NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Health Technology Evaluation

MTG Review Decision Document

Review of MTG32: HeartFlow FFRCT for estimating fractional flow reserve from coronary CT angiography

This guidance was issued in February 2017.

NICE proposes an amendment of published guidance if there are no changes to the technology, clinical environment or evidence base which are likely to result in a change to the recommendations. However the recommendations may need revision to correct any inaccuracies, usually in relation to providing a more accurate estimate of the results of the cost modelling. The decision to consult on an amendment of published guidance depends on the impact of the proposed amendments and on NICE's perception of their likely acceptance with stakeholders.

1. Recommendation

NICE guidance on HeartFlow FFRCT for estimating fractional flow reserve from coronary CT angiography remains valid. An amendment is required to update the outputs from the cost model.

The EAC costing report and clinical evidence review are provided in Appendix 3 at the end of this paper.

2. Original objective of guidance

To assess the case for adoption of HeartFlow FFRCT for estimating fractional flow reserve from coronary CT angiography.

3. Current guidance

1.1 The case for adopting HeartFlow FFRCT for estimating fractional flow reserve from coronary CT angiography (CCTA) is supported by the evidence. The technology is non-invasive and safe, and has a high level of diagnostic accuracy.

1.2 HeartFlow FFRCT should be considered as an option for patients with stable, recent onset chest pain who are offered CCTA as part of the NICE pathway on chest pain. Using HeartFlow FFRCT may avoid the need for invasive coronary angiography and revascularisation. For correct use, HeartFlow FFRCT requires access to 64-slice (or above) CCTA facilities.

1.3 Based on the current evidence and assuming there is access to appropriate CCTA facilities, using HeartFlow FFRCT may lead to cost savings of £214 per patient. By adopting this technology, the NHS in England may save a minimum of £9.1 million by 2022 through avoiding invasive investigation and treatment.

4. Rationale

During the guidance review, a substantial amount of new evidence was identified as well as changes to the cost of imaging modalities included in the cost case. Despite the large number of published studies on HeartFlow FFRCT, the evidence review found that the study results did not challenge the current recommendation and further supported the diagnostic performance, prognostic performance of HeartFlow FFRCT and reported improved clinical outcomes for patients. Furthermore, following updates to the cost model, HeartFlow FFRCT remains cost-saving. The updated cost model showed HeartFlow to be cost saving to a greater magnitude than the original cost model.

It is not expected that the new evidence or cost case would result in a material change to the recommendations and a guidance update is not required. However, minor changes to comparator costs included in the cost model and the magnitude of cost-savings should be reflected in amendments to the guidance.

5. New evidence

The search strategy from the original assessment report was re-run. References from April 2016 onwards were reviewed. Additional searches of clinical trials registries were also carried out and relevant guidance from NICE and other professional bodies was reviewed to determine whether there have been any changes to the care pathways. The company was asked to submit all new literature references relevant to their technology along with updated costs and details of any changes to the technology itself or the CE marked

indication for use for their technology. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

5.1 Technology availability and changes

The technology has undergone incremental software updates. The current version of the technology is HeartFlow FFRCT version 2.56 which was released in August 2020. The company state the current version 2.56 is not significantly different from version 1.7. The changes made primarily address security updates, compatibility updates and user experience improvements based on user feedback. New features of the technology include:

- Faster turnaround time from 48 hours to 6 hours
- Providing left coronary artery system analysis only when motion or artefact in the right coronary artery would otherwise prohibit case processing.
- Providing analysis for vessels without stents, when there is a stent present in another vessel.
- User features: use of HeartFlow FFRCT on mobile ISO provider, treatment planning features, integration with electronic health records and shared patient management updates, increased options of model viewing.

There have been no changes to the function and mode of action of the technology. The CE mark of the technology has been updated to include the above changes.

5.2 Clinical practice

There have been no changes to the NICE clinical guideline recent-onset chest pain of suspected cardiac origin: assessment and diagnosis (CG95) since the publication of MTG32 HeartFlow FFRCT.

Six clinical experts responded to NICE's request for information. Four of the clinical experts either have direct involvement in the use of HeartFlow FFTCR or refer patients for its use. The experts had conflicting opinions about the adoption and usefulness of the

technology. All experts agree that the technology is used in a secondary care cardiology setting. However, two experts believe the technology is being widely used across the NHS, one believes that only a small number of centres use the technology, and 2 experts do not have access to the technology locally (these comments may not be reflective of actual uptake, please see section 9 for more information). Two experts indicate that a range of different imaging modalities are available to cardiologists and the choice of imaging investigations is at the discretion of the reporting radiologist or cardiologist. All of the experts agree that there may be enough new evidence to impact the recommendation, four of the experts specially reference the cost case and want to see more evidence to support the cost savings reported in the guidance. The experts noted that the FORECAST UK-based RCT is the most relevant to MTG32 as it reports the resource utilisation and cost-effectiveness with FFRCT as an initial strategy in patient with stable chest pain. The trial is currently unpublished, and whilst preliminary evidence is available, a peer-reviewed full text publication would be required to fully evaluate the impact of this evidence on the cost case for adopting HeartFlow FFRCT.

5.3 NICE facilitated research

None

5.4 New studies

The EAC repeated the search strategies from the original guidance and reviewed the information supplied by experts, after duplicates were removed, there were 3,843 search results. Of these results, 70 full text studies and 11 abstracts were included for full text review. During full text review the EAC noted that there was little or no overlap between the scope of the population described for the guidance and the included existing literature. Clinical expert consensus was sought to establish the population descriptions that may be deemed to match the population described in the scope, for more information please see the review report. Following full-text eligibility review, 21 full texts and 2 unpublished records were included in the evidence review.

The new evidence comprises:

- 12 prospective observational studies (Shiono et al., 2019. [n=1,829]; Dreissen et al. 2019. [n=208]; Ibdayhid et al. 2019b. [n=206]; Colleran et al. 2017 [n=116; 2 groups]; Douglas et al. 2015 [n=584; 2 groups]; Douglas et al. 2016 [n=584; 2 groups]; Pontone et al. 2019. [n=147]; Lu et al. [n=271]; Sand et al. 2018. [n=143]; Jensen et al. 2018 [n=774; 2 groups]; Ko et al. 2019 [n=51]; Osawa et al. 2017. [n=20])
- 5 prospective real-world studies (Matsumura-Nakano et al. 2017 [n=90; feasibility conference abstract]; Matsumura-Nakano et al. 2019 [n=93; full text]; Rabbat et al. 2020 [n=431]; Norgaard et al. 2017a. [n=189]; Norgaard et al. 2017b. [n= 3,523])
- 2 retrospective analysis studies (Curzen et al. 2016. [n=22]; Koh et al. 2016 [n=116])
- 1 retrospective real world registry conference abstract (Argacha et al. 2019 [n=2,906])
- 1 Predictive modelling study (Rizvi et al. 2016 [n=612])
- 1 unpublished RCT (Curzen et al., 2020)
- 1 unpublished audit from one expert

The EAC reviewed the impact of the new evidence on the diagnostic and prognostic performance of the technology, its impact on invasive coronary angiography (ICA) rates and its impact on clinical outcomes.

Diagnostic performance – The new evidence on HeartFlow agrees with the conclusion of the guidance. The diagnostic accuracy, sensitivity, specificity, positive predictive value, negative predictive value and AUC of HeartFlow for detecting ischemia-causing lesions is equivalent or superior to the comparator technologies (PET, SPECT, CCTA + TAG320, CCTA and CCTA +Stress CTP).

Prognostic value – In a long term follow up study (median follow up time of 4.7 years) compared to a clinically significant stenosis at CCTA, a positive HeartFlow FFRCT result better predicted a composite endpoint of death, non-fatal myocardial infarction and any revascularization (Ihdayhid et al. 2019a and 2019b).

Impact on reduction in ICA – New evidence consistently reported that using FFRCT lead to a reduction in ICA procedures (Rabbat et al., 2020; Lu et al. 2017; Nørgaard et al. 2017b; unpublished RCT) or ICA cancellations (Jensen et al. 2018; Colleran et al. 2016; Douglas et al. 2015). One unpublished audit reported [redacted]

Clinical outcomes – New evidence reported fewer unnecessary invasive procedures with no death, myocardial infarction unstable angina and hospitalisation leading to unplanned revascularisation. Reports of major cardiac outcomes, quality of life and angina were similar or improved after the use of HeartFlow FFRCT compared with CCTA alone.

In conclusion, the findings of the new evidence do not challenge the conclusions drawn in the original MTG32 HeartFlow guidance and would not result in a material change in the current recommendations.

5.5 Cost update

There has been no change to the cost of the technology since the publication of MTG32, however, changes in comparator costs mean the cost case is no longer valid. King's Technology Evaluation Centre (KiTEC) EAC reviewed and updated the cost model (please see the EAC cost update). During the development of the original HeartFlow guidance the cost model was revised by the EAC to account for the new recommendations in the revised chest pain guideline (CG95).

In the revised model the standard of care arm, positive CCTA results in the treatment of stable angina. Treatment for stable angina is either percutaneous coronary intervention (PCI) or optimal medical therapy. In the interventional arm of the revised model a positive CCTA is further investigated with HeartFlow FFRCT, with positive FFRCTs resulting in the treatment of stable angina. In both arms an uncertain CCTA result leads to further functional imaging (SPECT, MRI, or ECHO). Uncertain functional imaging results lead to an invasive coronary angiogram. The model structure is illustrated in figure 1. The time horizon for the model was 1 year to capture the impact of diagnosis on the initial treatment. The model reported separate results for the three functional imaging modalities. The results showed that using HeartFlow FFRCT had a cost saving of £214, irrespective of the functional imaging test

used. Key drivers of the model were the diagnostic accuracy for CCTA, ICA and FFRCT and the cost of the technology.

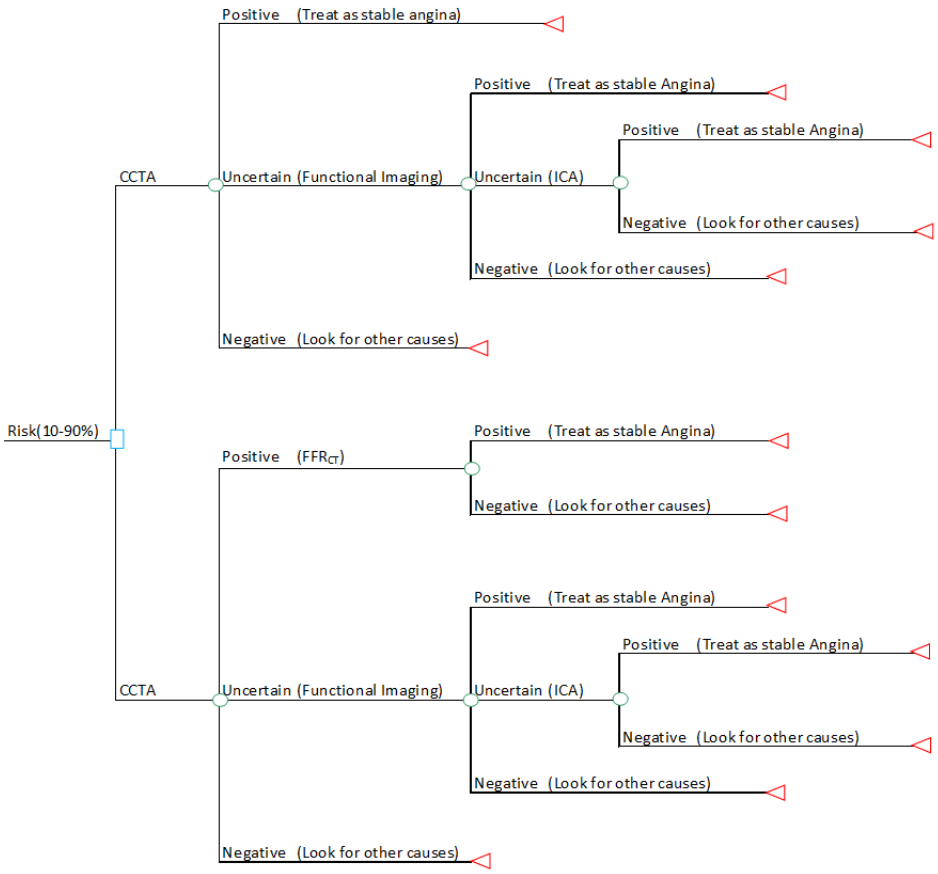

Figure 1 Model structure of the revised cost model used in the original guidance for MTG32 HeartFlow

The updated CG95 pathway remains valid, as does the structure of the revised model used during the development of MTG32 HeartFlow. The assumptions also remain valid, however, the EAC have updated some cost parameters to account for updated NHS reference costs. The updates to the

model do not impact the direction of the result and HeartFlow FFRCT remains cost saving.

The updated cost parameters are reported in table 1.

Test	Code, description	Original cost estimate	Updated cost estimate	Source	EAC comment
Calcium Scoring	RA08Z (£77) - Computerised Tomography Scan, one area, no contrast	£77	£70	NHS Tariffs, 2020 -21	Code changed to RD20A
ICA	EY43A to EY43F, Standard cardiac catheterisation	£1685	£2,369	NHS Tariffs, 2020 -21	Average
CTCA	RD28Z, Complex computerised tomography scan	£122	£290	NHS Tariffs, 2020 -21	
SPECT	RN21Z, Myocardial perfusion scan, stress only	£367	£282	NHS Tariffs, 2020 -21	
ECHO	EY50Z, Complex echocardiogram	£271	£199	NHS Tariffs, 2020 -21	
CMR	RA67Z, Cardiac magnetic resonance imaging scan, pre and post contrast	£515	£574	NHS Tariffs, 2020 -21	Code changed to RD10Z
PCI	EA31Z, Percutaneous Coronary Intervention (0-2 Stents) and EA49Z Percutaneous Coronary Interventions with 3 or more Stents, Rotablation, IVUS or Pressure Wire	£2832	£3526	NHS Tariffs, 2020 -21	Average, Codes EY41A-D, Standard Percutaneous Transluminal Coronary Angioplasty

	Weighted average				
PCI drugs	Aspirin and clopidogrel (annual cost)	£33	£36.48	BNF 2020	
OMT	Aspirin, simvastatin, glyceryl trinitrate and propranolol hydrochloride (annual cost)	£84	£75.36	BNF 2020	

With the updated parameters the results of the cost model showed that using HeartFlow FFRCT remains cost-saving but with an increased magnitude of £391, irrespective of function modality. The model results are reported in table 2.

	Average total cost per patient (patient based)		
	(Functional Imaging: SPECT) Model	**(Functional Imaging: MRI) Model**	**(Functional Imaging: ECHO) Model**
NICE Updated Guideline	£1,859	£1,841	£1,780
Adapted NICE Guideline using FFR_{CT}	£1,469	£1,450	£1,389
Difference (cost saving)	£391	£391	£391

A significant input parameter is the company's cost of HeartFlow FFRCT.

[redacted]

	[redacted]

	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

6. Additional information

7. Summary of new information and implications for review

The new evidence is consistent with the original MTG32 Heartflow Guidance and is unlikely to have a material impact on the recommendation and further supports the original positive recommendation. Similarly, the updated cost model reports that using HeartFlow remains cost-saving and that the magnitude of the cost-savings have increased due to comparator costs increasing.

There have been 91 MAUDE records for HeartFlow FFRCT reporting false negative results (results were restricted from 1st April 2016 to 10th February 2020).

8. Implementation

The technology is available in the NHS with 62 NHS England hospitals using HeartFlow at present. As of December 31, 2020, 15,754 patient scans have been referred for HeartFlow analysis.

There are an additional 29 NHSE hospitals currently in the process of implementing HeartFlow. One hospital in Wales and 1 in Scotland actively use HeartFlow at present. One hospital in Northern Ireland and 1 in the Channel Islands are currently implementing the use of HeartFlow.

In 2018, HeartFlow was selected for the ITP programme. HeartFlow was identified as an Accelerated Access Collaborative Rapid Uptake Product in late 2018 and uptake exceeded the annual projections. As a result, the ITP funding was extended for 2019 and 2020. In 2020, the eligibility criteria for a site to utilise the ITP scheme to procure HeartFlow at no cost were revised, and now a site is eligible if they conduct 300> CCTAs per year. Starting April 2021, the funding for HeartFlow will transition to the new MedTech Funding

Mandate. All NHSE providers and NHSE Commissioners will be expected to comply with the Mandate guidance and CCG's will be expected to fund HeartFlow from 1st April 2021.

9. Equality issues

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

No equality issues were raised in the original guidance. No new equality issues were identified during guidance review.

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Appendix 1 – explanation of options

If the published Medical Technologies Guidance needs updating NICE must select one of the options in the table below:

Options	**Consequences**	**Selected – 'Yes/No'**
Amend the guidance and consult on the review proposal	The guidance is amended but the factual changes proposed have no material effect on the recommendations.	No
Amend the guidance and do not consult on the review proposal	The guidance is amended but the factual changes proposed have no material effect on the recommendations.	Yes
Standard update of the guidance	A standard update of the Medical Technologies Guidance will be planned into NICE's work programme.	No
Update of the guidance within another piece of NICE guidance	The guidance is updated according to the processes and timetable of that programme.	No

If the published Medical Technologies Guidance does not need updating NICE must select one of the options in the table below:

Options	**Consequences**	**Selected – 'Yes/No'**
Transfer the guidance to the 'static guidance list'	The guidance remains valid and is designated as static guidance. Literature searches are carried out every 5 years to check whether any of the Medical Technologies Guidance on the static list should be flagged for review.	No
Defer the decision to review the guidance	NICE will reconsider whether a review is necessary at the specified date.	No
Withdraw the guidance	The Medical Technologies Guidance is no longer valid and is withdrawn.	No

Appendix 2 – supporting information

Relevant Institute work

Published

- Chronic heart failure in adults: diagnosis and management (2018) NICE guideline NG106
- Recent-onset chest pain of suspected cardiac origin: assessment and diagnosis (2010, updated 2016) NICE guideline CG95
- Stable angina: management (2011, updated 2016) NICE guideline CG126
- Optowire for measuring fractional flow reservev (2019) NICE medtech innovation briefing 199
- DyeVert for reducing contrast media in coronary and peripheral angiography (2019) NICE medtech innovation briefing 196
- DuraGraft for preserving vascular grafts (2019) NICE medtech innovation briefing 184
- CADScor system for ruling out coronary artery disease in people with symptoms of stable coronary artery disease (2019) NICE medtech innovation briefing 174
- QAngio XA 3D/QFR imaging software for assessing coronary obstructions (2018) NICE medtech innovation briefing 146
- VEST external stent for coronary artery bypass grafts (2017) NICE medtech innovation briefing 115
- Somatom Definition Edge CT scanner for imaging coronary artery disease in adults in whom imaging is difficult (2016, updated 2017) NICE medtech innovation briefing 54
- Aquilion PRIME CT scanner for imaging coronary artery disease in adults in whom imaging is difficult (2016, updated 2017) NICE medtech innovation briefing 53
- 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 (2012, updated 2017) NICE diagnostic guidance 3

In progress

None identified

Registered and unpublished trials

Trial name and registration number	Details
Fractional Flow Reserve Derived From Computed Tomography Coronary Angiography in the Assessment and Management of Stable Chest Pain (FORECAST). Two-Group Diagnostic RCT. **NCT03187639** https://clinicaltrials.gov/ct2/show/NCT03187639	FORECAST is a multi-site randomised controlled trial comparing 1400 patients with new onset pain who are assigned to either routine assessment or FFRct assessment (n=700 per group) Expected data: publication timing not known. Abstract presented October 2020 [Curzen et al. 2020] Company Update on 29 January 2021 that 1400 participants had been recruited across 11 sites
Heartflow (AFFECTS) (AFFECTS). Single Group Diagnostic Trial. Recruiting. **NCT02973126**. https://clinicaltrials.gov/ct2/show/NCT02973126	Assessment of Fractional Flow reservE Computed Tomography Versus Single Photon Emission Computed Tomography in the Diagnosis of Hemodynamically Significant Coronary Artery Disease. (AFFECTS) (n=270) Sing site observational study. Estimated study completion date: December 2021 Expected data: publication timing not known Company Update on 29 January 2021 reported that 58 participants had been recruited

Trial name and registration number	Details
Evaluation of Fractional Flow Reserve Calculated by Computed Tomography Coronary Angiography in Patients Undergoing TAVR (FORTUNA). **NCT03665389** https://clinicaltrials.gov/ct2/show/NCT03665389	A single arm prospective observational diagnostic study evaluating the use of HeartFlow in 25 patients having transcatheter aortic valve replacement. Single site study Expected data: estimated end of 2021 Company Update on 29 January 2021 reported that 24/25 participants have been recruited
The PRECISE Protocol: Prospective Randomized Trial of the Optimal Evaluation of Cardiac Symptoms and Revascularization (PRECISE). **NCT03702244**. https://clinicaltrials.gov/ct2/show/NCT03702244	An open-label, multi-site randomised parallel group trial comparing the diagnostic effectiveness of CCTA with selective FFRCT including Expected data: estimated Summer, 2022 Last Update Posted: January 31, 2020. Company Update on 29 January 2021 reported that between approx. 1800 participants have been recruited across 55 sites
Precise Percutaneous Coronary Intervention Plan (P3) Study (P3) **NCT03782688**. https://clinicaltrials.gov/ct2/show/NCT03782688	A prospective multi-site observational study evaluating the agreement and accuracy of the HeartFlow Planner with invasive FFR as a reference. (n=120) Expected data: Spring, 2021 Company Update on 29 January 2021 reported that 129 participants have been recruited across 6 sites.

