire fractional flow reserve measurement system for coronary artery disease. NICE advice, MIB2, February 2014. Available from: http://www.nice.org.uk/advice/mib2
- Acute coronary syndromes (November 2013) NICE Pathway. Available from: http://pathways.nice.org.uk/pathways/acute-coronary-syndromes
- Secondary prevention in acute coronary syndrome: rivaroxaban. NICE evidence summary: new medicine, ESNM27. October 2013. Available from: http://www.nice.org.uk/Advice/ESNM27
- Quality standard for stable angina. NICE quality standards, QS21, August 2012. Available from: http://www.nice.org.uk/guidance/QS21
- Services for the prevention of cardiovascular disease. NICE commissioning guides, CMG45, May 2012. Available from: http://www.nice.org.uk/guidance/cmg45
- Chronic heart failure quality standard. NICE quality standards, QS9, June 2011. Available from: http://www.nice.org.uk/guidance/QS9

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Cangrelor for reducing atherothrombotic events in people with coronary heart disease undergoing percutaneous coronary intervention and in people awaiting surgery requiring interruption of antiplatelet therapy. NICE technology appraisal guidance, in development, publication expected: August 2015. Available from: http://www.nice.org.uk/guidance/indevelopment/GID-TAG464

- Risk assessment of modifiable cardiovascular risk factors. NICE quality standards, in development, publication expected: September 2015. Available from: http://www.nice.org.uk/guidance/indevelopment/gid-qsd99

- Secondary prevention of myocardial infarction and cardiac rehabilitation. Risk assessment of modifiable cardiovascular risk factors. NICE quality

standards, in development, publication expected: September 2015. Available from: http://www.nice.org.uk/guidance/indevelopment/gid-qsd98

5 External organisations

5.1 Professional organisations

5.1.1 Professional organisations contacted for expert advice

At the selection stage, the following societies were contacted for expert clinical and technical advice:

- Royal College of Physicians under Cardiology
- Royal College of General Practitioners
- Royal College of Nursing
- The Association for Clinical Biochemistry
- Royal College of Pathologists
- British Association for Nursing in Cardiac Care
- British Cardiovascular Society
- British Cardiovascular Intervention Society
- The Vascular Society of Great Britain and Ireland
- The Society for Cardiothoracic Surgery in Great Britain and Ireland

5.1.2 Professional organisations invited to comment on the draft scope

The following societies have been alerted to the availability of the draft scope for comment:

- Royal College of Physicians under Cardiology
- Royal College of General Practitioners
- Royal College of Nursing
- The Association for Clinical Biochemistry
- Royal College of Pathologists
- British Association for Nursing in Cardiac Care
- British Cardiovascular Society

- British Cardiovascular Intervention Society
- The Vascular Society of Great Britain and Ireland
- The Society for Cardiothoracic Surgery in Great Britain and Ireland

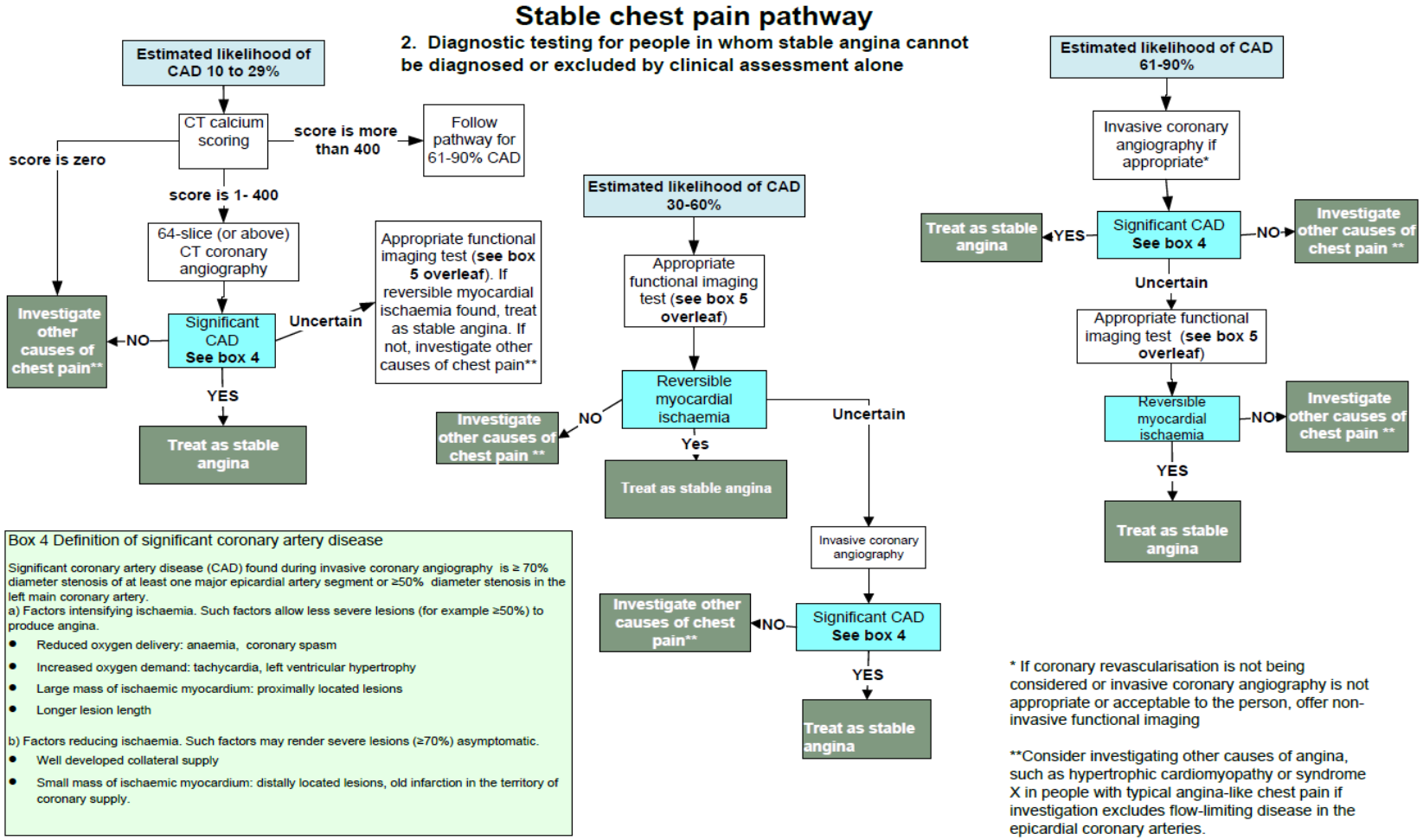
5.2 Patient organisations

At the selection stage, NICE's Public Involvement Programme contacted the following organisations for patient commentary and alerted them to the availability of the draft scope for comment:

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

Appendix 1.

Stable chest pain pathway algorithm



Box 5

When offering non-invasive functional imaging for myocardial ischaemia use:

- myocardial perfusion scintigraphy with single photon emission computed tomography (MPS with SPECT) or
- stress echocardiography or
- first-pass contrast-enhanced magnetic resonance (MR) perfusion or
- MR imaging for stress-induced wall motion abnormalities.

Take account of locally available technology and expertise, the person and their preferences, and any contraindications, when deciding on the imaging method.

Note: This recommendation updates and replaces recommendation 1.1 of NICE technology appraisal guidance 73.