Trial name and registration number	Details
The Heartflow Coronary Disease Progression Evaluation Study (THRONE) **NCT04052256**. https://clinicaltrials.gov/ct2/show/NCT04052256	This is a prospective observational study valuating disease progression in intermediate lesions using FFRCT and determine whether CT characteristics may help to identify lesions that are more susceptible to FFR decline. (n=250) Single site study Company Update on 29 January 2021 reported that approximately 140 participants have been recruited. Expected data: estimated 2022
Safety and Feasibility Evaluation of Planning and Execution of Surgical Revascularization Solely Based on Coronary CTA and FFRCT in Patients With Complex Coronary Artery Disease (FASTTRACK CABG) **NCT04142021** https://clinicaltrials.gov/ct2/show/NCT04142021	A multi-site, prospective observational study assessing the feasibility of CCTA and FFRCT to replace ICA as a guidance method for planning and execution of coronary artery bypass graft. (n=114) Company Update on 29 January 2021 repoted that approximately 10 participants had been recruited across 3 sites. Expected data: estimated end of 2021

Appendix 3 – changes to guidance

Table 1: proposed amendments to original guidance

Section of MTG	Original MTG	Proposed amendment
Page 1, 1.3	Based on the current evidence and assuming there is access to appropriate CCTA facilities, using HeartFlow FFRCT may lead to cost savings of £214 per patient. By adopting this technology, the NHS in England may save a minimum of £9.1 million by 2022 through avoiding invasive investigation and treatment.	Based on the current evidence and assuming there is access to appropriate CCTA facilities, using HeartFlow FFRCT may lead to cost savings of £391 per patient [2021]. By adopting this technology, the NHS in England may save a minimum of £9.4 million by 2022 through avoiding invasive investigation and treatment [2021].
5.19		For the guidance review, the external assessment centre revised the model to reflect 2021 costs. There were no changes to the cost of the technology, the main parameter changes were the cost of comparator tests. Further details of the 2021 revised model are in the costing report.
5.20		Based on the 2021 guidance review updated cost model, EAC found a base-case cost saving of £391 per patient for HeartFlow FFRCT compared with the current treatment pathway for all functional imaging tests (SPECT, MRI and ECHO). This cost saving will increase if the cost of HeartFlow FFRCT is reduced.

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Unpublished audit from one of the experts.

Appendix 4 – Evidence Review Report

Review report of MTG32: HeartFlow FFRCT for estimating fractional flow reserve from coronary CT angiography

Version no.	Date	Author	Purpose
1.0	08/01/21	F Shokraneh K Goddard J Erskine M Radhakrishnan Kartha	Sections 1,2,3,4,5 and appendices A, C, D, and E partially populated
2.0	15/01/21	F Shokraneh M Radhakrishnan Kartha	Economic sections were added
3.0	03/03/21	F Shokraneh J Erskine A Chalkidou	All the section were populated and checked.
4.0			

This medical technology guidance was published in February 2017 and reviewed in February 2021.

All medical technology guidance is usually reviewed 3 years after publication, unless NICE become aware of significant new information before the expected review date.

This review report summarises new evidence and information that has become available since this medical technology guidance was published, and that has been identified as relevant for the purposes of this report. This report will be used to inform NICE's decision on whether this guidance will be updated, amended, remain unchanged (static list) or withdrawn.

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Dr Ronak Rajani, Consultant Cardiologist and Reader in Cardiovascular Imaging, Guy's and St Thomas' NHS Foundation Trust

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Assigned with East Sussex Health Trust and Kings College University London.

Abbreviations

FFRCT	Fractional Flow Reserve derived from CT
ITP	The Innovation and Technology Payment
CT	Computed Tomography
CCTA	Coronary Computed Tomography Angiography
CAD	Coronary Artery Disease
ICA	Invasive Coronary Angiography
MACE	Major Adverse Cardiovascular Events
MACCE	Major Adverse Cardiovascular and Cerebrovascular Event
SPECT	Single-Photon Emission Computed Tomography
PET	Positron Emission Tomography
TAG	Transluminal Attenuation Gradient
HR	Hazard Ratio
RCT	Randomised Controlled Trial
CI	Confidence Interval
AUC	Area Under Curve
ROC	Receiver Operating Characteristic
CTP	Myocardial Computed Tomography Perfusion
NS	Non-Significant
OR	Odds Ration
TPR	Transmural Perfusion Ratio
iFFR	Invasive FFR
FFR	Fractional Flow Reserve
cFFR	Coronary FFR
LAD	Left Anterior Descending Artery
ACS	Acute Coronary Syndrome
PPV	Positive Predictive Value
NPV	Negative Predictive Value
UC	Usual Care
PCI	Percutaneous Coronary Intervention
iFR	Instantaneous Wave-Free Ratio

1. Original objective of guidance

To assess the clinical and cost effectiveness of HeartFlow FFRCT for estimating fractional flow reserve from coronary CT angiography.

2. Current guidance recommendations

1.1 The case for adopting HeartFlow FFR_{CT} for estimating fractional flow reserve from coronary CT angiography (CCTA) is supported by the evidence. The technology is non-invasive and safe and has a high level of diagnostic accuracy.

1.2 HeartFlow FFR_{CT} should be considered as an option for patients with stable, recent onset chest pain who are offered CCTA as part of the NICE pathway on chest pain. Using HeartFlow FFR_{CT} may avoid the need for invasive coronary angiography and revascularisation. For correct use, HeartFlow FFR_{CT} requires access to 64-slice (or above) CCTA facilities.

1.3 Based on the current evidence and assuming there is access to appropriate CCTA facilities, using HeartFlow FFR_{CT} may lead to cost savings of £214 per patient. By adopting this technology, the NHS in England may save a minimum of £9.1 million by 2022 through avoiding invasive investigation and treatment.

3. Methods of review

The EAC repeated the search strategies from the published Medical Technologies Guidance (MTG32) to update the searches supplemented by NICE. The EAC also reviewed the information supplied by the experts and the company.

The search date was limited to cover the literature between 2016 and the present.

Search results from all databases were collated into a library using EndNote X9 (Clarivate, Thomson Reuters Corporation, George Mason University) and the duplicate reports were removed from this library.

The EAC manually excluded any studies from the previous Assessment Report that appeared in the updated search. All search strategies conducted by the EAC are listed in Appendix C.

The literature updates provided by the manufacturers were cross-matched with the results of the systematic review. Of the 63 references provided by HeartFlow the following records were excluded in first sifting: one record was de-duplicated in the list; one record had no data; one record did not describe the study population; one systematic review reported heterogenous population; 22 records reported on different population that the one in the scope; and eight records were narrative reviews.

The EAC reviewed the remaining 29 records submitted by the company plus 3843 references found by the NICE and EAC searches. The titles and abstracts of all references were assessed for relevance by 2 reviewers using the inclusion and exclusion criteria outlined in the original DAR, leaving 70 full text studies and 11 conference abstracts for full text assessment.

At the full text assessment eligibility stage (as per PRISMA guidelines), all publications were reviewed by 2 reviewers and any disagreements about the relevance of a study were resolved by discussion and consensus. In total, 81 studies were reviewed, and 21 reports were included. We added 2 extra unpublished records to the list (one from an unpublished trial and one audit from a clinical expert). A PRISMA flow diagram is presented in Appendix C.

Pragmatic changes to the scope of this guidance review

Since there was little or no overlap between the scope of population described for this guidance review and the included patients in the existing literature, the EAC agreed with NICE to ask the clinical expert's opinion. The EAC shared the original guidance review scope and 34 descriptions of patient populations from the literature with six clinical experts. Five of them replied and marked the populations that potentially match the scope. At least three votes per description were required to establish consensus. Only the six following descriptions reached consensus among the experts and therefore, are included in this guidance review:

- Stable chest pain
- Stable chest pain and without known CAD

- Suspected CAD
- New onset chest pain
- Stable angina pectoris
- Stable typical angina pectoris

4. New evidence

4.1. Changes in technology

HeartFlow continues to increment its software with monthly releases to address minor feature updates, as well as security and efficiency improvements. The current version is 2.56, which was released 19 August 2020. It is not significantly different than the 1.7 version, but over the course of several releases, security and usability updates have been added:

- Security updates include multi-factor authentication as well as ISO 27001 and HITRUST certification.
- Monthly software revisions that incorporate feedback from providers using HeartFlow so the company can regularly address challenging clinical situations, enhance the user experience, and maintain a high level of data security.
- Compatibility with regular updates to software with which HeartFlow interacts, such as new versions of Windows, EHRs, iOS.
- New usability improvements such as:
    - Improving the turnaround time from an average of 48 hours to an average of 6 hours
    - Upon request, providing a Left Coronary Artery system analysis only when motion or artefact in the Right Coronary Artery would otherwise prohibit case processing
    - Providing analyses for vessels without stents when there is a stent present in another vessel
    - HeartFlow mobile: use of the HeartFlow Analysis on mobile iOS platforms to enhance provider use and facilitate patient education (at present, 11 NHSE hospitals have security approval for mobile use)

- A planning feature that allows the user to explore the model the company already provide and simulate opening of lesions to assess the potential FFRCT changes when opened [this feature has not yet launched in the UK]
- HeartFlow Care Teams: designates a team of clinicians to interact with the HeartFlow Analysis for shared patient management
- Electronic health record (EHR) integration: easier incorporation of the HeartFlow Analysis into each patient's records (still being rolled out across NHSE hospitals)
- Display angiographic projection angles as the FFR_{CT} model is rotated (available on web and mobile interfaces).

The new model performs the same function and use the same mode of action as the technology in MTG32. This model does not have a new CE marking; The original CE mark (for version 1.x) was updated to include 2.x.

In 2018, HeartFlow was selected for the ITP programme. HeartFlow was identified as an Accelerated Access Collaborative Rapid Uptake Product in late 2018 and the ITP funding was extended for 2019 and 2020. In 2020, the eligibility criteria for a site to utilise the ITP scheme to procure HeartFlow at no cost were revised, and now a site is eligible if they conduct 300> CCTAs per year. Starting April 2021, the funding for HeartFlow will transition to the new MedTech Funding Mandate. All NHSE providers and NHSE Commissioners will be expected to comply with the Mandate guidance and CCG's will be expected to fund HeartFlow from 1st April 2021.

The current price for the HeartFlow Analysis is £700 per analysis.

[redacted]

HeartFlow has also provided an update spreadsheet outlining the changes in tariffs used in the economic modelling from the 2016 submission. Please see additional information provided in Parameter updates to NICE modelling_vf xlsx in MTG32 HeartFlow Costing Report.

The technology is available in the NHS with 62 NHS England hospitals using HeartFlow at present. As of December 31, 2020, 15,754 patient scans have been referred for HeartFlow analysis.

There are an additional 29 NHSE hospitals currently in the process of implementing HeartFlow. One hospital in Wales and 1 in Scotland actively use HeartFlow at present. One hospital in Northern Ireland and 1 in the Channel Islands are currently implementing the use of HeartFlow.

4.2. Changes in care pathways

CG95 was updated in parallel with MTG32 in 2016. The guidance proposes to offer 64-slice (or above) CCTA if:

- clinical assessment indicates typical or atypical angina or
- clinical assessment indicates non-anginal chest pain but 12-lead resting ECG has been done and indicates ST-T changes or Q waves

It also proposes to:

- offer non-invasive functional imaging for myocardial ischaemia if 64-slice (or above) CCTA has shown CAD of uncertain functional significance or is non-diagnostic.
- and offer invasive coronary angiography as a third-line investigation when the results of non-invasive functional imaging are inconclusive.

The guidance also mentions that using HeartFlow may avoid the need for ICA and revascularisation for some patients.

Clinical experts

Half of the experts reported no changes to practice while two reported changes such as increase in using all imaging modalities to diagnose CAD not just CCTA. The position of ICA in the pathway remains unchanged as it has no competitors and the choice of the technology depends on cardiologists' preferences. There have been changes to waiting times for between 2016 and 2018. An expert report that prior to 2016, a stress echo was possible on the day of patients' first visit, in 2018, they have to wait for 6-10 weeks to have a CCTA scan and, with the addition of FFRCT they have to wait a further 48 hrs to get a result. These experts stated that the clinicians shifted to use more stress eco which meant re-deployment of staff and a dilution of skills in a modality that has extensive prognostic data, no radiation and is very cost effective in the management of patients with suspected stable angina.

Use of the technology will vary depending on clinicians' choices and experience, severity, prevalence of significant disease, locality of disease, percentage of stenosis, and imaging quality. One of the experts reported the main reason for less use of the technology would be the lack of data to show the superiority of FFRCT over the other non-invasive functional imaging modalities. HeartFlow improves specificity of CCTA and reduced false positives by as much as 50%. It does not improve sensitivity of the plain CCTA. CG95 recommends a perfusion scan as one of the options after a CCTA. If the guidance continues recommending a perfusion scan in addition to CCTA with HeartFlow, there is redundancy in the pathway and increased cost. The choice is now between CCTA followed by perfusion imaging before ICA (current NICE guideline) or CCTA with HeartFlow (no or very limited perfusion imaging) before ICA. The expert referred to the new ISCHEMIA trial and suggested that it will lead to an update of the current guidance [CG95] and use of FFRCT, FFRCT still might have a role in symptomatic patients with multivessel disease to identify target vessels for revascularisation if symptoms are not controlled by medical therapy. According to the expert the ISCHEMIA trial (the trial does not include FFRCT) suggests that patients with stable CAD can be managed safely by conservative care, without the need for ischaemia testing or invasive investigation or management.

Another expert added that although in theory, HeartFlow offers an enhanced pathway and improves time to diagnosis, in practice, the services are also becoming more protracted with long waits for CCTA compared with stress echo. Only coronary data is provided with CCTA so when a decision is made to revascularise, echocardiograms are being required for ventricular and valve data.

The experts reported that the number of referrals for FFRCT has varied between none (because of no access) to all CCTA’s with obstruction (because of being part of the NHS ITP programme). Other experts reported 2-3% of patients with moderate disease detected upon CCTA in whom they would otherwise suggest a further functional test to determine the significance of the disease or 20% to mild lesions.

Another expert mentioned that CG95 increased awareness and in that sense, it was useful but not influential to change the current practice. Half of the experts who used the technology found that the published guidance [CG95] was misused by HeartFlow and NHS England where it was cited that FFRCT was in the guidelines. It was not [in the guidelines] but was “recommended for

use" and suggested potential savings to the healthcare system which is not based on evidence. The other hidden costs are delayed pathways for patients, lack of additional data on valves and ventricles and the erosion of existing services. The data supported safety and validity of the technology but without a real-world trial – the guidance should have been moderate better following its release.

Four experts who used this technology listed patients with stable chest pain patients and moderate/equivocal disease detected upon CCTA as the main referred clinical scenario. One expert suggested that the recent evidence from the ISCHEMIA trial makes this indication questionable and another one added the lack of UK-wide data to decide on which patient categories can benefit more from using FFRCT. The last expert highlighted that in units that lack strong functional imaging services, HeartFlow maybe useful only if patients have timely access to CCTA. Most of the experts who have used the technology think that an update to the guidance in terms of making the recommendation transparent based on the new evidence (FORECAST and ISCHEMIA trials) is needed and they question the cost of this technology compared to the other modalities. The FORECAST trial is the only RCT of this technology and provides resource utilisation and economic data.

4.3. Results from the MTEP research commissioning workstream

There has not been any MTEP research commissioning workstream for HeartFlow.

4.4. New studies

FORECAST: This was the only RCT that was identified for HeartFlow presenting evidence on resource utilisation and cost-effectiveness with FFRCT as an initial strategy in patients with stable chest pain. The trial is currently unpublished, however, we identified preliminary evidence presented by the Principal Investigator at TCT Connect 2020. This trial compares the impact of CCTA + FFRCT vs. the routine clinical pathway recommended by NICE CG95 on resource utilisation at 9 months. It included1400 adult patients with chest pain deemed to require further investigation after attending Rapid Access Chest Pain Clinics (RACPC) across 11 UK centres. Only patients with a coronary stenosis of >40% in at least one major epicardial vessel of stentable/graftable diameter were referred to FFRCT. In the intervention arm, among 700 patients, 220 (31.5%) had FFRCT. The main reason for those 479

patients (68%) who did not have FFRCT was that they had no lesions >40% (415; 86.6%). The other two reasons were having no analysable images (8.2%) and not having undergone CCTA (5.2%). Based on FFRCT results, 100 patients (45.5%) had ICA and 14 (6.4%) had a non-invasive test. In 9-month follow-up, there was 14% lower ICA in the test vs. reference group (p=0.02) and 22% fewer patients had ICA in test vs. reference group (p=0.01). Total cost for the reference group was 1491.46 (mean) and 1605.50 for test group [currency unclear in the slides]. The number of clinical events in the reference group was slightly higher than the test group (MACCE: 74 vs. 61; hospitalisation: 74 vs. 69; CVA: 1 vs.) and lower for some other events (MI: 3 vs. 9; mortality: 0 vs. 2).It is not reported whether or not these findings were statistically significant. From the slides, it seems the mortality was because of co-morbidities such as metastatic lung cancer and community acquired pneumonia. The quality of life (EQ-5D) and angina status (SAQ-7) showed improvement in both groups but a significant difference was not observed. The investigators listed two limitations for FORECAST: 1. Pragmatic decision on sending patients with > 40% stenosis to FFRCT and 2. The increase on number of patients in reference group who underwent CCTA through the recruitment process (anticipated from CG95 NICE guideline) at the rate that was impossible to model in the start of the trial (Curzen et al. 2020 [conference abstract]). The EAC contacted the company for additional data on this trial but haven't received further information. Since this trial is not published and we relied on unpublished conference slides, we were not able to assess the risk of bias for this trial. The trial is funded by the company.

ADVANCE Register: This multi-country register contains the records of over 5000 patients who have been referred to FFRCT and has been used to provide retrospective evidence. A study of 1829 patients with suspected CAD from Japan showed that access to FFRCT results led to reclassification of treatment strategy between CCTA alone and CCTA + FFRCT in 55.8% of site investigations and in 56.9% in the core laboratory analysis (Shiono et al. 2019).

PACIFIC: A prospective sub-study of this study on 208 patients with suspected stable CAD reported that the diagnostic accuracy, sensitivity, and specificity of FFRCT were 87%, 90%, and 86% on a per-vessel basis and 78%, 96%, and 63% on a per-patient basis, respectively; AUC for identification of ischemia-causing lesions was significantly greater for FFRCT (0.94 and 0.92) in comparison with CCTA alone (0.83 and 0.81; p < 0.01 for

both) and SPECT (0.70 and 0.75; p<0.01 for both), on a per-vessel and -patient level, respectively; FFRCT also outperformed PET on a per-vessel basis (AUC 0.87; p < 0.01), but not on a per-patient basis (AUC 0.91; p=0.56). However, in the intention-to-diagnose analysis, PET showed the highest per-patient and -vessel AUC followed by FFRCT (0.86 vs. 0.83; p=0.157; and 0.90 vs. 0.79; p=0.005, respectively) (Driessen et al. 2019).

NXT: The evidence from this study has already been reviewed in the original assessment of this technology. This was a retrospective, single-centre sub-study of NXT on 200 patients with stable chest pain reported that involving FFRCT data in decision making changed the allocated management category based on CCTA alone in 72 cases (36%) (Curzen et al. 2016).

A prospective follow-up sub-study of NXT with 206 patients suspected of having stable CAD investigated the prognostic value of FFRCT vs. CCTA. At median follow-up of 4.7 years, there were no cardiac deaths or MI in participants with normal FFRCT. The primary end point was a composite of death from any cause, nonfatal myocardial infarction, and any revascularization. The incidence of the primary end point was more frequent in participants with positive FFRCT compared with clinically significant stenosis at CCTA (73.4% [80 of 109] vs. 48.7% [91 of 187], respectively; P<.001), with the majority of outcomes being planned revascularization (HR 9.2; 95% CI: 5.1, 17; P<.001) for FFRCT and HR 5.9; 95% CI: 1.5, 24; P = .01 for CCTA). FFRCT was a better predictor compared with CCTA for the primary end point (C-index FFRCT, 0.76 vs. CCTA, 0.54; P= .001) and MACE (FFRCT, 0.71 vs CCTA, 0.52; P = .001). Frequency of MACE was higher in participants with positive FFRCT compared with CCTA (15.6% [17 of 109] vs 10.2% [19 of 187], respectively; P = .02), driven by unplanned revascularization. MACE HR was 5.5 (95% CI: 1.6, 19; P = .006) for FFRCT and 2.0 (95% CI: 0.3, 14; P = .46) for CCTA (Ihdayhid et al. 2019a and 2019b).

The last retrospective sub-study of NXT included 61 patients suspected of having CAD and compared the diagnostic performance of FFRCT, transluminal attenuation gradient (TAG; TAG320), and CCTA alone. Per-vessel accuracy, sensitivity, specificity, and positive and negative predictive values for TAG320 (Spearman p,15.37) were 78%, 58%, 86%, 64%, and 83%, respectively; and those of FFRCT were 83%, 92%, 79%, 65%, and 96%, respectively. ROC curve analysis showed a significantly larger AUC for

FFRCT (0.93) compared with that for TAG320 (0.72; P=.003) and CCTA alone (0.68; P=.008) (Ko et al. 2016).

PLATFORM: The evidence from this study has already been reviewed in the original assessment report. This prospective observational cohort sub-study of PLATFORM included 116 patients with suspected CAD in two groups of CCTA/FFRCT (n=52) vs. UC (n=64). ICA was cancelled in 77% of the 52 patients having CCTA + FFRCT. No obstructive CAD was found at ICA in 4 of 52 patients (7.7%) in the CCTA + FFRCT group and in 55 of 64 patients (85.9%) in the UC group (risk difference 78.2%, 95% CI: 67.1-89.4%, p<0-0001). There were no cases of death, MI, unstable angina, and hospitalisation leading to unplanned revascularisation up to 90 days. There were 2 (3.1%) MACE or vascular complications in UC group (CI 0.38 to 10.84) and none for CCTA + FFRCT group (CI 0.00 to 6.85). The mean radiation exposure was lower in the FFRCT vs. the usual care group (7.28 vs 9.80 mSv, p<0.001). Mean estimated costs in the CTA + FFRCT group were $4,486 (USD) vs. $ 9,344 in UC (p<0.0001) (€4217 (EUR) for CTA/FFRCT vs. €6894 for UC, p<0.001). Improvement in QOL (EQ-5D score) was greater in the FFRCT (+0.09 units) vs. the usual care cohort (+0.03 units), p=0.04. (Colleran et al. 2016 [conference abstract], 2017).

In another prospective cohort of PLATFORM with one-year follow-up including 584 patients with new onset chest pain, CCTA + FFRCT (n=296) was compared to UC (n=287). Among those with intended ICA (FFRCT-guided, n=193; UC, n=187), no obstructive CAD was found at ICA in 24 (12%) in the CTA + FFRCT arm and 137 (73%) in the UC arm (risk difference 61%, 95%CI: 53–69, P<0.0001), with similar mean cumulative radiation exposure (9.9 vs. 9.4 mSv, P=0.20). ICA was cancelled in 61% of the cases after receiving CCTA + FFRCT results. Among those with intended non-invasive testing, the rates of finding no obstructive CAD at ICA were 13% (CCTA + FFRCT) and 6% (UC; P=0.95). Clinical event rates within 90 days were low in both arms (Douglas et al. 2015). With an extended report from this cohort (Douglas et al. 2016), in the planned invasive stratum, mean costs were 33% lower with CCTA /FFRCT ($8,127 vs. $12,145 UC; p<0.0001); in the planned non-invasive stratum, mean costs did not differ when using an FFRCT cost weight of 0 ($3,049 FFRCT vs. $2,579; p=0.82), but were higher when using an FFRCT cost weight equal to CCTA. QOL scores improved overall at 1 year (p<0.001), with similar improvements in both groups, apart from the 5-item

EuroQOL scale scores in the non-invasive stratum (mean change of 0.12 for FFRCT vs. 0.07 for usual care; p=0.02) (Douglas et al. 2016).

CREDENCE: A predictive model was built based on the results of CREDENCE (prospective cohort 18-23 sites in 8 countries) including 612 adults with symptoms suspicious of CAD with an invasive FFR of 0.80 or less measured in 26.5% of their 1727 vessels. In the derivation cohort, CCTA vessel-specific factors associated with FFR 0.80 or less were stenosis severity, percentage of noncalcified atheroma volume, lumen volume, the number of lesions with high-risk plaque (≥2 of low attenuation plaque, positive remodelling, napkin ring sign, or spotty calcification), and the number of lesions with stenosis >30%. FFRCT was not additive to this model including stenosis and atherosclerotic plaque. Significant myocardial perfusion imaging predictors were the summed rest and difference scores. In the validation cohort, the AUC were 0.81 for CCTA vs 0.67 for myocardial perfusion imaging (P<.001) (Rizvi et al. 2016).

PERFECTION: This was an Italian prospective cohort study including 147 symptomatic patients with suspected CAD comparing the diagnostic accuracy of CCTA vs. CCTA + FFRCT vs. CCTA + Stress-CTP and ICA + invasive FFR as reference standard.

Vessel-based and patient-based sensitivity, specificity, and negative predictive values, and positive predictive values, and accuracy rates of CCTA were 99%, 76%, 100%, 61%, 82%, and 95%, 54%, 94%, 63%, 73%, respectively.

CCTA + FFRCT showed vessel-based and patient-based sensitivity, specificity, and negative predictive values, and positive predictive values and accuracy rates of 88%, 94%, 95%, 84%, 92%, and 90%, 85%, 92%, 83%, 87%, respectively.

CCTA + Stress-CTP showed vessel-based and patient-based sensitivity, specificity, and negative predictive values, and positive predictive values and accuracy rates of 92%, 95%, 97%, 87%, 94% and 98%, 87%, 99%, 86%, 92%, respectively.

Both FFRCT and Stress-CTP significantly improved specificity and positive predictive values compared to those of CCTA alone.

The AUC to detect flow-limiting stenoses of CCTA, CCTA+FFRCT, and CCTA+CTP were 0.89, 0.93, 0.92, and 0.90, 0.94, and 0.93 in a vessel-based and patient-based model, respectively, with significant additional values for both CCTA+FFRCT and CCTA+CTP vs. CCTA alone ($p < 0.001$) but no differences between CCTA+FFRCT vs. CCTA+CTP (Pontone et al. 2019).

PROMISE: The evidence from this study has already been reviewed in the original assessment report. In a sub-study from this prospective cohort, FFRCT + CTA was compared to CTA alone among 271 participants with stable chest pain and without known CAD. FFRCT was calculated in 67% (181 of 271) of eligible patients (mean age 62 years; 36% women). FFRCT was discordant with stenosis in 31% (57 of 181) for CTA and 29% (52 of 181) for ICA. Most patients undergoing coronary revascularization had an FFRCT ≤0.80 (91%; 80 of 88). An FFRCT ≤0.80 was a significantly better predictor for revascularization or major adverse cardiac events than severe CTA stenosis (HR: 4.3 [95% confidence interval [CI]: 2.4 to 8.9] vs. 2.9 [95% CI: 1.8 to 5.1]; $p = 0.033$). Reserving ICA for patients with an FFRCT ≤0.80 could decrease ICA without ≥50% stenosis by 44% and increase the proportion of ICA leading to revascularization by 24% (Lu et al. 2017).

REAL-FFRCT and REAL-FFRCT 2: A single-centre in Japan conducted this prospective real-world feasibility study on 93 patients (139 vessels) with suspected CAD to report the diagnostic performance of FFRCT vs. invasive FFR ≤0.80.

Per-vessel accuracy, sensitivity, specificity, positive predictive value, and negative predictive value were 73%, 95%, 59%, 61%, and 94% for the cut-off value of FFRCT ≤0.80; 81%, 86%, 78%, 73%, and 89% for FFRCT ≤0.75; and 83%, 74%, 89%, 82%, and 83% for FFRCT ≤0.70, respectively.

Per-vessel accuracy across the different ranges of FFRCT ≤0.60, 0.61 to 0.70, 0.71 to 0.80, 0.81 to 0.90, and >0.90 with the cut-off value of FFRCT ≤0.80 were 95%, 74%, 32%, 93%, and 100%, respectively.

Setting a grey zone of FFRCT 0.71 to 0.80 provided high positive predictive value (82%; n=42/51) in the range of FFRCT ≤0.70 and high negative predictive value (94%; n=48/51) in FFRCT >0.80 (Matsumura-Nakano et al. 2017 [conference abstract], 2019).

ReASSESS: This prospective Danish study included 143 patients with stable angina pectoris and investigated the per-patient diagnostic performance of FFRCT vs. SPECT FFR using an FFR value of ≤0.80 as reference. Per-patient diagnostic performance for identifying ischemia (95% confidence interval [CI]), FFRCT vs. SPECT, were sensitivity of 91% (95% CI: 81% to 97%) vs. 41% (95% CI: 29% to 55%; p < 0.001); specificity of 55% (95% CI: 44% to 66%) vs. 86% (95% CI: 77% to 93%; p < 0.001); negative predictive value of 90% (95% CI: 82% to 98%) vs. 68% (95% CI: 59% to 77%; p = 0.001); positive predictive value of 58% (95% CI: 48% to 68%) vs. 67% (95% CI: 51% to 82%; p = NS); and accuracy of 70% (95% CI: 62% to 77%) vs. 68% (95% CI: 60% to 75%; p = NS) respectively (Sand et al. 2018).

Argacha et al. 2019 [conference abstract]: In a retrospective real-world register-based study [unclear if this is from ADVANCE register], the authors compared FFRCT vs. ICA among 2906 patients referred to CCTA for suspected CAD. FFRCT was performed in 757 (26%) and was abnormal in 323 (42.7%) of the patients. An ICA was performed in 622 (21.4%) patients and was abnormal in 292 (46.9%). After propensity score weighting, adding FFRCT was associated with an increase in ICA (OR=1.58, 95% CI: 1.23–2.02, p<0.01). There were no significant changes regarding ICA showing obstructive CAD with FFRCT (OR=1.13, 95% CI: 0.78–1.66, p=0.5) but a trend towards an increase of revascularization (OR=1.48, 95% CI: 0.98–2.24, p=0.06). In patients undergoing an ICA, a FFRCT ≥0.8 was associated with a decrease the presence of significant CAD (OR=0.27, 95% CI: 0.16–0.48, p<0.001), whereas a FFRCT <0.8 increased the rate of revascularization (OR=24.7, 95% CI: 12.3–49.7, p<0.001).

Jensen et al. 2018: This study compared a Danish prospective cohort of 774 stable patients with typical angina pectoris in a low-intermediate risk group vs. a high-risk group. CCTA was performed in 745 participants (96%) in whom FFRCT was prescribed in 212 (28%) participants. In the high- vs. low-intermediate-risk group, ICA was cancelled in 75% vs. 91%. Coronary revascularization was performed more frequently in high-risk than in low-intermediate-risk patients, 76% vs. 52% (P = 0.03). Serious clinical events occurred in four patients, but not in any patients with cancelled ICA by CCTA with selective FFRCT testing.

Ko et al. 2019: In this Australian prospective study, diagnostic performance of FFRCT vs. static rest/stress CTP was compared among 51 participants (96 vessels) with suspected CAD. Per-vessel sensitivity, specificity, and

diagnostic accuracy for FFRCT were 81%, 85%, 84%, for visual CTP were 50%, 89%, 75% and for TPR were 69%, 48%, 56% respectively. ROC curve analysis demonstrated larger per vessel AUC for FFRCT (0.89) compared with visual CTP (0.70; $p < 0.001$), TPR (0.58; $p < 0.001$) and CTA (0.70; $p = 0.0007$); AUC for CTA + FFRCT (0.91) was higher than CTA + visual CTP (0.77, $p = 0.008$) and CTA + TPR (0.74, $p < 0.001$). Per-patient AUC for FFRCT (0.90) was higher than visual CTP (0.69; $p = 0.0016$), TPR (0.56; $p < 0.0001$) and CTA (0.68; $p = 0.001$).

Rabbat et al. 2020: This was a single centre, prospective real-world study from the USA involving 431 patients with suspected CAD to compare FFRCT + CCTA (n=387) vs. CCTA alone (44). Using CCTA and selective FFRCT, 121 patients (32%) had at least one vessel with ≥50% diameter stenosis; 67/121 (55%) patients had at least one vessel with FFRCT ≤ 0.80; 55/121 (45%) underwent ICA; and 34 were revascularized. The proportion of ICA patients undergoing revascularization was 62% (34 of 55). The number of patients with vessels with 30–50% diameter of stenosis was 90 (23%); 28/90 (31%) patients had at least one vessel with FFRCT ≤ 0.80; 8/90 (9%) underwent ICA; and five were revascularized. Compared to CCTA alone, CCTA + FFRCT reduced the rates of ICA (45% vs. 80%) for those with obstructive CAD. Using CCTA + FFRCT, no major adverse cardiac events occurred over a mean follow-up of 440 days.

Osawa et al. 2017: This single centre prospective study from Japan, reports the diagnostic performance of FFRCT + CCTA for a total of 20 patients (29 vessels) with suspected CAD. Diagnostic accuracy, sensitivity, and specificity of FFRCT per-vessel basis were 81, 100, and 69%, respectively.

Nørgaard et al. 2017a: This single centre, Danish, real-world study involved 189 symptomatic patients with suspected CAD and compared FFRCT vs. ICA. FFRCT was ≤0.80 in 31% of patients and 10% of vessels. After FFRCT testing, invasive angiography was performed in 29%, with FFR measured in 19% and iFR in 1% of patients (with a tendency toward declining FFR-iFR guidance during the study period). FFRCT ≤0.80 correctly classified 73% (27 of 37) of patients and 70% (37 of 53) of vessels using FFR ≤0.80 or iFR ≤0.90 as reference standard. In patients with FFRCT>0.80 being deferred from ICA, no adverse cardiac events occurred during a median follow-up period of 12 (range 6 to 18) months.

Nørgaard et al. 2017b: This single centre, Danish study involving symptomatic patients with suspected CAD compared myocardial perfusion imaging (n=1332) vs. FFRCT implementation (n=800) vs. clinical use (n=1391). This study investigated the association of replacing standard myocardial perfusion imaging with FFRCT testing with downstream utilization of ICA and the diagnostic yield of ICA (rate of no obstructive disease, and rate of revascularization). After adjusting for baseline risk characteristics, they report a reduction in downstream ICA utilization (absolute risk difference: -4.2; 95% CI, -6.9 to -1.6; P=0.002). In patients referred to ICA, findings of no obstructive CAD decreased (-12.8%; 95% CI, -22.2 to -3.4; P=0.008) and rate of coronary revascularization increased (14.1%; 95% CI, 3.3–24.9; P=0.01), as did availability of functional information for guidance of revascularization (27.8%; 95% CI, 11.3–44.4; P<0.001) after clinical adoption of FFRCT.

Unpublished audit from one of experts:

[redacted]

Quality of the evidence

Apart from FORECAST, the remaining studies provided observational evidence based on retrospectively or prospectively collected data. Most of the major studies were funded by HeartFlow and the independent studies had either a small sample size or their researchers had received funding or support from HeartFlow that potentially could cause conflicts of interest and bias. The quality of reporting methods and results was acceptable and no potential bias because of quality of design or reported data was found.

Heterogeneity in the descriptions of population scope, diagnostic criteria, and FFR cut-off points prevents a conclusive overview of the evidence.

4.5. Ongoing trials

The EAC requested for information from HeartFlow on seven ongoing studies and listed the updated in Appendix B. All these trials are ongoing. Only FORECAST has finished recruitment, but its results are unpublished.

4.6. Changes in cost case

No published economic studies found in the literature that included the incorporation of HeartFlow into the NICE CG95 pathway. Cost parameters have been updated in line with the most recent NHS tariffs and BNF prices. With the updated cost parameters, the cost saving per patient has increased to £391 per patient, irrespective of the functional imaging used (appendix B). Since there are no changes to the CG95 guidance or pathway, the original guidance remains the same [redacted]

Other relevant information

Versions of Computational Fluid Dynamics (CFD) software

There have been at least five reported versions of CFD software: 1.0; 1.2; 1.4, 1.7 and 2.56. These versions have not been reported explicitly in the published reports. The EAC requested the company for more information whether each version has different performance, diagnostic accuracy and safety profiles and they clarified: HeartFlow's "internal data validate that changes in versions do not make any difference to performance, diagnostic accuracy, or safety".

Similar technologies

Two technologies calculate FFRCT: HeartFlow (in a centralized core laboratory) and Siemens cFFR (on-site). Based on the literature and comments from the experts, Siemens cFFR (Version 3.0 is the latest reported version) is still being investigated and has not been marketed commercially yet.

Experts' opinions

1. Barriers to access and use of this technology

The experts verified that the technology is only available in some NHS practices. Low availability, few referrals, costly IT infrastructure requirements, delays in integration with PACS, and unsuccessful ITP applications are among the reasons that limit the use of this technology. The experts stated that the composition of expertise in cardiology teams and their workloads leads to more radiologists using CCTA rather than cardiologists. In turn, this contributes to less or no input from cardiologists.

2. Facilities, Training and Functioning

The experts mention that no specific HeartFlow training is required; however, they were aware that using CCTA requires training, following instructions and standards, and the procurement and use of required facilities. There is a consensus among five experts that obtaining high quality images requires training. They also highlighted that up to 25% of CCTA scans in clinical trials have not been suitable for FFRCT analysis.

Patients must be given sublingual GTN prior to the CCTA scan. Heart rate must be adequately controlled. Heart rate control may require administration of oral or intravenous beta-blockers prior to image acquisition. Drug administration can be an issue when scans are carried out by radiographers rather than medical staff.

Three experts reported that a minimum requirement for FFRCT analysis is a 64-slice CT scanner. A CCTA scan requires a strict protocol to optimise image acquisition, such as that recommended by the Society of Cardiovascular Computed Tomography. Apart from additional administrative requirement to have an addendum after FFRCT reads (usually 48 hrs later), most of the experts refer to a secure network connection requirement by radiology and IT in each hospital. Local servers link to a UK based AWS to allow anonymisation of data before it is sent to the USA for analysis.

3. Issues related to functioning, reliability, and maintenance of this technology

Where there is no absolute protocol, some experts raise the need for inhouse technology expert to support a secure decision after having system support or technical advice.

Another expert noted concerns after an audit on disproportionately higher number of FFRCT +ve left anterior descending (LAD) lesions that do not appear to concur with invasive studies. As stress echo has a high degree of

accuracy for LAD lesions if a stress echo is not performed in this group, there will be more patients referred for unnecessary ICA. In addition, one expert noted that the threshold of observed stenosis for referral to FFRCT is gradually beginning to be lowered in their unit and more ‘mild’ lesions are being sent for FFRCT. This, the expert noted, is a common change whenever a new technology is introduced; however, the associated cost is not prohibitive. Since Health Innovation is paying for the technology, there appears to be no commissioning restrictions for its use.

The delay between transferring data to the US for analysis and receiving the results for elective patients is not an issue particularly in the context of the UK NHS clinical practice. However, if the volume of scans greatly increases, the infrastructure should be able to upscale. The delay would be problematic clinically should use of HeartFlow be extended to ACS patients. Rejection of low-quality images, 48 hours delay between image submission and receiving FFRCT results, and the cost of integrating the technology in current IT systems are other issues.

4. Costs

Cost saving is secondary to cardiologists' preferences in using the technologies and availability of the technology in NHS may not lead to an increase in use when there are many existing and emerging cardiac imaging technologies.

An expert stated that the pathway prior to the introduction of the technology was a CCTA scan followed by functional imaging with stress echo rather than FFRCT. The stress echo tariff is <£200 compared with FFRCT tariff of >£700 per patient and there is no data to support the superiority of one technology over another.

Another expert reported that based on their knowledge, currently HeartFlow analysis is funded in 30 NHS hospital trusts [the correct number is 62] as part of the ITP programme. Where this not the case, the cost of HeartFlow may be borne by the hospital. The cost of HeartFlow is not covered by the CCTA scan tariff. One expert expressed concerns that there is no mechanism for the hospital to invoice commissioners for HeartFlow. Use of HeartFlow will reduce the number of diagnostic angiograms carried out in hospital and hospitals will therefore lose income from reduced angiography as well as paying for HeartFlow analysis. HeartFlow may also reduce the overall cost of the stable

chest pain patient pathway but could be a de facto transfer of cost from commissioners to hospital trusts. This would be a disincentive to secondary care to introduce HeartFlow. During exploratory talks with local commissioners to introduce HeartFlow for a trial period, the potential cost savings from published studies were not accepted by the commissioners as sufficient evidence to proceed with funding of HeartFlow.

5. Conclusion

Diagnostic performance

The existing evidence on HeartFlow confirm the findings of MTG32 that the diagnostic accuracy, sensitivity, specificity, PPV, and AUC for detecting ischemia-causing lesions (flow-limiting stenosis) of FFRCT is equivalent or superior of the comparators (PET, SPECT, CCTA + TAG320, CCTA, and CCTA + Stress-CTP).

In absence of Stress-CTP, FFRCT has performed better than any imaging modality for NPV (evidence from PACIFIC and NXT); however, introducing Stress-CPT results in superior NPV than FFRCT (evidence from PERFECTION).

Prognostic value

In long-term follow-up of up to 4.7 years (from NXT), a normal FFRCT had prognostic value over CCTA for cardiac death and MI outcomes; the incidence of the composite primary end point of MACE, death, MI, and any revascularization was more frequent for a positive FFRCT than for a clinically significant stenosis at CCTA with the majority of outcomes being planned revascularization.

Impact on reduction in ICA

The studies that measured the impact of FFRCT on ICA rates reported that use of FFRCT lead to cancellation and/or reduction of ICA rates and ICA can be reserved for patients at higher risk:

- Based on FORECAST RCT and in 9-month follow-up, there was 14% lower ICA in the CCTA + FFRCT vs. reference group (p=0.02) and 22% fewer

patients had ICA in CCTA + FFRCT vs. reference group (p=0.01). The RCT was powered to detect a difference in ICA rates between the two groups.

- In two separate reports from PLATFORM, ICA was cancelled in 77% of patients having CCTA + FFRCT in one report and it was cancelled in 61% of the cases after receiving CCTA + FFRCT results in another report. This study was powered to detect a 50% reduction in the frequency of ICA documenting non-obstructive CAD.
- Rabbat et al. (2020) found that compared to CCTA alone, CCTA + FFRCT reduced the rates of ICA (45% vs. 80%) for those with obstructive CAD.
- PROMISE findings suggested that reserving ICA for patients with an FFRCT of ≤0.80 could decrease ICA by 44% and increase the proportion of ICA leading to revascularization by 24%.
- Jensen et al. (2018) reported that in the high- vs. low-intermediate-risk group, ICA was cancelled in 75% vs. 91% of patients. Coronary revascularization was performed more frequently in high-risk than in low-intermediate-risk patients, 76% vs. 52% (P = 0.03).
- Nørgaard et al. (2017b) investigated the association of replacing standard myocardial perfusion imaging with FFRCT testing with downstream utilization of ICA and reported a reduction in downstream ICA utilization (absolute risk difference: -4.2; 95% CI, -6.9 to -1.6; P=0.002).
- [redacted]

Clinical outcomes

Introducing FFRCT led to changes in management strategy of patients and preventing unnecessary invasive procedures (PROMISE; Jensen et al. 2018) with no death, MI, unstable angina, and hospitalisation leading to unplanned revascularisation up to 90 days; there was a lower MACE in 90 days, a lower mean radiation exposure, and a higher quality of life improvement for FFRCT group than UC group; in one-year follow-up, both groups had similar mean radiation exposure (PLATFORM cohort). In the unpublished and the only RCT (FORECAST) and compared to the UC, it showed similar results in both groups for the major cardiac outcomes, quality of life and angina status in 9 months.

An unpublished audit of 1500 patients from one of NHS experts concluded that no patient had a MACE event during 12 months of follow-up. In few

discrepant patients, having data from ICA and FFR there was no difference in the accuracy of FFRCT and stress echo.

Cost

In FORECAST, total costs for reference group was 1491.46 (mean) and 1605.50 for test group [currency unclear in slides].

In both PLATFORM one-year cohort and FORECAST 9-month RCT, the quality of life improved for both study groups.

In PLATFORM, mean estimated costs in the CCTA + FFRCT group were $4,486 (USD) vs. $ 9,344 in UC (€4217 (EUR) for CCTA + FFRCT vs. €6,894 for UC). In the planned invasive stratum, mean costs were 33% lower with CCTA and selective FFRCT ($8,127 vs. $12,145 usual care); in the planned non-invasive stratum, mean costs did not differ when using an FFRCT cost weight of zero ($3,049 FFRCT vs. $2,579), but were higher when using an FFRCT cost weight equal to CCTA.

The current price for the HeartFlow Analysis is £700 per analysis.

[redacted]

The original guidance is based on evidence that details the impact of HeartFlow on diagnostic accuracy and resource utilisation and the assumption that there is access to appropriate CCTA facilities. This original guidance suggests that using HeartFlow FFRCT leads to a cost savings of £214 per patient. With the updated cost parameters, the cost saving per patient has increased by £177 to £391 per patient. Since there are no changes to the CG95 guidance or pathway, the original guidance remains the same[redacted]

Ongoing trials

The experts noted that the from the existing evidence the FORECAST UK-based RCT is the most relevant to the MTG32. The EAC agrees that as

FFRCT materialises its value proposition mainly via its impact on the use of ICA it is important to review the published full-text results for FORECAST before concluding on the impact of the available evidence on MTG32.

Appendix A – Relevant guidance

To be supplied by the NICE gIS team

NICE guidance – published

NICE guidelines (clinical, public health, social care, medicine practice guidelines, safe staffing)

- Chronic heart failure in adults: diagnosis and management (2018) NICE guideline NG106
- Recent-onset chest pain of suspected cardiac origin: assessment and diagnosis (2010, updated 2016) NICE guideline CG95
- Stable angina: management (2011, updated 2016) NICE guideline CG126

All other NICE guidance and advice products

- Optowire for measuring fractional flow reservev (2019) NICE medtech innovation briefing 199
- DyeVert for reducing contrast media in coronary and peripheral angiography (2019) NICE medtech innovation briefing 196
- DuraGraft for preserving vascular grafts (2019) NICE medtech innovation briefing 184
- CADScor system for ruling out coronary artery disease in people with symptoms of stable coronary artery disease (2019) NICE medtech innovation briefing 174
- QAngio XA 3D/QFR imaging software for assessing coronary obstructions (2018) NICE medtech innovation briefing 146
- VEST external stent for coronary artery bypass grafts (2017) NICE medtech innovation briefing 115
- Somatom Definition Edge CT scanner for imaging coronary artery disease in adults in whom imaging is difficult (2016, updated 2017) NICE medtech innovation briefing 54

- Aquilion PRIME CT scanner for imaging coronary artery disease in adults in whom imaging is difficult (2016, updated 2017) NICE medtech innovation briefing 53

- 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 (2012, updated 2017) NICE diagnostic guidance 3

NICE pathways

- Chest pain (2020) NICE pathway
- Myocardial infarction with ST-segment elevation (2020) NICE pathway

NICE guidance – in development

NICE guidelines (clinical, public health, social care, medicine practice guidelines, safe staffing)

None identified

All other NICE guidance and advice products

- QAngio XA 3D/ QFR and CAAS vFFR imaging software for assessing the functional significance of coronary obstructions during invasive coronary angiography. NICE diagnostic guidance. Publication expected February 2021
- Coronary sinus stent insertion for refractory angina. NICE interventional procedure guidance. Publication date to be confirmed

Suspended or terminated

NB: Suspended technology appraisals should be recorded as 'in development' with a publication date 'to be confirmed'

None identified

In topic selection

None identified

Guidance from other professional bodies

None identified

Appendix B – Costing report (if available)

1. Background

The sponsor submitted a decision tree model based on NICE CG95. It was proposed that HeartFlow's non-invasive FFRCT technology will be used in conjunction with CCTA, in place of CCTA alone in the pathway for a likelihood of disease of 10% to 29%; appropriate functional imaging tests in the pathway for a likelihood of disease 30% to 60%; and ICA in the pathway for a likelihood of disease 61% to 90%.

The NICE guideline on chest pain (NICE clinical guideline CG95) was reviewed during the assessment process and new evidence was identified relating to the use of non-invasive tests for the diagnosis of coronary artery disease (CAD) in people with stable chest pain of suspected cardiac origin. The review also identified new evidence on clinical prediction models which impacted on the assessment of the pre-test likelihood of CAD in this population. Based on the evidence and economic analysis, changes were made to the clinical guideline. The most important recommendation was offering 64-slice (or above) coronary CT angiograph (CCTA) to patients with features of typical or atypical angina based on clinical assessment, irrespective of pre-test likelihood scoring (10-90%). The use of non-invasive functional imaging for myocardial ischaemia was recommended if 64-slice (or above) CCTA indicates CAD of uncertain functional significance or is non-diagnostic. The updated guideline also recommended offering ICA as a second-line investigation when the results of non-invasive functional imaging are inconclusive.

Updated HeartFlow model

Based on the new recommendations in the revised chest pain guideline, the HeartFlow cost model submitted by the sponsor was subsequently revised by the EAC. The key changes to the model were as follows.

1. Different pathways (from CG95) for the three likelihood groups were replaced with a single pathway (Figure 1). All the patients with pre-test likelihood of 10-90% were now offered 64-slice (or above) CCTA as the first line of investigation. Functional imaging is offered following uncertain CCTA results and ICA is offered if the results of functional imaging are also uncertain.

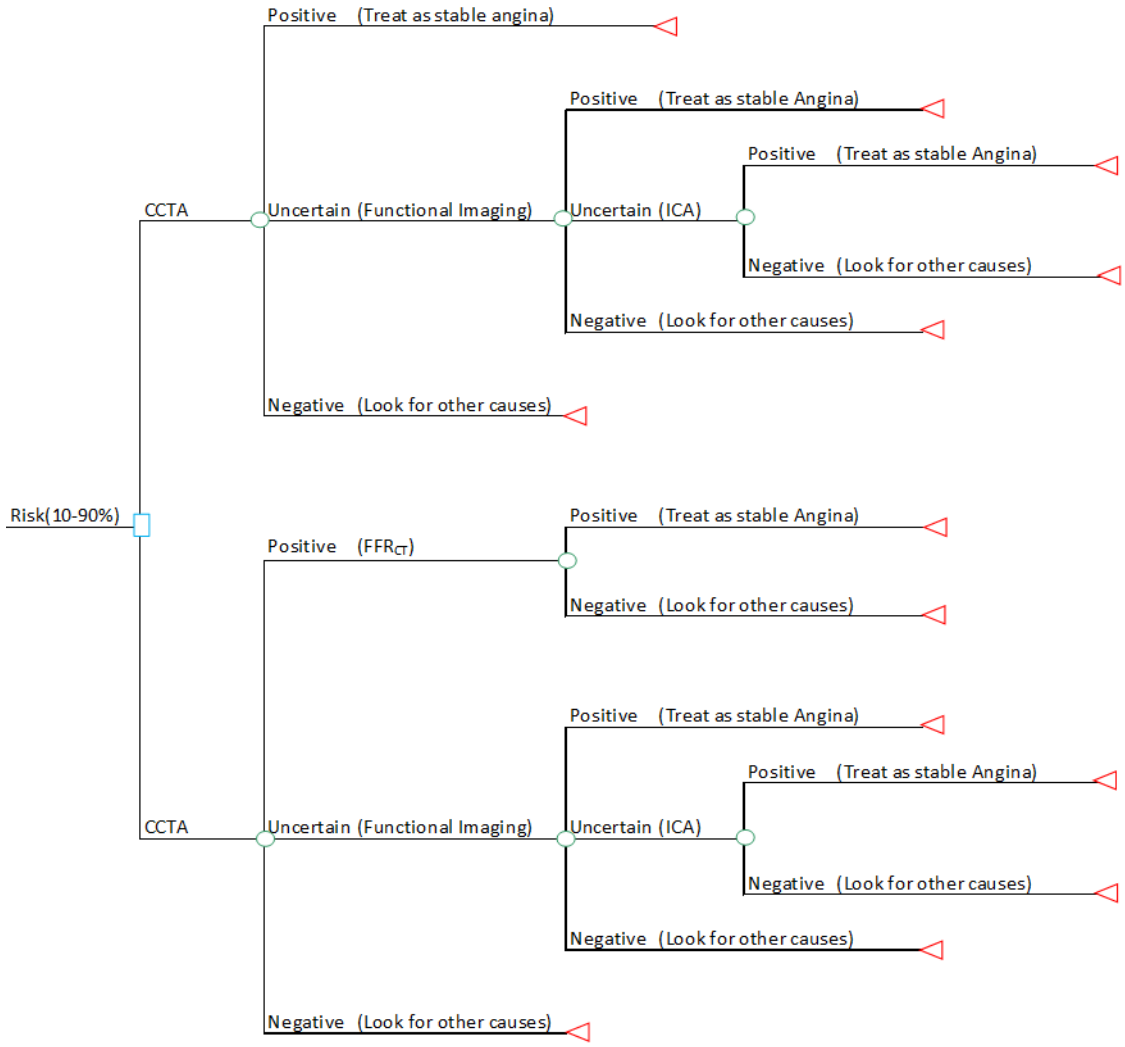

Figure 1: Updated chest pain model structure

2. Two strategies were compared in the updated model 1) using CCTA to inform treatment of stable angina and 2) using FFRCT (HeartFlow) after a positive CCTA result to inform treatment. The terminal nodes in the model indicate treatment for stable angina with either PCI or optimal medical therapy. The time horizon for the model was 1 year to capture the impact of diagnosis on initial treatment.

3. The diagnostic accuracy for CCTA, ICA and functional imaging were estimates from the EAC meta-analysis of per-patient based diagnostic accuracy

4. For the economic model in the revised guideline, test costs were taken from the NHS reference costs

Three separate model results using different functional imaging techniques (SPECT, MRI and ECHO) were estimated by the EAC. The results showed that the adapted pathway using FFRCT had a cost saving of £214, irrespective of the functional imaging test used. The main drivers of the cost were the diagnostic accuracy of CCTA, ICA and FFRCT and the price of the technology.

The objective of this report is to check the current validity of the model and update input parameters if new estimates are available.

2. Current validity of model

The updated CG95 pathway is still valid and so is the updated model. There are no changes to the original assumptions in the model. Some of the parameters, especially the test costs taken from the NHS reference costs have changed and needs updating in the model.

3. Updated input parameters

A significant input parameter update is the company's price of HeartFlow technology [redacted] With the current price being applicable from next year onward, the original price has been retained for this update and the new price included in a scenario analysis. Other cost parameters have been updated in line with the most recent NHS tariffs and BNF prices. If the original HRG codes have been changed or not available, then the most appropriate/available codes have been used. The updated cost estimates are presented in Table 1.

Table 1: Updated cost estimates.

Test	Code, description	Original cost estimate	Updated cost estimate	Source	EAC comment
Calcium Scoring	RA08Z (£77) - Computerised Tomography Scan, one area, no contrast	£77	£70	NHS Tariffs, 2020 -21	Code changed to RD20A

ICA	EY43A to EY43F, Standard cardiac catheterisation	£1685	£2,369	NHS Tariffs, 2020 -21	Average
CCTA	RD28Z, Complex computerised tomography scan	£122	£290	NHS Tariffs, 2020 -21	
SPECT	RN21Z, Myocardial perfusion scan, stress only	£367	£282	NHS Tariffs, 2020 -21	
ECHO	EY50Z, Complex echocardiogram	£271	£199	NHS Tariffs, 2020 -21	
CMR	RA67Z, Cardiac magnetic resonance imaging scan, pre and post contrast	£515	£574	NHS Tariffs, 2020 -21	Code changed to RD10Z
PCI	EA31Z, Percutaneous Coronary Intervention (0-2 Stents) and EA49Z Percutaneous Coronary Interventions with 3 or more Stents, Rotablation, IVUS or Pressure Wire Weighted average	£2832	£3526	NHS Tariffs, 2020 -21	Average, Codes EY41A-D, Standard Percutaneous Transluminal Coronary Angioplasty
PCI drugs	Aspirin and clopidogrel (annual cost)	£33	£36.48	BNF 2020	
OMT	Aspirin, simvastatin, glyceryl trinitrate and propranolol hydrochloride (annual cost)	£84	£75.36	BNF 2020	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4. Results from updated model

Results of three models using different functional imaging (SPECT, MRI and ECHO) are presented in Table 2. Results of a scenario analysis including the updated HeartFlow price from April 2021 are presented in Table 3. Irrespective of the functional imaging used, the cost saving is £391 per

patient.
[redacted]

Table 2: Updated base case results (patient based)

	Average total cost per patient (patient based)		
	(Functional Imaging: SPECT) Model	**(Functional Imaging: MRI) Model**	**(Functional Imaging: ECHO) Model**
NICE Updated Guideline	£1,859	£1,841	£1,780
Adapted NICE Guideline using FFR_{CT}	£1,469	£1,450	£1,389
Difference (cost saving)	£391	£391	£391

Table 3: Scenario analysis results (patient based)

	[redacted]		
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

5. Conclusion

The original guidance is based on evidence that details the impact of HeartFlow on diagnostic accuracy and resource utilisation and the assumption that there is access to appropriate CCTA facilities. This original guidance suggests that using HeartFlow FFRCT leads to a cost savings of £214 per patient. With the updated cost parameters, the cost saving per patient has increased by £177 to £391 per patient. Since there are no changes to the CG95 guidance or pathway, the original guidance remains the same[redacted]

6. References

NHS Improvement. 2020. National tariff payment system 2020-2021, Available at https://improvement.nhs.uk/resources/national-tariff/#h2-202021-national-tariff-payment-system , Accessed 25 Nov 2020

NICE.2020. British National Formulary, Available at https://bnf.nice.org.uk/ , Accessed 11 Nov 2020

Appendix C – Details of studies and ongoing trials

C.1 Completed studies

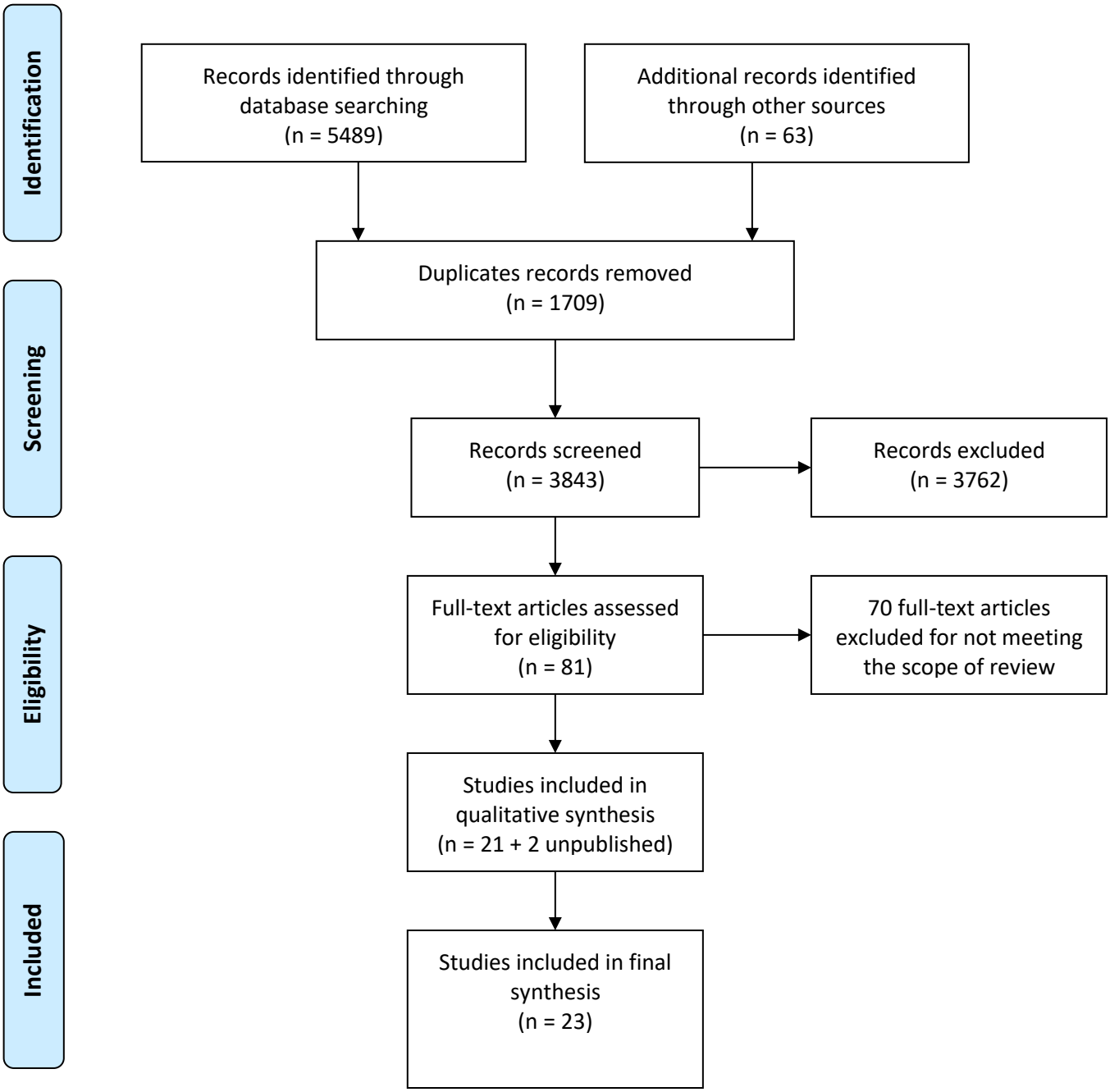

Table 4: Characteristics of included studies

Study	Design/Setting	Population	Comparators	Outcome
ADVANCE Registry (Shiono et al. 2019)	Prospective, single group Japan	1829 patients suspected of CAD	Reclassification of treatment strategy between CCTA alone vs. CCTA + FFRCT	• Reclassification of treatment strategy between CCTA alone and CCTA + FFRCT occurred in 55.8% of site investigations and in 56.9% in the core laboratory analysis.
PACIFIC (Driessen et al. 2019)	Prospective, sub-study	208 patients with suspected stable CAD	Diagnostic performance of FFRCT vs. CCTA vs. SPECT vs. PET (invasively measured FFR≤0.80 as the reference standard)	• 505 of 612 (83%) vessels could be evaluated with FFRCT. • Diagnostic accuracy, sensitivity, and specificity of FFRCT were 87%, 90%, and 86% on a per-vessel basis and 78%, 96%, and 63% on a per-patient basis, respectively. • AUC for identification of ischemia-causing lesions was significantly greater for FFRCT (0.94 and 0.92) in comparison with coronary CCTA (0.83 and 0.81; p < 0.01 for both) and SPECT (0.70 and 0.75; p<0.01 for both), on a per-vessel and -patient level, respectively; • FFRCT also outperformed PET on a per-vessel basis (AUC 0.87; p < 0.01), but not on a per-patient basis (AUC 0.91; p=0.56). • In the intention-to-diagnose analysis, PET showed the highest per-patient and -vessel AUC followed by FFRCT (0.86 vs. 0.83; p=0.157; and 0.90 vs. 0.79; p=0.005, respectively).
NXT (Curzenet al. 2016)	Retrospective sub-study, single group	200 patients with stable chest pain	CTA alone vs. FFRCT + CTA	• Involving FFRCT data in decision making, there was a change in the allocated management category based on CTA alone in 72 cases (36%).
NXT (Ihdayhid et al. 2019b)	Prospective follow-up sub-study, single group	206 patients suspected of having stable CAD	Prognostic value of FFRCT vs. CCTA	• At median follow-up of 4.7 years, there were no cardiac deaths or myocardial infarctions in participants with normal FFRCT. • The incidence of the primary end point was more frequent in participants with positive FFRCT compared with clinically significant stenosis at CCTA (73.4% [80 of 109] vs 48.7% [91 of 187], respectively; P<.001), with the majority of outcomes being planned revascularization. Corresponding hazard ratios (HRs) were 9.2 (95% confidence interval [CI]: 5.1, 17; P= .001) for FFRCT and 5.9 (95% CI: 1.5, 24; P = .01) for CCTA. • FFRCT was a superior predictor compared with CCTA for primary end point (C-index FFRCT, 0.76 vs CCTA, 0.54; P, .001) and MACE (FFRCT, 0.71 vs coronary CT angiography, 0.52; P = .001). • Frequency of MACE was higher in participants with positive FFRCT compared with CCTA (15.6% [17 of 109] vs 10.2% [19 of 187], respectively; P = .02), driven by unplanned revascularization. • MACE HR was 5.5 (95% CI: 1.6, 19; P = .006) for FFRCT and 2.0 (95% CI: 0.3, 14; P = .46) for CCTA. Each 0.05-unit FFRCT reduction was independently associated with greater incidence of primary end point (HR, 1.7; 95% CI: 1.4, 1.9; P<.001) and MACE (HR, 1.4; 95% CI: 1.1, 1.8; P<.001).
NXT (Ko et al. 2016)	Retrospective sub-study Australia, Japan	61 patients suspected of having CAD	Diagnostic performance of 320-detector row CCTA-derived FFRCT), transluminal attenuation gradient (TAG; TAG320), and CCTA alone	• FFRCT exhibited a stronger correlation with invasive FFR compared with TAG320 (Spearman r, 0.78 vs 0.47, respectively). • Per-vessel accuracy, sensitivity, specificity, and positive and negative predictive values for TAG320 (Spearman p,15.37) were 78%, 58%, 86%, 64%, and 83%, respectively; and those of FFRCT were 83%, 92%, 79%, 65%, and 96%, respectively. • ROC curve analysis showed a significantly larger AUC for FFRCT (0.93) compared with that for TAG320 (0.72; P=.003) and CT coronary angiography alone (0.68; P=.008).
PLATFORM (Colleran et al. 2017)	Prospective observational cohort, two-group, sub-study, 1-year follow-up Germany sites	116 patients with suspected CAD	CCTA/FFRCT (n=52) vs. UC (n=64)	• Percentage of patients planned for ICA, with no obstructive CAD on ICA within 90 days were 7.7% (4 of 52) in the CTA/FFRCT group and 85.9% (55 of 64) in UC group (risk difference 78.2%, 95% CI 67.1% to 89.4%, p<0.001). • ICA was cancelled in 40 of the 52 patients (77%) who underwent CCTA/FFRCT. • MACE or vascular complications were 2 (3.1%) in UC group (CI 0.38 to 10.84) and none for CTA/FFRCT group (CI 0.00 to 6.85). • The mean radiation exposure was lower in the FFRCT vs. the usual care group (7.28 vs 9.80 mSv, p<0.001).

				• Mean estimated medical costs were €4217 (CTA/FFRCT) vs. €6894 (usual care), p<0.001. Improvement in QOL (EQ-5D score) was greater in the FFRCT (+0.09 units) vs. the usual care cohort (+0.03 units), p=0.04.
PLATFORM (Douglas et al. 2015)	Prospective observational cohort, two-group, sub-study, 1-year follow-up 11 Europe and 1 USA sites	584 patients with new onset chest pain	CCTA/FFRCT (n=296) vs. UC (n=287)	• Among those with intended ICA (FFRCT-guided=193; UC=187), no obstructive CAD was found at ICA in 24 (12%) in the CCTA/FFRCT arm and 137 (73%) in the UC arm (risk difference 61%, 95% confidence interval 53–69, P<0.0001), with similar mean cumulative radiation exposure (9.9 vs. 9.4 mSv, P=0.20). • ICA was cancelled in 61% after receiving CCTA/FFRCT results. • Among those with intended non-invasive testing, the rates of finding no obstructive CAD at ICA were 13% (CCTA/FFRCT) and 6% (UC; P=0.95). • Clinical event rates within 90 days were low in usual care and CCTA/FFRCT arms.
PLATFORM (Douglas et al. 2016)	Prospective observational cohort, two-group, sub-study, 1-year follow-up	584 stable patients with new onset chest pain	CCTA/FFRCT (n=297) vs. UC (n=287)	• At 1 year, MACE were infrequent, with 2 in each arm of the planned invasive group and 1 in the planned non-invasive cohort (UC). • In the planned invasive stratum, mean costs were 33% lower with CTA/FFRCT ($8,127 vs. $12,145 UC; p<0.0001); in the planned non-invasive stratum, mean costs did not differ when using an FFRCT cost weight of zero ($3,049 FFRCT vs. $2,579; p=0.82), but were higher when using an FFRCT cost weight equal to CTA. • QOL scores improved overall at 1 year (p < 0.001), with similar improvements in both groups, apart from the 5-item EuroQOL scale scores in the non-invasive stratum (mean change of 0.12 for FFRCT vs. 0.07 for usual care; p=0.02).
CREDENCE (Rizvi et al. 2016)	Predictive modelling based on prospective observational cohort 18-23 sites in USA (8), Canada, China, Italy, Japan, Korea, Latvia, the Netherlands	612 adults with symptoms suspicious of CAD	Diagnostic performance of CCTA (FFRCT) vs. MPS against invasive FFR reference standard	• An invasive FFR of 0.80 or less was measured in 26.5% of 1727 vessels. • In the derivation cohort, CCTA vessel-specific factors associated with FFR 0.80 or less were stenosis severity, percentage of noncalcified atheroma volume, lumen volume, the number of lesions with high-risk plaque (≥2 of low attenuation plaque, positive remodelling, napkin ring sign, or spotty calcification), and the number of lesions with stenosis greater than 30%. • FFRCT was not additive to this model including stenosis and atherosclerotic plaque. • Significant myocardial perfusion imaging predictors were the summed rest and difference scores. • In the validation cohort, the AUC were 0.81 for CCTA vs 0.67 for myocardial perfusion imaging (P<.001).
PERFECTION (Pontone et al. 2019)	Prospective cohort Italy	147 symptomatic patients symptomatic patients with suspected CAD	Diagnostic accuracy of CCTA vs. CCTA+FFRCT vs. CCTA + Stress-CTP) and ICA + invasive FFR as reference standard	• Vessel-based and patient-based sensitivity, specificity, and negative predictive values, and positive predictive values, and accuracy rates of CCTA were 99%, 76%, 100%, 61%, 82%, and 95%, 54%, 94%, 63%, 73%, respectively. • CCTA+FFRCT showed vessel-based and patient-based sensitivity, specificity, and negative predictive values, and positive predictive values and accuracy rates of 88%, 94%, 95%, 84%, 92%, and 90%, 85%, 92%, 83%, 87%, respectively. • CCTA + Stress-CTP showed vessel-based and patient-based sensitivity, specificity, and negative predictive values, and positive predictive values and accuracy rates of 92%, 95%, 97%, 87%, 94% and 98%, 87%, 99%, 86%, 92%, respectively. • Both FFRCT and Stress-CTP significantly improved specificity and positive predictive values compared to those of CCTA alone. • The AUC to detect flow-limiting stenoses of CCTA, CCTA+FFRCT, and CCTA+CTP were 0.89, 0.93, 0.92, and 0.90, 0.94, and 0.93 in a vessel-based and patient-based model, respectively, with significant additional values for both CCTA+FFRCT and CCTA+CTP vs. CCTA alone (p < 0.001) but no differences between CCTA+FFRCT vs. CCTA+CTP.
PROMISE (Lu et al. 2017)	Prospective observational cohort, sub-study	271 with stable chest pain and without known CAD	FFRCT + CTA vs. CTA alone	• FFRCT was calculated in 67% (181 of 271) of eligible patients (mean age 62 years; 36% women). • FFRCT was discordant with stenosis in 31% (57 of 181) for CTA and 29% (52 of 181) for ICA.

				• Most patients undergoing coronary revascularization had an FFRCT of ≤0.80 (91%; 80 of 88). • An FFRCT of ≤0.80 was a significantly better predictor for revascularization or major adverse cardiac events than severe CTA stenosis (HR: 4.3 [95% confidence interval [CI]: 2.4 to 8.9] vs. 2.9 [95% CI: 1.8 to 5.1]; p = 0.033). • Reserving ICA for patients with an FFRCT of ≤0.80 could decrease ICA without ≥50% stenosis by 44% and increase the proportion of ICA leading to revascularization by 24%.
REAL-FFRCT and REAL-FFRCT 2 (Matsumura-Nakano et al. 2017) Conference abstract	Prospective real-world feasibility study Single centre, Japan	90 patients (134 vessels) with suspected CAD	Diagnostic performance of FFRCT vs. invasive FFR ≤0.80 as reference standard	• Per-vessel accuracy, sensitivity, specificity, positive predictive value, and negative predictive value were 72%, 93%, 58%, 61%, and 92% for the cut-off value of FFRCT≤0.80, 81%, 85%, 77%, 72%, and 88% for FFRCT≤0.75, and 83%, 75%, 89%, 82%, and 83% for FFRCT≤0.70, respectively. • The false-positive and -negative rates were 25% (N=33) and 3.0% (N=4) for FFRCT≤0.80, 13% (N=18) and 6.0% (N=8) for FFRCT≤0.75, and 6.7% (N=9) and 10% (N=14) for FFRCT≤0.70, respectively.
REAL-FFRCT and REAL-FFRCT 2 (Matsumura-Nakano et al. 2019)	Prospective real-world feasibility study Single centre, Japan	93 patients with 139 vessels, who had suspected CAD	Diagnostic performance of FFRCT vs. invasive FFR ≤0.80 as reference standard	• Per-vessel accuracy, sensitivity, specificity, positive predictive value, and negative predictive value were 73%, 95%, 59%, 61%, and 94% for the cut-off value of FFRCT ≤0.80, 81%, 86%, 78%, 73%, and 89% for FFRCT ≤0.75, and 83%, 74%, 89%, 82%, and 83% for FFRCT ≤0.70, respectively. • Per-vessel accuracy across the different ranges of FFRCT ≤0.60, 0.61 to 0.70, 0.71 to 0.80, 0.81 to 0.90, and >0.90 with the cut-off value of FFRCT ≤0.80 were 95%, 74%, 32%, 93%, and 100%, respectively. • Setting a grey zone of FFRCT 0.71 to 0.80 provided high positive predictive value (82%; n=42/51) in the range of FFRCT ≤0.70 and high negative predictive value (94%; n=48/51) in FFRCT >0.80.
ReASSESS (Sand et al. 2018)	Prospective Single centre, Denmark	143 patients with stable angina pectoris	Per-patient diagnostic performance of FFRCT SPECT FFR using a FFR value of ≤0.80 as reference	• Per-patient diagnostic performance for identifying ischemia (95% confidence interval [CI]), FFRCT vs. SPECT, were sensitivity of 91% (95% CI: 81% to 97%) vs. 41% (95% CI: 29% to 55%; p < 0.001); specificity of 55% (95% CI: 44% to 66%) vs. 86% (95% CI: 77% to 93%; p < 0.001); negative predictive value of 90% (95% CI: 82% to 98%) vs. 68% (95% CI: 59% to 77%; p = 0.001); positive predictive value of 58% (95% CI: 48% to 68%) vs. 67% (95% CI: 51% to 82%; p = NS); and accuracy of 70% (95% CI: 62% to 77%) vs. 68% (95% CI: 60% to 75%; p = NS) respectively.
Argacha et al. 2019 Conference abstract	Retrospective real-world register-based study	2906 patients referred to CTA for suspected CAD	FFRCT vs. ICA	• FFRCT was performed in 757 (26%) and was abnormal in 323 (42.7%) of the patients. An ICA was performed in 622 (21.4%) patients and was abnormal in 292 (46.9%). • After propensity score weighting, FFRCT was associated with an increase in ICA (OR=1.58, 95% CI: 1.23–2.02, p<0.01). • There were no significant changes regarding ICA showing obstructive CAD with FFRCT (OR=1.13, 95% CI: 0.78–1.66, p=0.5) but a trend towards an increase of revascularization (OR=1.48, 95% CI: 0.98–2.24, p=0.06). • In patient undergoing an ICA, a FFRCT ≥0.8 was decreasing the presence of significant CAD (OR=0.27, 95% CI: 0.16–0.48, p<0.001), whereas a FFRCT <0.8 increased the rate of revascularization (OR=24.7, 95% CI: 12.3–49.7, p<0.001).

Jensen et al. 2018	Prospective cohort, two groups Single centre, Denmark	774 stable patients with typical angina pectoris	Low-intermediate risk group vs. high-risk group	• CCTA was performed in 745 (96%) in whom FFRCT was prescribed in 212 (28%) patients. • In the high- vs. low-intermediate-risk group, ICA was cancelled in 75% vs. 91%. • Coronary revascularization was performed more frequently in high-risk than in low-intermediate-risk patients, 76% • vs. 52% (P = 0.03). • Serious clinical events occurred in four patients, but not in any patients with cancelled ICA by CCTA with selective FFRCT testing.
Ko et al. 2019	Prospective study Single centre, Austalia	51 patients (96 vessels) with suspected CAD	Diagnostic performance of FFRCT vs. static rest/stress CTP	• FFRCT, visual CTP and TPR analysis was feasible in 96%, 92% and 92% of patients respectively. • Per-vessel sensitivity, specificity, and diagnostic accuracy for FFRCT were 81%, 85%, 84%, for visual CTP were 50%, 89%, 75% and for TPR were 69%, 48%, 56% respectively. • ROC curve analysis demonstrated larger per vessel AUC for FFRCT (0.89) compared with visual CTP (0.70; $p < 0.001$), TPR (0.58; $p < 0.001$) and CTA (0.70; $p = 0.0007$); AUC for CTA + FFRCT (0.91) was higher than CTA + visual CTP (0.77, $p = 0.008$) and CTA + TPR (0.74, $p < 0.001$). • Per-patient AUC for FFRCT (0.90) was higher than visual CTP (0.69; $p = 0.0016$), TPR (0.56; $p < 0.0001$) and CTA (0.68; $p = 0.001$).
Rabbat et al. 2020	Prospective real-world study Single-centre, USA	431 patients with suspected CAD	FFRCT + CCTA (n=387) vs. CCTA alone (44)	• Using CCTA and selective FFRCT, 121 patients (32%) had at least one vessel with ≥50% diameter stenosis; 67/121 (55%) patients had at least one vessel with FFRCT ≤ 0.80; 55/121 (45%) underwent ICA; and 34 were revascularized. • The proportion of ICA patients undergoing revascularization was 62% (34 of 55). The number of patients with vessels with 30–50% diameter of stenosis was 90 (23%); 28/90 (31%) patients had at least one vessel with FFRCT ≤ 0.80; 8/90 (9%) underwent ICA; and five were revascularized. • Compared to CCTA alone, CCTA + FFRCT reduced the rates of ICA (45% vs. 80%) for those with obstructive CAD. • Using CCTA + FFRCT, no major adverse cardiac events occurred over a mean follow-up of 440 days.
Osawa et al. 2017	Prospective study Single centre, Japan	A total of 20 patients (29 vessels) with suspected CAD	FFRCT + CCTA vs. CCTA alone	• The diagnostic accuracy, sensitivity, and specificity of FFR-CT per-vessel basis were 81, 100, and 69 %, respectively.
Nørgaard et al. 2017a	Real-world study Single-centre, Denmark	189 symptomatic patients with suspected CAD	FFRCT vs. ICA reference standard	• FFRCT was ≤0.80 in 31% of patients and 10% of vessels. After FFRCT testing, invasive angiography was performed in 29%, with FFR measured in 19% and iFR in 1% of patients (with a tendency toward declining FFR-iFR guidance during the study period). • FFRCT ≤0.80 correctly classified 73% (27 of 37) of patients and 70% (37 of 53) of vessels using FFR ≤0.80 or iFR ≤0.90 as reference standard. • In patients with FFRCT>0.80 being deferred from ICA, no adverse cardiac events occurred during a median follow-up period of 12 (range 6 to 18 months) months.

Nørgaard et al. 2017b	Single centre	Symptomatic patients with suspected coronary artery: myocardial perfusion imaging (n=1332) or FFRCT implementation (n=800) or clinical use (n=1391)	Association of replacing standard myocardial perfusion imaging with FFRCT testing with downstream utilization of ICA and the diagnostic yield of ICA (rate of no obstructive disease, and rate of revascularization)	• After adjusting for baseline risk characteristics, there was a reduction in downstream ICA utilization (absolute risk difference: -4.2; 95% CI, -6.9 to -1.6; P=0.002). • In patients referred to ICA, findings of no obstructive coronary artery disease decreased (-12.8%; 95% CI, -22.2 to -3.4; P=0.008) and rate of coronary revascularization increased (14.1%; 95% CI, 3.3–24.9; P=0.01), as did availability of functional information for guidance of revascularization (27.8%; 95% CI, 11.3–44.4; P<0.001) after clinical adoption of FFRCT.

C.1 Ongoing studies

Table 5: Characteristics of ongoing studies

Study	NCT03187639 (FORECAST)	NCT02973126 (AFFECTS)	NCT03665389 (FORTUNA)	NCT03702244 (PRECISE)	NCT03782688 (P3)	NCT04052256 (THRONE)	NCT04142021 (FASTTRACK CABG)
Design	RCT	DTA	Before/After trial	RCT	Single-arm cohort	Single-arm cohort	Single-arm cohort
Population	1400 patients with new onset pain	270 patients scheduled for ICA based on abnormal SPECT myocardial perfusion scans	25 patients Undergoing transcatheter aortic valve replacement (TAVR)	2100 patients with stable typical or atypical symptoms suggesting possible significant CAD	120 patients with an indication for PCI	250 patients who who have undergone ICA and have a minimum of one non-treated coronary artery with a measured invasive FFR of 0.81-0.90	114 patients with complex CAD candidates for CABG
Interventions	FFRCT	FFRCT	iFR / FFR measurement before TAVR	CCTA with selective FFRCT	HeartFlow Planner	FFRCT	FFRCT
Comparator	UC	SPECT	iFR / FFR measurement after TAVR	UC	iFFR	iFFR	iFFR
Primary outcome	Resource utilisation	Positive finding of hemodynamically significant CAD according to SPECT/FFRCT/ ICA +/- iFFR	FFRct before TAVR	Composite of Death / MI / ICA without obstructive disease	Agreement on post-PCI FFR between virtual treatment based on FFRCT planner and measured post-PCI iFFR	Coronary atherosclerotic disease progression	Feasibility expressed in percentage of CABG planning and execution solely based on coronary CTA; Safety
Secondary outcome	Quality of Life; MACE	Physician intuition after review of FFRct results; Cumulative radiation exposure; Potential economic impact	FFRct after TAVR; FFR after TAVR; iFR before TAVR and after TAVR; Stenosis degree in coronary angiography before TAVR	-	-	Target lesion failure Target vessel failure; Any coronary revascularisation	-
Current status	Active, not recruiting	Recruiting	Not yet recruiting	Recruiting	Recruiting	Recruiting	Recruiting
Estimated completion	December 1, 2020	December 2021	March 31, 2022	August 2021	January 15, 2022	October 2023	December 31, 2021

NCT03187639. Fractional Flow Reserve Derived From Computed Tomography Coronary Angiography in the Assessment and Management of Stable Chest Pain (FORECAST). Two-Group Diagnostic RCT. Recruiting. Last Updated Posted: October 22, 2020. https://clinicaltrials.gov/ct2/show/NCT03187639

Company Update on 29 January 2021:
# of sites = 11
enrolled = 1400 (final)
Expected data: publication timing not known. Abstract presented October 2020 [Curzen et al. 2020]

NCT02973126. Heartflow (AFFECTS) (AFFECTS). Single Group Diagnostic Trial. 270 Participants. Recruiting. Last Update Posted: January 22, 2020. https://clinicaltrials.gov/ct2/show/NCT02973126

Company Update on 29 January 2021:
# of sites = 1
enrolled = 58 (final)
Expected data: publication timing not known

NCT03665389. Evaluation of Fractional Flow Reserve Calculated by Computed Tomography Coronary Angiography in Patients Undergoing TAVR (FORTUNA). Single-Group Diagnostic Trial. 25 Participants. Not Yet Recruiting. Last Update Posted: September 13, 2018. https://clinicaltrials.gov/ct2/show/NCT03665389

Company Update on 29 January 2021:
# of sites = 1
enrolled = ~20/25
Expected data: estimated end of 2021

NCT03702244. The PRECISE Protocol: Prospective Randomized Trial of the Optimal Evaluation of Cardiac Symptoms and Revascularization (PRECISE). Randomised Parallel Group Open Label Trial. 2100 Participants. Recruiting. Last Update Posted: January 31, 2020. https://clinicaltrials.gov/ct2/show/NCT03702244
Company Update on 29 January 2021:
# of sites = ~55
enrolled = ~1800/2100
Expected data: estimated Summer, 2022

NCT03782688. Precise Percutaneous Coronary Intervention Plan (P3) Study (P3). Prospective Cohort. 120 Participants. Recruiting. Last Update Posted: August 17, 2020. https://clinicaltrials.gov/ct2/show/NCT03782688
Company Update on 29 January 2021:
# of sites = 6
enrolled = 129 (final)
Expected data: Spring, 2021

NCT04052256. The Heartflow Coronary Disease Progression Evaluation Study (THRONE). Prospective Cohort. 250 Participants. Recruiting. Last Update Posted: September 30, 2019. https://clinicaltrials.gov/ct2/show/NCT04052256
Company Update on 29 January 2021:
# of sites = 1
enrolled = ~140/150
Expected data: estimated 2022

NCT04142021. Safety and Feasibility Evaluation of Planning and Execution of Surgical Revascularization Solely Based on Coronary CTA and FFRCT in Patients With Complex Coronary Artery Disease (FASTTRACK CABG). Prospective Cohort. 114 Participants. Recruiting. Last Update Posted: October 23, 2020. https://clinicaltrials.gov/ct2/show/NCT04142021
Company Update on 29 January 2021:
# of sites = 3
enrolled = ~10/114
Expected data: estimated end of 2021

Appendix D – Literature search strategy

D.1 Search by NICE's Information Specialist based on EAC's 2016 Search Strategies

1 **Diagnostic evidence**

Database: Medline
Strategy used:
1 heartflow.ti,ab. (11)
2 non-invasive.ti,ab. (68104)
3 noninvasive.ti,ab. (83758)
4 or/2-3 (149980)
5 Fractional Flow Reserve, Myocardial/ or (fractional flow reserve* or FFR).ti,ab. (3770)
6 4 and 5 (482)
7 CT-based FFR.ti,ab. (5)
8 FFRct.ti,ab. (148)
9 coronary CT angiograph*.ti,ab. (1555)
10 CCTA.ti,ab. (1451)
11 coronary angiograph*.ti,ab. or Coronary Angiography/ (75520)
12 nuclear myocardial perfusion*.ti,ab. (84)
13 cardiac SPECT.ti,ab. (299)
14 myocardial perfusion scintigraph*.ti,ab. (987)
15 magnetic resonance perfusion*.ti,ab. (306)
16 Magnetic Resonance Imaging/ or (MRI or magnetic resonance imaging).ti,ab. (498352)
17 15 or 16 (498452)
18 perfusion*.ti,ab. (149339)
19 stress.ti,ab. (624582)
20 17 and 18 and 19 (831)
21 stress echocardiograph*.ti,ab. or Echocardiography, Stress/ (5022)
22 Myocardial Perfusion Imaging/ or stress myocardial perfusion*.ti,ab. (4942)
23 stress perfusion*.ti,ab. (579)
24 Dobutamine/ or dobutamine stress.ti,ab. (7019)
25 1 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 20 or 21 or 22 or 23 or 24 (88598)
26 fractional flow reserve*.ti,ab. or Fractional Flow Reserve, Myocardial/ (3001)
27 FFR.ti,ab. (2312)
28 26 or 27 (3770)
29 "Sensitivity and Specificity"/ or diagnostic accuracy.ti,ab. (371322)
30 ROC Curve/ or ROC.ti,ab. (79976)
31 prognosis.ti,ab. or Prognosis/ (685605)
32 "Predictive Value of Tests"/ or predictive.ti,ab. (414821)
33 or/29-32 (1354727)

34	25 and 28 and 33 (1099)
35	limit 34 to english language (1071)
36	limit 35 to ed=20160401-20201231 (624)
37	animals/ not humans/ (4696381)
38	36 not 37 (618)

Database: Medline in process & ePub ahead

Strategy used:

1	heartflow.ti,ab. (2)
2	non-invasive.ti,ab. (15539)
3	noninvasive.ti,ab. (12302)
4	or/2-3 (27401)
5	Fractional Flow Reserve, Myocardial/ or (fractional flow reserve* or FFR).ti,ab. (739)
6	4 and 5 (115)
7	CT-based FFR.ti,ab. (1)
8	FFRct.ti,ab. (49)
9	coronary CT angiograph*.ti,ab. (254)
10	CCTA.ti,ab. (408)
11	coronary angiograph*.ti,ab. or Coronary Angiography/ (3779)
12	nuclear myocardial perfusion*.ti,ab. (15)
13	cardiac SPECT.ti,ab. (50)
14	myocardial perfusion scintigraph*.ti,ab. (111)
15	magnetic resonance perfusion*.ti,ab. (43)
16	Magnetic Resonance Imaging/ or (MRI or magnetic resonance imaging).ti,ab. (59867)
17	15 or 16 (59890)
18	perfusion*.ti,ab. (12464)
19	stress.ti,ab. (119904)
20	17 and 18 and 19 (103)
21	stress echocardiograph*.ti,ab. or Echocardiography, Stress/ (386)
22	Myocardial Perfusion Imaging/ or stress myocardial perfusion*.ti,ab. (78)
23	stress perfusion*.ti,ab. (77)
24	Dobutamine/ or dobutamine stress.ti,ab. (170)
25	1 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 20 or 21 or 22 or 23 or 24 (4917)
26	fractional flow reserve*.ti,ab. or Fractional Flow Reserve, Myocardial/ (592)
27	FFR.ti,ab. (549)
28	26 or 27 (739)
29	"Sensitivity and Specificity"/ or diagnostic accuracy.ti,ab. (7327)
30	ROC Curve/ or ROC.ti,ab. (10506)
31	prognosis.ti,ab. or Prognosis/ (61162)
32	"Predictive Value of Tests"/ or predictive.ti,ab. (50118)
33	or/29-32 (119292)
34	25 and 28 and 33 (97)
35	limit 34 to english language (95)
36	limit 35 to dt=20160401-20201231 (87)

37 animals/ not humans/ (1)
38 36 not 37 (87)

Database: Embase

Strategy used:

1 heartflow.ti,ab. (43)
2 non-invasive.ti,ab. (142259)
3 noninvasive.ti,ab. (125901)
4 or/2-3 (261357)
5 fractional flow reserve/ or (fractional flow reserve* or FFR).ti,ab. (8470)
6 4 and 5 (1052)
7 CT-based FFR.ti,ab. (9)
8 FFRct.ti,ab. (349)
9 computed tomographic angiography/ or coronary CT angiograph*.ti,ab. (59028)
10 CCTA.ti,ab. (4037)
11 coronary angiograph*.ti,ab. or angiocardiography/ (106312)
12 nuclear myocardial perfusion*.ti,ab. (193)
13 SPECT.ti,ab. or single photon emission computer tomography/ (71371)
14 cardiac.ti,ab. or cardiac imaging/ (867743)
15 13 and 14 (8964)
16 myocardial perfusion scintigraph*.ti,ab. (1813)
17 magnetic resonance perfusion*.ti,ab. (469)
18 nuclear magnetic resonance imaging/ or MRI.ti,ab. (866284)
19 17 or 18 (866451)
20 heart perfusion/ or heart muscle perfusion/ or perfusion/ or perfusion*.ti,ab. (237398)
21 stress/ or stress.ti,ab. (971531)
22 19 and 20 and 21 (1499)
23 stress echocardiograph*.ti,ab. or stress echocardiography/ (10041)
24 myocardial perfusion imaging/ or stress myocardial perfusion*.ti,ab. (10104)
25 stress perfusion*.ti,ab. (1269)
26 dobutamine/ or dobutamine stress.ti,ab. (25215)
27 fractional flow reserve*.ti,ab. or fractional flow reserve/ (6930)
28 FFR.ti,ab. (5532)
29 27 or 28 (8470)
30 1 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 15 or 16 or 22 or 23 or 24 or 25 or 26 or 29 (205281)
31 diagnostic accuracy.ti,ab. or diagnosis/ or diagnostic accuracy/ (1591623)
32 "sensitivity and specificity"/ or diagnostic accuracy.ti,ab. (407504)
33 roc curve/ or receiver operating characteristic/ or area under the curve/ or ROC.ti,ab. (270744)
34 prognosis.ti,ab. or prognosis/ (855842)
35 predictive value/ or predictive validity/ or predictive.ti,ab. (547761)
36 or/31-35 (3119167)

37 29 and 30 and 36 (3093)
38 limit 37 to english language (3041)
39 limit 38 to dc=20160401-20201231 (1628)
40 nonhuman/ not human/ (4676613)
41 39 not 40 (1615)

2 **Clinical evidence**

Database: Medline

Strategy used:
1 heartflow.ti,ab. (11)
2 non-invasive.ti,ab. (68104)
3 noninvasive.ti,ab. (83758)
4 or/2-3 (149980)
5 fractional flow reserve.ti,ab. or Fractional Flow Reserve, Myocardial/ (3001)
6 4 and 5 (448)
7 CT-based FFR.ti,ab. (5)
8 FFRct.ti,ab. (148)
9 coronary CT angiograph*.ti,ab. (1555)
10 CCTA.ti,ab. (1451)
11 coronary angiograph*.ti,ab. or Coronary Angiography/ (75520)
12 nuclear myocardial perfusion*.ti,ab. (84)
13 SPECT.ti,ab. or Tomography, Emission-Computed, Single-Photon/ (37087)
14 Cardiac Imaging Techniques/ or cardiac.ti,ab. (539197)
15 13 and 14 (4152)
16 Magnetic Resonance Imaging/ or (MRI or magnetic resonance imaging).ti,ab. (498352)
17 Myocardial Perfusion Imaging/ or Perfusion Imaging/ or Perfusion/ or perfusion.ti,ab. (174756)
18 stress.ti,ab. (624582)
19 16 and 17 and 18 (863)
20 stress echocardiograph*.ti,ab. or Echocardiography, Stress/ (5022)
21 myocardial perfusion imaging.ti,ab. or Myocardial Perfusion Imaging/ (6726)
22 Dobutamine/ or dobutamine stress.ti,ab. (7019)
23 fractional flow reserve.ti,ab. or Fractional Flow Reserve, Myocardial/ (3001)
24 FFR.ti,ab. (2312)
25 23 or 24 (3770)
26 1 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 15 or 19 or 20 or 21 or 22 or 25 (93232)
27 treatment outcome.ti,ab. or Treatment Outcome/ (990110)
28 percutaneous coronary intervention.ti,ab. or Percutaneous Coronary Intervention/ (33073)
29 major adverse cardiac event.ti,ab. (749)
30 stent.ti,ab. or Stents/ (88409)
31 myocardial infarction.ti,ab. or Myocardial Infarction/ (225577)

32 balloon angioplasty.ti,ab. or Angioplasty, Balloon/ (21856)
33 PCI.ti,ab. (21561)
34 coronary artery bypass.ti,ab. or Coronary Artery Bypass/ (60519)
35 CABG.ti,ab. (15760)
36 Radiation, Ionizing/ or radiation.ti,ab. (296984)
37 heart catheterization.ti,ab. or Cardiac Catheterization/ (50950)
38 ICA rate$.ti,ab. (7)
39 Myocardial Revascularization/ or revascularization.ti,ab. (50817)
40 mortality.ti,ab. or Mortality/ (669021)
41 Death/ or Death, Sudden, Cardiac/ or death.ti,ab. (627501)
42 heart infarction.ti,ab. (215)
43 MI.ti,ab. (40461)
44 quality of life.ti,ab. or "Quality of Life"/ (291994)
45 test utilization.ti,ab. (310)
46 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 (2802495)
47 stable coronary artery disease.ti,ab. (2915)
48 stable CAD.ti,ab. (1307)
49 stable angina.ti,ab. or Angina, Stable/ (7832)
50 47 or 48 or 49 (10994)
51 26 and 46 and 50 (1904)
52 limit 51 to english language (1688)
53 limit 52 to ed=20160401-20201231 (557)
54 animals/ not humans/ (4696381)
55 53 not 54 (557)

Database: Medline in process and ePub ahead

Strategy used:

1 heartflow.ti,ab. (2)
2 non-invasive.ti,ab. (15539)
3 noninvasive.ti,ab. (12302)
4 or/2-3 (27401)
5 fractional flow reserve.ti,ab. or Fractional Flow Reserve, Myocardial/ (591)
6 4 and 5 (109)
7 CT-based FFR.ti,ab. (1)
8 FFRct.ti,ab. (49)
9 coronary CT angiograph*.ti,ab. (254)
10 CCTA.ti,ab. (408)
11 coronary angiograph*.ti,ab. or Coronary Angiography/ (3779)
12 nuclear myocardial perfusion*.ti,ab. (15)
13 SPECT.ti,ab. or Tomography, Emission-Computed, Single-Photon/ (3406)
14 Cardiac Imaging Techniques/ or cardiac.ti,ab. (63657)

15 13 and 14 (421)
16 Magnetic Resonance Imaging/ or (MRI or magnetic resonance imaging).ti,ab. (59867)
17 Myocardial Perfusion Imaging/ or Perfusion Imaging/ or Perfusion/ or perfusion.ti,ab. (12366)
18 stress.ti,ab. (119904)
19 16 and 17 and 18 (99)
20 stress echocardiograph*.ti,ab. or Echocardiography, Stress/ (386)
21 myocardial perfusion imaging.ti,ab. or Myocardial Perfusion Imaging/ (600)
22 Dobutamine/ or dobutamine stress.ti,ab. (170)
23 fractional flow reserve.ti,ab. or Fractional Flow Reserve, Myocardial/ (591)
24 FFR.ti,ab. (549)
25 23 or 24 (738)
26 1 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 15 or 19 or 20 or 21 or 22 or 25 (5871)
27 treatment outcome.ti,ab. or Treatment Outcome/ (3475)
28 percutaneous coronary intervention.ti,ab. or Percutaneous Coronary Intervention/ (5242)
29 major adverse cardiac event.ti,ab. (130)
30 stent.ti,ab. or Stents/ (10568)
31 myocardial infarction.ti,ab. or Myocardial Infarction/ (17494)
32 balloon angioplasty.ti,ab. or Angioplasty, Balloon/ (802)
33 PCI.ti,ab. (4348)
34 coronary artery bypass.ti,ab. or Coronary Artery Bypass/ (4053)
35 CABG.ti,ab. (2234)
36 Radiation, Ionizing/ or radiation.ti,ab. (58938)
37 heart catheterization.ti,ab. or Cardiac Catheterization/ (595)
38 ICA rate$.ti,ab. (2)
39 Myocardial Revascularization/ or revascularization.ti,ab. (5378)
40 mortality.ti,ab. or Mortality/ (110945)
41 Death/ or Death, Sudden, Cardiac/ or death.ti,ab. (86569)
42 heart infarction.ti,ab. (8)
43 MI.ti,ab. (7067)
44 quality of life.ti,ab. or "Quality of Life"/ (49025)
45 test utilization.ti,ab. (52)
46 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 (311569)
47 stable coronary artery disease.ti,ab. (447)
48 stable CAD.ti,ab. (205)
49 stable angina.ti,ab. or Angina, Stable/ (620)
50 47 or 48 or 49 (1138)
51 26 and 46 and 50 (163)
52 limit 51 to english language (161)
53 limit 52 to dt=20160401-20201231 (121)
54 animals/ not humans/ (1)
55 53 not 54 (121)

Database: Embase

Strategy used:

1 heartflow.ti,ab. (43)
2 non-invasive.ti,ab. (142259)
3 noninvasive.ti,ab. (125901)
4 or/2-3 (261357)
5 (fractional flow reserve* or FFR).ti,ab. or fractional flow reserve/ (8470)
6 4 and 5 (1052)
7 CT-based FFR.ti,ab. (9)
8 FFRct.ti,ab. (349)
9 computed tomographic angiography/ or coronary CT angiograph*.ti,ab. (59028)
10 CCTA.ti,ab. (4037)
11 coronary angiograph*.ti,ab. or angiocardiography/ (106312)
12 nuclear myocardial perfusion*.ti,ab. (193)
13 SPECT.ti,ab. or single photon emission computer tomography/ (71371)
14 cardiac.ti,ab. or cardiac imaging/ (867743)
15 13 and 14 (8964)
16 myocardial perfusion scintigraph*.ti,ab. (1813)
17 MRI.ti,ab. (420180)
18 magnetic resonance imaging.ti,ab. or nuclear magnetic resonance imaging/ (866358)
19 17 or 18 (919296)
20 heart perfusion/ or heart muscle perfusion/ or perfusion*.ti,ab. or perfusion/ (237398)
21 stress.ti,ab. or stress/ (971531)
22 19 and 20 and 21 (1748)
23 stress echocardiograph*.ti,ab. or stress echocardiography/ (10041)
24 myocardial perfusion imaging.ti,ab. or myocardial perfusion imaging/ (12042)
25 stress perfusion*.ti,ab. (1269)
26 dobutamine/ or dobutamine stress.ti,ab. (25215)
27 fractional flow reserve.ti,ab. or fractional flow reserve/ (6929)
28 FFR.ti,ab. (5532)
29 treatment outcome.ti,ab. or treatment outcome/ (870953)
30 Percutaneous Coronary Intervention.ti,ab. or percutaneous coronary intervention/ (83760)
31 Major adverse cardiac event.ti,ab. (1638)
32 coronary stent/ or Stent.ti,ab. or stent/ (166207)
33 Myocardial Infarction.ti,ab. (264543)
34 balloon angioplasty.ti,ab. or percutaneous transluminal angioplasty/ (33930)
35 PCI.ti,ab. (58330)
36 coronary artery bypass.ti,ab. or coronary artery bypass graft/ (89960)
37 coronary artery bypass surgery/ or CABG.ti,ab. (45479)
38 radiation/ or radiation dose/ or radiation.ti,ab. (530160)
39 heart catheterization/ or cardiac catheterization rate*.ti,ab. (61672)
40 ICA rate*.ti,ab. (18)
41 heart muscle revascularization/ or revascularization/ or revascularization.ti,ab. (105844)
42 cardiovascular mortality/ or mortality/ or mortality.ti,ab. (1365753)

43 death/ or death.ti,ab. or heart death/ (1085521)
44 acute heart infarction/ or heart infarction/ or myocardial infraction.ti,ab. (335427)
45 MI.ti,ab. (86433)
46 quality of life.ti,ab. or "quality of life"/ (586986)
47 test utilization.ti,ab. (648)
48 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 (4354924)
49 stable coronary artery disease.ti,ab. (5739)
50 stable CAD.ti,ab. (3209)
51 stable angina.ti,ab. or stable angina pectoris/ (16714)
52 49 or 50 or 51 (23412)
53 1 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 15 or 16 or 22 or 23 or 24 or 25 or 26 or 27 or 28 (206501)
54 48 and 52 and 53 (4139)
55 limit 54 to english language (3846)
56 limit 55 to dc=20160401-20201231 (1242)
57 nonhuman/ not human/ (4676613)
58 56 not 57 (1224)

3 **Economic evidence**

Database: Medline

Strategy used:

1 heartflow.ti,ab. (11)
2 non-invasive.ti,ab. (68104)
3 noninvasive.ti,ab. (83758)
4 or/2-3 (149980)
5 (FFR or fractional flow reserve).ti,ab. or Fractional Flow Reserve, Myocardial/ (3770)
6 4 and 5 (482)
7 CT-based FFR.ti,ab. (5)
8 FFRct.ti,ab. (148)
9 fractional flow reserve.ti,ab. or Fractional Flow Reserve, Myocardial/ (3001)
10 4 and 9 (448)
11 coronary CT angiograph*.ti,ab. (1555)
12 CCTA.ti,ab. (1451)
13 coronary angiograph*.ti,ab. or Coronary Angiography/ (75520)
14 nuclear myocardial perfusion*.ti,ab. (84)
15 cardiac SPECT.ti,ab. (299)
16 myocardial perfusion scintigraph*.ti,ab. (987)
17 magnetic resonance perfusion*.ti,ab. (306)
18 Magnetic Resonance Imaging/ or (MRI or magnetic resonance imaging).ti,ab. (498352)
19 17 or 18 (498452)

20 perfusion*.ti,ab. (149339)
21 stress.ti,ab. (624582)
22 19 and 20 and 21 (831)
23 stress echocardiograph*.ti,ab. or Echocardiography, Stress/ (5022)
24 Myocardial Perfusion Imaging/ or stress myocardial perfusion*.ti,ab. (4942)
25 stress perfusion*.ti,ab. (579)
26 Dobutamine/ or dobutamine stress.ti,ab. (7019)
27 fractional flow reserve.ti,ab. or Fractional Flow Reserve, Myocardial/ (3001)
28 FFR.ti,ab. (2312)
29 1 or 6 or 7 or 8 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 22 or 23 or 24 or 25 or 26 or 27 or 28 (90231)
30 (economic* or cost*).ti,ab. (660812)
31 29 and 30 (2010)
32 (CAD or coronary artery disease).ti,ab. (86738)
33 31 and 32 (738)
34 limit 33 to english language (665)
35 limit 34 to ed=20160401-20201231 (140)
36 animals/ not humans/ (4696381)
37 35 not 36 (139)

Database: Medline in process and ePub ahead

Strategy used:

1 heartflow.ti,ab. (2)
2 non-invasive.ti,ab. (15539)
3 noninvasive.ti,ab. (12302)
4 or/2-3 (27401)
5 (FFR or fractional flow reserve).ti,ab. or Fractional Flow Reserve, Myocardial/ (738)
6 4 and 5 (115)
7 CT-based FFR.ti,ab. (1)
8 FFRct.ti,ab. (49)
9 fractional flow reserve.ti,ab. or Fractional Flow Reserve, Myocardial/ (591)
10 4 and 9 (109)
11 coronary CT angiograph*.ti,ab. (254)
12 CCTA.ti,ab. (408)
13 coronary angiograph*.ti,ab. or Coronary Angiography/ (3779)
14 nuclear myocardial perfusion*.ti,ab. (15)
15 cardiac SPECT.ti,ab. (50)
16 myocardial perfusion scintigraph*.ti,ab. (111)
17 magnetic resonance perfusion*.ti,ab. (43)
18 Magnetic Resonance Imaging/ or (MRI or magnetic resonance imaging).ti,ab. (59867)
19 17 or 18 (59890)
20 perfusion*.ti,ab. (12464)
21 stress.ti,ab. (119904)

22 19 and 20 and 21 (103)
23 stress echocardiograph*.ti,ab. or Echocardiography, Stress/ (386)
24 Myocardial Perfusion Imaging/ or stress myocardial perfusion*.ti,ab. (78)
25 stress perfusion*.ti,ab. (77)
26 Dobutamine/ or dobutamine stress.ti,ab. (170)
27 fractional flow reserve.ti,ab. or Fractional Flow Reserve, Myocardial/ (591)
28 FFR.ti,ab. (549)
29 1 or 6 or 7 or 8 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 22 or 23 or 24 or 25 or 26 or 27 or 28 (5362)
30 (economic* or cost*).ti,ab. (158632)
31 29 and 30 (210)
32 (CAD or coronary artery disease).ti,ab. (11960)
33 31 and 32 (98)
34 limit 33 to english language (98)
35 limit 34 to dt=20160401-20201231 (56)
36 animals/ not humans/ (1)
37 35 not 36 (56)

Database: Embase

Strategy used:
1 heartflow.ti,ab. (43)
2 non-invasive.ti,ab. (142259)
3 noninvasive.ti,ab. (125901)
4 or/2-3 (261357)
5 (fractional flow reserve or FFR).ti,ab. or fractional flow reserve/ (8470)
6 4 and 5 (1052)
7 CT-based FFR.ti,ab. (9)
8 FFRct.ti,ab. (349)
9 computed tomographic angiography/ or coronary CT angiograph*.ti,ab. (59028)
10 CCTA.ti,ab. (4037)
11 coronary angiograph*.ti,ab. or angiocardiography/ (106312)
12 nuclear myocardial perfusion*.ti,ab. (193)
13 SPECT.ti,ab. or single photon emission computer tomography/ (71371)
14 cardiac.ti,ab. or cardiac imaging/ (867743)
15 13 and 14 (8964)
16 myocardial perfusion scintigraph*.ti,ab. (1813)
17 MRI.ti,ab. (420180)
18 magnetic resonance imaging.ti,ab. or nuclear magnetic resonance imaging/ (866358)
19 17 or 18 (919296)
20 heart perfusion/ or heart muscle perfusion/ or perfusion*.ti,ab. or perfusion/ (237398)
21 stress.ti,ab. or stress/ (971531)
22 19 and 20 and 21 (1748)
23 stress echocardiograph*.ti,ab. or stress echocardiography/ (10041)
24 myocardial perfusion imaging.ti,ab. or myocardial perfusion imaging/ (12042)

25 stress perfusion*.ti,ab. (1269)
26 dobutamine/ or dobutamine stress.ti,ab. (25215)
27 fractional flow reserve.ti,ab. or fractional flow reserve/ (6929)
28 FFR.ti,ab. (5532)
29 1 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 15 or 16 or 22 or 23 or 24 or 25 or 26 or 27 or 28 (206501)
30 (econom* or cost*).ti,ab. (1098394)
31 29 and 30 (4984)
32 limit 31 to english language (4617)
33 limit 32 to dc=20160401-20201231 (1359)
34 (CAD or coronary artery disease).ti,ab. (156151)
35 33 and 34 (414)

Database: Econlit

Strategy used:

1 (Fractional flow reserve* or FFR or FFRct).ti,ab. (27)
2 (coronary artery disease* or CAD).ti,ab. (167)
3 1 or 2 (194)
4 (cost* or economic*).ti,ab. (441368)
5 3 and 4 (68)
6 limit 5 to yr="2016 - 2020" (21)

Database: Cochrane

Strategy used:

#1 (fractional flow reserve* or FFR):ti,ab 534
#2 MeSH descriptor: [Fractional Flow Reserve, Myocardial] this term only 108
#3 FFRct:ti,ab 19
#4 #1 or #2 or #3 555
#5 (non-invasive* or noninvasive*):ti,ab 16919
#6 heartflow:ti,ab 2
#7 #5 or #6 16919
#8 #7 and #4 59
#9 (CT-based ffr):ti,ab 1
#10 (computed tomographic angiograph* or coronary CT angiograph*):ti,ab 941
#11 MeSH descriptor: [Computed Tomography Angiography] this term only 216
#12 CCTA:ti,ab 301
#13 (coronary angiograph* or angiocardiograph*):ti,ab 8934
#14 MeSH descriptor: [Angiocardiography] this term only 82
#15 MeSH descriptor: [Coronary Angiography] this term only 4201
#16 (nuclear myocardial perfusion*):ti,ab 106
#17 (SPECT or single photon emission computer tomograph*):ti,ab 1728

#18	(MRI or magnetic resonance imaging):ti,ab 28403
#19	MeSH descriptor: [Magnetic Resonance Imaging] this term only 6790
#20	(heart perfusion* or heart muscle perfusion*):ti,ab 1993
#21	stress:ti,ab 47815
#22	#19 and #20 and #21 2
#23	(myocardial perfusion imaging*):ti,ab 814
#24	(stress echocardiograph*):ti,ab 1050
#25	(stress perfusion*):ti,ab 1001
#26	(dobutamine or dobutamine stress):Ti,ab 1171
#27	MeSH descriptor: [Dobutamine] this term only 532
#28	#5 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #22 or #23 or #24 or #25 or #26 or #27 57955
#29	(economic* or cost*):ti,ab 73452
#30	#28 and #29 2765
#31	(coronary artery disease or cad):ti,ab 15551
#32	MeSH descriptor: [Coronary Artery Disease] this term only 6414
#33	#31 or #32 18917
#34	#30 and #33 with Cochrane Library publication date Between Apr 2016 and Aug 2020 179

Database: CRD
Strategy used:

1	(fractional flow reserve* or FFR)	102
2	MeSH DESCRIPTOR Fractional Flow Reserve, Myocardial	22
3	(FFRct)	1
4	(#1 or #2 or #3)	102
5	(non-invasive* or noninvasive*)	722
6	(heartflow)	0
7	(#5 or #6)	722
8	(#7 and #4)	4
9	(CT-based ffr)	0
10	(computed tomographic angiograph* or coronary CT angiograph*)	51
11	MeSH DESCRIPTOR Computed Tomography Angiography	0
12	(CCTA)	4
13	(coronary angiograph* or angiocardiograph*)	454
14	MeSH DESCRIPTOR Angiocardiography	1
15	MeSH DESCRIPTOR Coronary Angiography	341
16	(nuclear myocardial perfusion*)	0
17	(SPECT or single photon emission computer tomograph*)	118
18	(MRI or magnetic resonance imaging)	1179
19	MeSH DESCRIPTOR Magnetic Resonance Imaging	693
20	(heart perfusion* or heart muscle perfusion*)	0
21	(stress)	1385
22	(#19 and #20 and #21)	0
23	(myocardial perfusion imaging*)	52
24	(stress echocardiograph*)	43
25	(stress perfusion*)	8
26	(dobutamine or dobutamine stress)	56
27	MeSH DESCRIPTOR Dobutamine	20
28	(#5 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #22 or #23 or #24 or #25 or #26 or #27)	2371
29	(economic* or cost*)	26452
30	(#28 and #29)	906
31	(coronary artery disease or cad)	1334
32	MeSH DESCRIPTOR Coronary Artery Disease	587
33	(#31 or #32)	1334
34	(#30 and #33) IN NHSEED, HTA WHERE LPD FROM 01/04/2016 TO 01/09/2020	0
35	(#30 and #33) IN NHSEED, HTA FROM 2016 TO 2020	0
36	#34 OR #35	0

D.2 Update Search by EAC's Information Specialist based on EAC's 2016 Search Strategies

1 Diagnostic evidence

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to January 04, 2021>	
1	heartflow.ti,ab. (14)

2	non-invasive.ti,ab. (86706)
3	noninvasive.ti,ab. (98297)
4	or/2-3 (182616)
5	Fractional Flow Reserve, Myocardial/ or (fractional flow reserve* or FFR).ti,ab. (4699)
6	4 and 5 (622)
7	CT-based FFR.ti,ab. (6)
8	FFRct.ti,ab. (217)
9	coronary CT angiograph*.ti,ab. (1868)
10	CCTA.ti,ab. (1974)
11	coronary angiograph*.ti,ab. or Coronary Angiography/ (80507)
12	nuclear myocardial perfusion*.ti,ab. (101)
13	cardiac SPECT.ti,ab. (349)
14	myocardial perfusion scintigraph*.ti,ab. (1106)
15	magnetic resonance perfusion*.ti,ab. (357)
16	Magnetic Resonance Imaging/ or (MRI or magnetic resonance imaging).ti,ab. (571781)

17	15 or 16 (571908)
18	perfusion*.ti,ab. (163973)
19	stress.ti,ab. (767621)
20	17 and 18 and 19 (952)
21	stress echocardiograph*.ti,ab. or Echocardiography, Stress/ (5480)
22	Myocardial Perfusion Imaging/ or stress myocardial perfusion*.ti,ab. (5189)
23	stress perfusion*.ti,ab. (678)
24	Dobutamine/ or dobutamine stress.ti,ab. (7227)
25	1 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 20 or 21 or 22 or 23 or 24 (94977)
26	fractional flow reserve*.ti,ab. or Fractional Flow Reserve, Myocardial/ (3742)
27	FFR.ti,ab. (2977)
28	26 or 27 (4699)
29	"Sensitivity and Specificity"/ or diagnostic accuracy.ti,ab. (383312)
30	ROC Curve/ or ROC.ti,ab. (94892)
31	prognosis.ti,ab. or Prognosis/ (767368)

32	"Predictive Value of Tests"/ or predictive.ti,ab. (479213)
33	or/29-32 (1511832)
34	25 and 28 and 33 (1273)
35	limit 34 to english language (1240)
36	limit 35 to ed=20200831-20211231 (74)
37	limit 35 to dt=20200831-20211231 (21)
38	36 or 37 (93)
39	animals/ not humans/ (4739001)
40	38 not 39 (93)

Database: Embase <1974 to 2020 Week 53>	
1	heartflow.ti,ab. (46)
2	non-invasive.ti,ab. (147414)
3	noninvasive.ti,ab. (129337)
4	or/2-3 (269724)
5	fractional flow reserve/ or (fractional flow reserve* or FFR).ti,ab. (8811)

6	4 and 5 (1090)
7	CT-based FFR.ti,ab. (9)
8	FFRct.ti,ab. (370)
9	computed tomographic angiography/ or coronary CT angiograph*.ti,ab. (61617)
10	CCTA.ti,ab. (4180)
11	coronary angiograph*.ti,ab. or angiocardiography/ (107503)
12	nuclear myocardial perfusion*.ti,ab. (198)
13	SPECT.ti,ab. or single photon emission computer tomography/ (72240)
14	cardiac.ti,ab. or cardiac imaging/ (889001)
15	13 and 14 (9085)
16	myocardial perfusion scintigraph*.ti,ab. (1842)
17	magnetic resonance perfusion*.ti,ab. (480)
18	nuclear magnetic resonance imaging/ or MRI.ti,ab. (889882)
19	17 or 18 (890055)
20	heart perfusion/ or heart muscle perfusion/ or perfusion/ or perfusion*.ti,ab. (242110)

21	stress/ or stress.ti,ab. (1002767)
22	19 and 20 and 21 (1531)
23	stress echocardiograph*.ti,ab. or stress echocardiography/ (10217)
24	myocardial perfusion imaging/ or stress myocardial perfusion*.ti,ab. (10377)
25	stress perfusion*.ti,ab. (1302)
26	dobutamine/ or dobutamine stress.ti,ab. (25574)
27	fractional flow reserve*.ti,ab. or fractional flow reserve/ (7220)
28	FFR.ti,ab. (5730)
29	27 or 28 (8811)
30	1 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 15 or 16 or 22 or 23 or 24 or 25 or 26 or 29 (209900)
31	diagnostic accuracy.ti,ab. or diagnosis/ or diagnostic accuracy/ (1611700)
32	"sensitivity and specificity"/ or diagnostic accuracy.ti,ab. (421822)
33	roc curve/ or receiver operating characteristic/ or area under the curve/ or ROC.ti,ab. (282962)
34	prognosis.ti,ab. or prognosis/ (880797)

35	predictive value/ or predictive validity/ or predictive.ti,ab. (568168)
36	or/31-35 (3190458)
37	29 and 30 and 36 (3207)
38	limit 37 to english language (3150)
39	limit 38 to dc=20200831-20211231 (138)
40	nonhuman/ not human/ (4756689)
41	39 not 40 (137)

2 **Clinical evidence**

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to January 04, 2021>	
1	heartflow.ti,ab. (14)
2	non-invasive.ti,ab. (86706)
3	noninvasive.ti,ab. (98297)
4	or/2-3 (182616)
5	fractional flow reserve.ti,ab. or Fractional Flow Reserve, Myocardial/ (3741)
6	4 and 5 (580)

7	CT-based FFR.ti,ab. (6)
8	FFRct.ti,ab. (217)
9	coronary CT angiograph*.ti,ab. (1868)
10	CCTA.ti,ab. (1974)
11	coronary angiograph*.ti,ab. or Coronary Angiography/ (80507)
12	nuclear myocardial perfusion*.ti,ab. (101)
13	SPECT.ti,ab. or Tomography, Emission-Computed, Single-Photon/ (41028)
14	Cardiac Imaging Techniques/ or cardiac.ti,ab. (615271)
15	13 and 14 (4640)
16	Magnetic Resonance Imaging/ or (MRI or magnetic resonance imaging).ti,ab. (571781)
17	Myocardial Perfusion Imaging/ or Perfusion Imaging/ or Perfusion/ or perfusion.ti,ab. (189371)
18	stress.ti,ab. (767621)
19	16 and 17 and 18 (982)
20	stress echocardiograph*.ti,ab. or Echocardiography, Stress/ (5480)
21	myocardial perfusion imaging.ti,ab. or Myocardial Perfusion Imaging/ (7498)

22	Dobutamine/ or dobutamine stress.ti,ab. (7227)
23	fractional flow reserve.ti,ab. or Fractional Flow Reserve, Myocardial/ (3741)
24	FFR.ti,ab. (2977)
25	23 or 24 (4698)
26	1 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 15 or 19 or 20 or 21 or 22 or 25 (100663)
27	treatment outcome.ti,ab. or Treatment Outcome/ (1014957)
28	percutaneous coronary intervention.ti,ab. or Percutaneous Coronary Intervention/ (39823)
29	major adverse cardiac event.ti,ab. (913)
30	stent.ti,ab. or Stents/ (101161)
31	myocardial infarction.ti,ab. or Myocardial Infarction/ (246623)
32	balloon angioplasty.ti,ab. or Angioplasty, Balloon/ (22922)
33	PCI.ti,ab. (26800)
34	coronary artery bypass.ti,ab. or Coronary Artery Bypass/ (65357)
35	CABG.ti,ab. (18418)
36	Radiation, Ionizing/ or radiation.ti,ab. (363217)

37	heart catheterization.ti,ab. or Cardiac Catheterization/ (52216)
38	ICA rate$.ti,ab. (9)
39	Myocardial Revascularization/ or revascularization.ti,ab. (57430)
40	mortality.ti,ab. or Mortality/ (805993)
41	Death/ or Death, Sudden, Cardiac/ or death.ti,ab. (733703)
42	heart infarction.ti,ab. (227)
43	MI.ti,ab. (48944)
44	quality of life.ti,ab. or "Quality of Life"/ (352409)
45	test utilization.ti,ab. (378)
46	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 (3192417)
47	stable coronary artery disease.ti,ab. (3458)
48	stable CAD.ti,ab. (1574)
49	stable angina.ti,ab. or Angina, Stable/ (8547)
50	47 or 48 or 49 (12343)
51	26 and 46 and 50 (2119)

52	limit 51 to english language (1899)
53	limit 52 to ed=20200831-20211231 (37)
54	limit 52 to dt=20200831-20211231 (39)
55	53 or 54 (68)
56	animals/ not humans/ (4739001)
57	55 not 56 (68)

Database: Embase <1974 to 2020 Week 53>	
1	heartflow.ti,ab. (46)
2	non-invasive.ti,ab. (147414)
3	noninvasive.ti,ab. (129337)
4	or/2-3 (269724)
5	(fractional flow reserve* or FFR).ti,ab. or fractional flow reserve/ (8811)
6	4 and 5 (1090)
7	CT-based FFR.ti,ab. (9)
8	FFRct.ti,ab. (370)

9	computed tomographic angiography/ or coronary CT angiograph*.ti,ab. (61617)
10	CCTA.ti,ab. (4180)
11	coronary angiograph*.ti,ab. or angiocardiography/ (107503)
12	nuclear myocardial perfusion*.ti,ab. (198)
13	SPECT.ti,ab. or single photon emission computer tomography/ (72240)
14	cardiac.ti,ab. or cardiac imaging/ (889001)
15	13 and 14 (9085)
16	myocardial perfusion scintigraph*.ti,ab. (1842)
17	MRI.ti,ab. (432859)
18	magnetic resonance imaging.ti,ab. or nuclear magnetic resonance imaging/ (889311)
19	17 or 18 (944468)
20	heart perfusion/ or heart muscle perfusion/ or perfusion*.ti,ab. or perfusion/ (242110)
21	stress.ti,ab. or stress/ (1002767)
22	19 and 20 and 21 (1789)
23	stress echocardiograph*.ti,ab. or stress echocardiography/ (10217)

24	myocardial perfusion imaging.ti,ab. or myocardial perfusion imaging/ (12321)
25	stress perfusion*.ti,ab. (1302)
26	dobutamine/ or dobutamine stress.ti,ab. (25574)
27	fractional flow reserve.ti,ab. or fractional flow reserve/ (7219)
28	FFR.ti,ab. (5730)
29	treatment outcome.ti,ab. or treatment outcome/ (885722)
30	Percutaneous Coronary Intervention.ti,ab. or percutaneous coronary intervention/ (86380)
31	Major adverse cardiac event.ti,ab. (1676)
32	coronary stent/ or Stent.ti,ab. or stent/ (169596)
33	Myocardial Infarction.ti,ab. (270195)
34	balloon angioplasty.ti,ab. or percutaneous transluminal angioplasty/ (34474)
35	PCI.ti,ab. (59902)
36	coronary artery bypass.ti,ab. or coronary artery bypass graft/ (91717)
37	coronary artery bypass surgery/ or CABG.ti,ab. (46425)
38	radiation/ or radiation dose/ or radiation.ti,ab. (543600)

39	heart catheterization/ or cardiac catheterization rate*.ti,ab. (63044)
40	ICA rate*.ti,ab. (18)
41	heart muscle revascularization/ or revascularization/ or revascularization.ti,ab. (108284)
42	cardiovascular mortality/ or mortality/ or mortality.ti,ab. (1413159)
43	death/ or death.ti,ab. or heart death/ (1117617)
44	acute heart infarction/ or heart infarction/ or myocardial infraction.ti,ab. (341353)
45	MI.ti,ab. (88846)
46	quality of life.ti,ab. or "quality of life"/ (608299)
47	test utilization.ti,ab. (672)
48	29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 (4477253)
49	stable coronary artery disease.ti,ab. (5893)
50	stable CAD.ti,ab. (3297)
51	stable angina.ti,ab. or stable angina pectoris/ (16973)
52	49 or 50 or 51 (23858)

53	1 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 15 or 16 or 22 or 23 or 24 or 25 or 26 or 27 or 28 (211120)
54	48 and 52 and 53 (4219)
55	limit 54 to english language (3923)
56	limit 55 to dc=20200831-20211231 (97)
57	nonhuman/ not human/ (4756689)
58	56 not 57 (97)

3 **Economic evidence**

Databases: Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials (Date/time: 05/01/2021 13:10:56)		
#1	(fractional flow reserve* or FFR):ti,ab	563
#2	[mh "Fractional Flow Reserve, Myocardial"]	116
#3	FFRct:ti,ab	20
#4	#1 or #2 or #3	585
#5	(non-invasive* or noninvasive*):ti,ab	17809
#6	heartflow:ti,ab	2
#7	#5 or #6	17809
#8	#7 and #4	61
#9	(CT-based ffr):ti,ab	1
#10	(computed tomographic angiograph* or coronary CT angiograph*):ti,ab	977
#11	[mh "Computed Tomography Angiography"]	229
#12	CCTA:ti,ab	323
#13	(coronary angiograph* or angiocardiograph*):ti,ab	9141
#14	[mh Angiocardiography]	82
#15	[mh "Coronary Angiography"]	4233
#16	(nuclear myocardial perfusion*):ti,ab	107
#17	(SPECT or single photon emission computer tomograph*):ti,ab	1752
#18	(MRI or magnetic resonance imaging):ti,ab	29713
#19	[mh "Magnetic Resonance Imaging"]	7799
#20	(heart perfusion* or heart muscle perfusion*):ti,ab	2042
#21	stress:ti,ab	49878

#22	#19 and #20 and #21	9
#23	(myocardial perfusion imaging*):ti,ab	834
#24	(stress echocardiograph*):ti,ab	1082
#25	(stress perfusion*):ti,ab	1020
#26	(dobutamine or dobutamine stress):Ti,ab	1191
#27	[mh Dobutamine]	534
#28	#5 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #22 or #23 or #24 or #25 or #26 or #27	60394
#29	(economic* or cost*):ti,ab	76027
#30	#28 and #29	2896
#31	(coronary artery disease or cad):ti,ab	16030
#32	[mh "Coronary Artery Disease"]	6541
#33	#31 or #32	19462
#34	#30 and #33 with Cochrane Library publication date Between Aug 2020 and Jan 2021	9

Database: EconLit via ProQuest 05 January 2021 12:59		
S1	ti(Fractional flow reserve* OR FFR OR FFRct) OR ab(Fractional flow reserve* OR FFR OR FFRct)	34
S2	ti(coronary artery disease* OR CAD) OR ab(coronary artery disease* OR CAD)	184
S3	(ti(Fractional flow reserve* OR FFR OR FFRct) OR ab(Fractional flow reserve* OR FFR OR FFRct)) OR (ti(coronary artery disease* OR CAD) OR ab(coronary artery disease* OR CAD))	218
S4	ti(cost* OR economic*) OR ab(cost* OR economic*)	448896
S5	((ti(Fractional flow reserve* OR FFR OR FFRct) OR ab(Fractional flow reserve* OR FFR OR FFRct)) OR (ti(coronary artery disease* OR CAD) OR ab(coronary artery disease* OR CAD))) AND (ti(cost* OR economic*) OR ab(cost* OR economic*))	85
S6	((ti(Fractional flow reserve* OR FFR OR FFRct) OR ab(Fractional flow reserve* OR FFR OR FFRct)) OR (ti(coronary artery disease* OR CAD) OR ab(coronary artery disease* OR CAD))) AND (ti(cost* OR economic*) OR ab(cost* OR economic*)) AND pd(20200827-20211231)	0

Database: Embase <1974 to 2020 Week 53>	
1	heartflow.ti,ab. (46)
2	non-invasive.ti,ab. (147414)
3	noninvasive.ti,ab. (129337)
4	or/2-3 (269724)
5	(fractional flow reserve or FFR).ti,ab. or fractional flow reserve/ (8811)
6	4 and 5 (1090)
7	CT-based FFR.ti,ab. (9)

8	FFRct.ti,ab. (370)
9	computed tomographic angiography/ or coronary CT angiograph*.ti,ab. (61617)
10	CCTA.ti,ab. (4180)
11	coronary angiograph*.ti,ab. or angiocardiography/ (107503)
12	nuclear myocardial perfusion*.ti,ab. (198)
13	SPECT.ti,ab. or single photon emission computer tomography/ (72240)
14	cardiac.ti,ab. or cardiac imaging/ (889001)
15	13 and 14 (9085)
16	myocardial perfusion scintigraph*.ti,ab. (1842)
17	MRI.ti,ab. (432859)
18	magnetic resonance imaging.ti,ab. or nuclear magnetic resonance imaging/ (889311)
19	17 or 18 (944468)
20	heart perfusion/ or heart muscle perfusion/ or perfusion*.ti,ab. or perfusion/ (242110)
21	stress.ti,ab. or stress/ (1002767)
22	19 and 20 and 21 (1789)
23	stress echocardiograph*.ti,ab. or stress echocardiography/ (10217)
24	myocardial perfusion imaging.ti,ab. or myocardial perfusion imaging/ (12321)
25	stress perfusion*.ti,ab. (1302)
26	dobutamine/ or dobutamine stress.ti,ab. (25574)
27	fractional flow reserve.ti,ab. or fractional flow reserve/ (7219)
28	FFR.ti,ab. (5730)
29	1 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 15 or 16 or 22 or 23 or 24 or 25 or 26 or 27 or 28 (211120)
30	(econom* or cost*).ti,ab. (1138731)
31	29 and 30 (5091)
32	limit 31 to english language (4723)
33	limit 32 to dc=20200831-20211231 (133)
34	(CAD or coronary artery disease).ti,ab. (160297)
35	33 and 34 (32)

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to January 04, 2021>	
1	heartflow.ti,ab. (14)
2	non-invasive.ti,ab. (86706)
3	noninvasive.ti,ab. (98297)
4	or/2-3 (182616)
5	(FFR or fractional flow reserve).ti,ab. or Fractional Flow Reserve, Myocardial/ (4698)
6	4 and 5 (622)
7	CT-based FFR.ti,ab. (6)
8	FFRct.ti,ab. (217)
9	fractional flow reserve.ti,ab. or Fractional Flow Reserve, Myocardial/ (3741)
10	4 and 9 (580)
11	coronary CT angiograph*.ti,ab. (1868)
12	CCTA.ti,ab. (1974)
13	coronary angiograph*.ti,ab. or Coronary Angiography/ (80507)

14	nuclear myocardial perfusion*.ti,ab. (101)
15	cardiac SPECT.ti,ab. (349)
16	myocardial perfusion scintigraph*.ti,ab. (1106)
17	magnetic resonance perfusion*.ti,ab. (357)
18	Magnetic Resonance Imaging/ or (MRI or magnetic resonance imaging).ti,ab. (571781)
19	17 or 18 (571908)
20	perfusion*.ti,ab. (163973)
21	stress.ti,ab. (767621)
22	19 and 20 and 21 (952)
23	stress echocardiograph*.ti,ab. or Echocardiography, Stress/ (5480)
24	Myocardial Perfusion Imaging/ or stress myocardial perfusion*.ti,ab. (5189)
25	stress perfusion*.ti,ab. (678)
26	Dobutamine/ or dobutamine stress.ti,ab. (7227)
27	fractional flow reserve.ti,ab. or Fractional Flow Reserve, Myocardial/ (3741)
28	FFR.ti,ab. (2977)
29	1 or 6 or 7 or 8 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 22 or 23 or 24 or 25 or 26 or 27 or 28 (97117)
30	(economic* or cost*).ti,ab. (846078)
31	29 and 30 (2257)
32	(CAD or coronary artery disease).ti,ab. (100809)
33	31 and 32 (842)
34	limit 33 to english language (769)
35	limit 34 to ed=20200831-20211231 (13)
36	limit 34 to dt=20200831-20211231 (14)
37	35 or 36 (23)
38	animals/ not humans/ (4739001)
39	37 not 38 (22)

Appendix E – References

E.1 Selected 8 studies among 63 studies supplied by the Company that were reviewed and excluded

Anastasius, M. (2021). The clinical utility of FFRCT stratified by age. J Cardiovasc CT, https://doi.org/10.1016/j.jcct.2020.08.006

Feuchtner, G. M., Langer, C., Senoner, T., Barbieri, F., Beyer, C., Bonaros, N., . . . Plank, F. (2020). Differences in coronary vasodilatory capacity and atherosclerosis in endurance athletes using coronary CTA and computational fluid dynamics (CFD): Comparison with a sedentary lifestyle. Eur J Radiol, 130, 109168. doi:10.1016/j.ejrad.2020.109168

Holmes, K. R., Fonte, T. A., Weir-McCall, J., Anastasius, M., Blanke, P., Payne, G. W., . . . Sellers, S. L. (2019). Impact of sublingual nitroglycerin dosage on FFRCT assessment and coronary luminal volume-to-myocardial mass ratio. Eur Radiol, 29(12), 6829-6836. doi:10.1007/s00330-019-06293-7

Kueh, S. H., Mooney, J., Ohana, M., Kim, U., Blanke, P., Grover, R., . . . Leipsic, J. A. (2017). Fractional flow reserve derived from coronary computed tomography angiography reclassification rate using value distal to lesion compared to lowest value. J Cardiovasc Comput Tomogr, 11(6), 462-467. doi:10.1016/j.jcct.2017.09.009

McNabney, C. G., Sellers, S. L., Wilson, R. J. A., Hart, S., Rosenblatt, S. A., Murphy, D. T., . . . Weir-McCall, J. R. (2019). Prognosis of CT-derived Fractional Flow Reserve in the Prediction of Clinical Outcomes. Radiology: Cardiothoracic Imaging, 1(2). doi:10.1148/ryct.2019190021

Packard, R. R., Li, D., Budoff, M. J., & Karlsberg, R. P. (2017). Fractional flow reserve by computerized tomography and subsequent coronary revascularization. Eur Heart J Cardiovasc Imaging, 18(2), 145-152. doi:10.1093/ehjci/jew148

E.2 Selected 73 studies from update searches done by NICE and EAC's Information Specialists

Included Reports

Argacha, J. F., Vandeloo, B., Mizukami, T., Tanaka, K., Belsack, D., Lochy, S., . . . Cosyns, B. (2019). FFRct analysis for screening of obstructive coronary artery disease: A propensity score adjusted study. European Heart Journal, 40(supplement1), 1672. doi:10.1093/eurheartj/ehz748.1038

Colleran, R., Douglas, P. S., Hadamitzky, M., Gutberlet, M., Lehmkuhl, L., Foldyna, B., . . . Byrne, R. A. (2016). An FFR CT diagnostic strategy vs. usual care in patients with suspected coronary artery disease planned for coronary angiography at German sites: Results of a subgroup analysis of the PLATFORM study. EuroIntervention, 175. Retrieved from http://www.pcronline.com/eurointervention/download_full_pdf.php?issue=AbstractsEuroPCR2016_issue&issue_id=171

Colleran, R., Douglas, P. S., Hadamitzky, M., Gutberlet, M., Lehmkuhl, L., Foldyna, B., . . . Byrne, R. A. (2017). An FFRCT diagnostic strategy versus usual care in patients with suspected coronary artery disease planned for invasive coronary angiography at German sites: One-year results of a subgroup analysis of the PLATFORM (Prospective Longitudinal Trial of FFRCT: Outcome and Resource Impacts) study. Open Heart, 4(1), e000526. doi:10.1136/openhrt-2016-000526

Curzen, N. P., Nolan, J., Zaman, A. G., Norgaard, B. L., & Rajani, R. (2016). Does the Routine Availability of CT-Derived FFR Influence Management of Patients With Stable Chest Pain Compared to CT Angiography Alone?: The FFRCT RIPCORD Study. JACC. Cardiovascular imaging, 9(10), 1188-1194. doi:10.1016/j.jcmg.2015.12.026

Curzen., Nicholas, Z., Stuart, B., Wilding, S., Hill, K., Shambrook, J., et al. Fractional Flow Reserve Derived from Computed Tomography Coronary Angiography in the Assessment & Management of Stable Chest Pain. TCT Connect 2020; 16 October 2020 [Slides].

Douglas, P. S., De Bruyne, B., Pontone, G., Patel, M. R., Norgaard, B. L., Byrne, R. A., . . . Platform, I. (2016). 1-Year Outcomes of FFRCT-Guided Care in Patients With Suspected Coronary Disease: The

PLATFORM Study. Journal of the American College of Cardiology, 68(5), 435-445. doi:10.1016/j.jacc.2016.05.057

Douglas, P. S., Pontone, G., Hlatky, M. A., Patel, M. R., Norgaard, B. L., Byrne, R. A., . . . Platform, I. (2015). Clinical outcomes of fractional flow reserve by computed tomographic angiography-guided diagnostic strategies vs. usual care in patients with suspected coronary artery disease: the prospective longitudinal trial of FFR(CT): outcome and resource impacts study. European Heart Journal, 36(47), 3359-3367. doi:10.1093/eurheartj/ehv444

Driessen, R. S., Danad, I., Stuijfzand, W. J., Raijmakers, P. G., Schumacher, S. P., van Diemen, P. A., . . . Knaapen, P. (2019). Comparison of Coronary Computed Tomography Angiography, Fractional Flow Reserve, and Perfusion Imaging for Ischemia Diagnosis. Journal of the American College of Cardiology, 73(2), 161-173. doi:10.1016/j.jacc.2018.10.056

Ihdayhid, A. R., Norgaard, B. L., Gaur, S., Leipsic, J., Nerlekar, N., Osawa, K., . . . Ko, B. S. (2019). Prognostic Value and Risk Continuum of Noninvasive Fractional Flow Reserve Derived from Coronary CT Angiography. Radiology, 292(2), 343-351. doi:10.1148/radiol.2019182264

Ihdayhid, A. R., Norgaard, B. L., Khav, N., Gaur, S., Leipsic, J., Nerlekar, N., . . . Ko, B. (2019). Prognostic value and incremental benefit of ischaemic myocardial burden subtended by non-invasive CT-derived fractional flow reserve (FFRCT) significant stenoses. European Heart Journal, 40(supplement1), 1305. doi:10.1093/eurheartj/ehz748.0716

Jensen, J. M., Botker, H. E., Mathiassen, O. N., Grove, E. L., Ovrehus, K. A., Pedersen, K. B., . . . Norgaard, B. L. (2018). Computed tomography derived fractional flow reserve testing in stable patients with typical angina pectoris: Influence on downstream rate of invasive coronary angiography. European Heart Journal Cardiovascular Imaging, 19(4), 405-414. doi:10.1093/ehjci/jex068

Ko, B. S., Linde, J. J., Ihdayhid, A.-R., Norgaard, B. L., Kofoed, K. F., Sorgaard, M., . . . Seneviratne, S. K. (2019). Non-invasive CT-derived fractional flow reserve and static rest and stress CT myocardial perfusion imaging for detection of haemodynamically significant coronary stenosis. The international journal of cardiovascular imaging, 35(11), 2103-2112. doi:10.1007/s10554-019-01658-x

Ko, B. S., Wong, D. T. L., Norgaard, B. L., Leong, D. P., Cameron, J. D., Gaur, S., . . . Seneviratne, S. K. (2016). Diagnostic Performance of Transluminal Attenuation Gradient and Noninvasive Fractional Flow Reserve Derived from 320-Detector Row CT Angiography to Diagnose Hemodynamically Significant Coronary Stenosis: An NXT Substudy. Radiology, 279(1), 75-83. doi:10.1148/radiol.2015150383

Lu, M. T., Ferencik, M., Roberts, R. S., Lee, K. L., Ivanov, A., Adami, E., . . . Hoffmann, U. (2017). Noninvasive FFR Derived From Coronary CT Angiography: Management and Outcomes in the PROMISE Trial. JACC. Cardiovascular imaging, 10(11), 1350-1358. doi:10.1016/j.jcmg.2016.11.024

Matsumura-Nakano, Y., Kawaji, T., Shiomi, H., Kawai-Miyake, K., Kataoka, M., Koizumi, K., . . . Kimura, T. (2019). Optimal Cutoff Value of Fractional Flow Reserve Derived From Coronary Computed Tomography Angiography for Predicting Hemodynamically Significant Coronary Artery Disease. Circulation. Cardiovascular imaging, 12(8), e008905. doi:10.1161/circimaging.119.008905

Matsumura-Nakano, Y., Shiomi, H., Kawaji, T., Kataoka, M., Miyake-Kawai, K., Taylor, C. A., . . . Kimura, T. (2017). Optimal cut-off value for fractional flow reserve derived from coronary computed tomography angiography for predicting hemodynamically significant coronary artery disease. Circulation, 136(supplement1). Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed18&NEWS=N&AN=619985752

Norgaard, B. L., Gormsen, L. C., Botker, H. E., Parner, E., Nielsen, L. H., Mathiassen, O. N., . . . Jensen, J. M. (2017). Myocardial Perfusion Imaging Versus Computed Tomography Angiography-Derived Fractional Flow Reserve Testing in Stable Patients With Intermediate-Range Coronary Lesions: Influence on Downstream Diagnostic Workflows and Invasive Angiography Findings. Journal of the American Heart Association, 6(8). doi:10.1161/jaha.117.005587

Norgaard, B. L., Hjort, J., Gaur, S., Hansson, N., Botker, H. E., Leipsic, J., . . . Jensen, J. M. (2017). Clinical Use of Coronary CTA-Derived FFR for Decision-Making in Stable CAD. JACC. Cardiovascular imaging, 10(5), 541-550. doi:10.1016/j.jcmg.2015.11.025

Osawa, K., Miyoshi, T., Miki, T., Koide, Y., Kawai, Y., Ejiri, K., . . . Ito, H. (2017). Coronary lesion characteristics with mismatch between fractional flow reserve derived from CT and invasive catheterization in clinical practice. Heart and Vessels, 32(4), 390-398. doi:10.1007/s00380-016-0892-0

Pontone, G., Baggiano, A., Andreini, D., Guaricci, A. I., Guglielmo, M., Muscogiuri, G., . . . Pepi, M. (2019). Stress Computed Tomography Perfusion Versus Fractional Flow Reserve CT Derived in Suspected Coronary Artery Disease: The PERFECTION Study. JACC. Cardiovascular imaging, 12(8pt1), 1487-1497. doi:10.1016/j.jcmg.2018.08.023

Rabbat, M., Leipsic, J., Bax, J., Kauh, B., Verma, R., Doukas, D., . . . Lopez, J. (2020). Fractional Flow Reserve Derived from Coronary Computed Tomography Angiography Safely Defers Invasive Coronary Angiography in Patients with Stable Coronary Artery Disease. J Clin Med, 9(2). doi:10.3390/jcm9020604

Rizvi, A., Hartaigh, B. O., Knaapen, P., Leipsic, J., Shaw, L. J., Andreini, D., . . . Min, J. K. (2016). Rationale and Design of the CREDENCE Trial: computed TomogRaphic evaluation of atherosclerotic DEtermiNants of myocardial IsChEmia. BMC Cardiovascular Disorders, 16(1), 190. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med13&NEWS=N&AN=27716131

Sand, N. P. R., Veien, K. T., Nielsen, S. S., Norgaard, B. L., Larsen, P., Johansen, A., . . . Jensen, L. O. (2018). Prospective Comparison of FFR Derived From Coronary CT Angiography With SPECT Perfusion Imaging in Stable Coronary Artery Disease: The ReASSESS Study. JACC. Cardiovascular imaging, 11(11), 1640-1650. doi:10.1016/j.jcmg.2018.05.004

Shiono, Y., Matsuo, H., Kawasaki, T., Amano, T., Kitabata, H., Kubo, T., . . . Akasaka, T. (2019). Clinical impact of coronary computed tomography angiography-derived fractional flow reserve on Japanese population in the ADVANCE registry. Circulation Journal, 83(6), 1293-1301. doi:10.1253/circj.cj-18-1269

Unpublished audit from one of the experts.

Excluded Reports

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References

Please see the supplementary excel document attached titled MTG32 Publication update 9.20 final.

Appendix 1 –Company update

- **National Institute for Health and Care Excellence**

Medical Technologies Evaluation Programme

Information request from the company

MTEP review of MTG32: HeartFlow FFRCT for estimating fractional flow reserve from coronary CT angiography

Review of MTG32: HeartFlow FFRCT for estimating fractional flow reserve from coronary CT angiography

The original guidance was issued in February 2017

The review date for this guidance is August 2020

Company Update

1.	Changes in the technology: MTG32 was on HeartFlow FFRCT version 1.7 HeartFlow continues to increment its software with monthly releases to address minor feature updates, as well as security and efficiency improvements. Currently, the HeartFlow FFRCT version 2.56 is in production.
a.	Is the technology still available to the NHS in the UK?

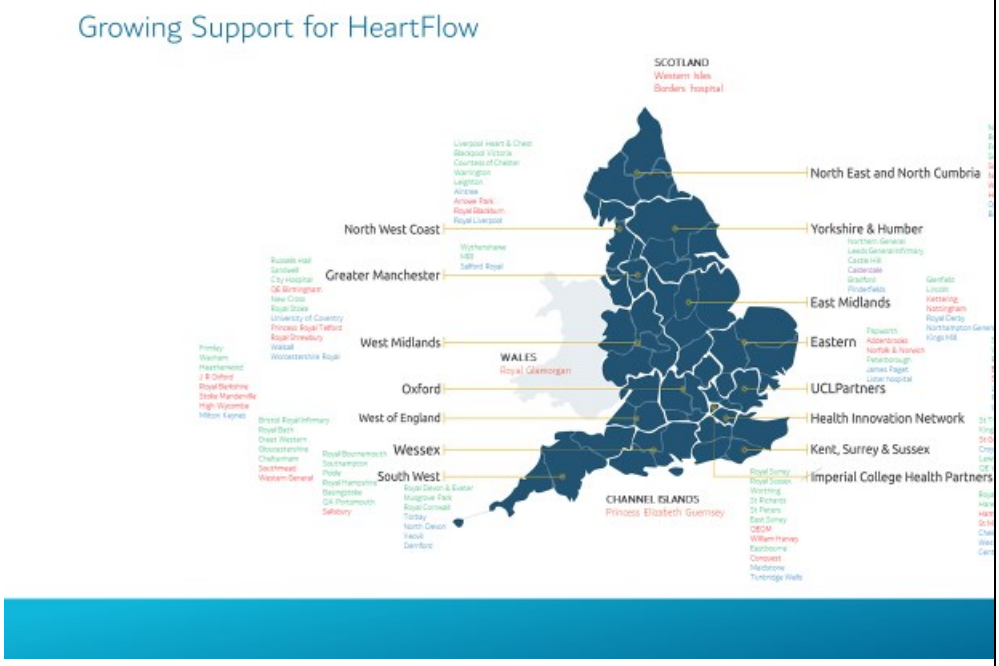
	Yes, the technology is still available to NHS hospitals. In 2018 HeartFlow was selected for the ITP programme, which enables NHS England trusts to adopt innovations and new technologies by removing financial and procurement barriers. HeartFlow was identified as an Accelerated Access Collaborative Rapid Uptake Product late 2018 and the ITP funding was extended for 2019 and 2020. In 2020 the eligibility criteria for a site to utilise the ITP scheme to procure HeartFlow at no cost was revised, and now a site is eligible if they conduct 300> CCTAs per year. [redacted]
b.	If the technology has changed, what it the latest current version and when was this model first marketed in the UK? Please provide technical specifications which show the differences. The current version is 2.56, which was released August 19 2020. It is not significantly different than the 1.7 version, but over the course of several releases security and usability updates have been added. One of the benefits of HeartFlow's business model is that we provide access to a continuously improving product. This is because HeartFlow invests in important product developments and enhancements that deliver improved performance regularly as follows: ● Security updates include multi-factor authentication as well as ISO 27001 and HITRUST certification. ● Monthly software revisions that incorporate feedback from providers using HeartFlow so we can regularly address challenging clinical situations, enhance the user experience and maintain a high level of data security. ● Compatibility with regular updates to software with which HeartFlow interacts, such as new versions of Windows, EHRs, iOS. ● New usability improvements such as: - Improving the turnaround time from average of 48 hours to average of 6 hours - Upon request, providing a Left Coronary Artery system analysis only when motion or artefact in the Right Coronary Artery would otherwise prohibit case processing

	- Providing analyses for vessels without stents, when there is a stent present in another vessel - HeartFlow mobile: use of the HeartFlow Analysis on mobile iOS platforms to enhance provider use and facilitate patient education (at present, 11 NHSE hospitals have security approval for mobile use) - A planning feature that allows the user to explore the model we already provide and simulate opening of lesions to assess the potential FFRct changes when opened. - HeartFlow Care Teams: designates a team of clinicians to interact with the HeartFlow Analysis for shared patient management - Electronic health record (EHR) integration: easier incorporation of the HeartFlow Analysis into each patient's records (still being rolled out across NHSE hospitals) - Display angiographic projection angles as the FFR_{CT} model is rotated (available on web and mobile interfaces)
c.	Does the new model perform the same function and use the same mode of action as the technology in MTG32? Yes.
d.	Does the new model have a new CE mark? No. The original CE mark (for version 1.x) was updated to include 2.x.
e.	Has the cost of the technology changed since the original guidance? Please give details (this can be kept commercial-in-confidence). The current price for the HeartFlow Analysis is £700 per analysis. [redacted]

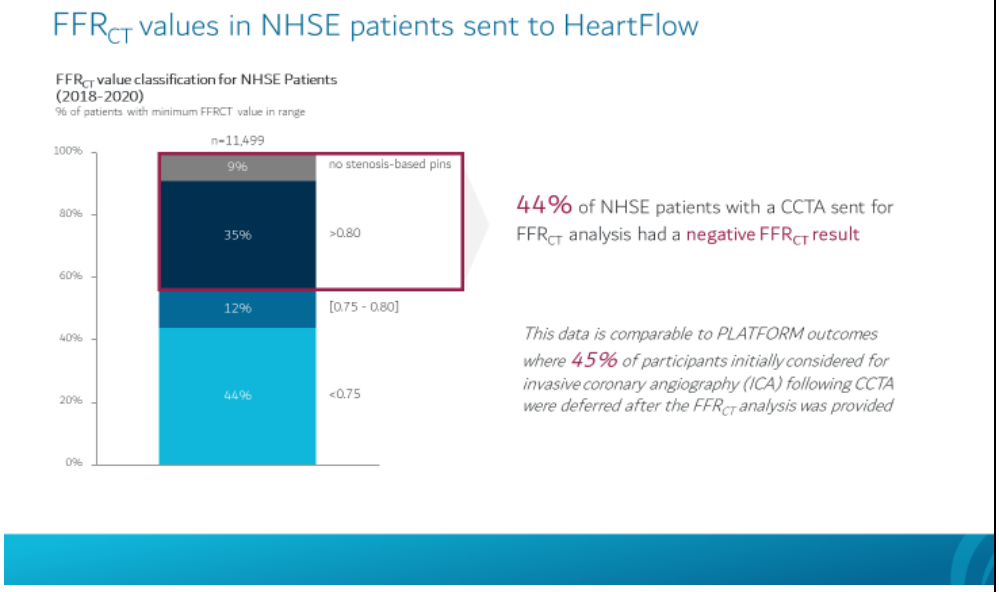
	HeartFlow has also provided an update spreadsheet outlining the changes in tariffs used in the economic modelling from the 2016 submission. Please see attached Parameter updates to NICE modelling_vf *xlsx*

2	Is the company aware of any new clinical evidence on the use of HeartFlow FFRCT, available since the original evaluation (i.e. after April 2016)? If new evidence is available, please give brief details, a reference for published evidence or a title and one line description for unpublished evidence – please complete a form in appendix 1 for each piece of unpublished evidence.	Please see attached excel titled MTG32.Publication update.9.20.Final *xlsx*

3	Is the company aware of any adoption or usage data (such as audit) from the NHS or elsewhere? Please give details where possible, this can be kept	**Summary of site adoption of HeartFlow** 56 NHS England hospitals actively use HeartFlow at present. As of August 27, 2020, physicians have chosen the HeartFlow Analysis for NHSE patients a total of 12970 times. There are an additional 28 NHSE hospitals implementing. We are also working with 1 hospital in Wales, 2 hospitals in Scotland, and 1 hospital in the Channel Islands to expand use of HeartFlow outside of NHS England.

	commercial-in-confidence as required.	 **<u>Monthly key performance indicator reporting</u>** As part of the ITP Programme partnership with the NHSE, HeartFlow tracks monthly progress across all NHSE sites and collecting key performance indicators. These include: • # of cases sent to HeartFlow • Turnaround time • Complaint rates • Duration of onboarding • Invasive Coronary Angiography referral decisions following HeartFlow • Acceptance rates by trusts • COVID recovery progress for FFRct analysis by trust

		Linked is a copy of the most recent ITP report produced for the NHSE for July 2020. Also provided as an attachment titled HeartFlow NHSE ITP Report July 20 *pdf* **Summary of FFRct values in NHSE patients sent to HeartFlow** We have queried our data on cases submitted to HeartFlow for FFR_{CT} analysis from 56 UK sites over the past 24 months. We are able to assess the number of cases which have at least one coronary artery narrowing of > 30% by our measurements, and we also are able to stratify the population by the lowest FFR_{CT} value associated with a coronary artery narrowing. In the last 24 months, there were ~11,500 UK patients sent to HeartFlow. Of these: • 91% of patients had at least one stenosis > 30% by our measurement; the remaining 9% of patients can likely be deferred from invasive testing or treatment • 35% of patients with at least one coronary artery narrowing of > 30% by our measurements had no FFR_{CT} value ≤ 0.80; a negative FFR_{CT} result (no FFR_{CT} value ≤ 0.80) can aid physicians in deciding to defer invasive testing or treatment safely • 44% of patients had at least one FFR_{CT} value ≤ 0.75; a positive FFR_{CT} result (at least one FFR_{CT} value ≤ 0.75) can aid physicians deciding to proceed with invasive testing or treatment The implications of this across the NHSE are that among patients with Coronary Computed Tomography Angiography (CCTA) who were sent for FFR_{CT} analysis, 44% had a negative FFR_{CT} result. This is perfectly in line with the outcomes of the PLATFORM study in which approximately 45% of participants who would have been referred for invasive coronary angiography (ICA) following CCTA were deferred after the FFR_{CT} analysis was provided.



Single-center experiences

There have been several single-center experiences reported by NHSE centers. The Table below summarises the key findings and we have appended copies of each report as it has appeared online and/or at a medical conference.

Author	Centre	No. of FFRCT cases	Key Findings	Attachment
Beattie et al.	The Newcastle Upon Tyne Hospitals Foundation Trust	89	• Post implementation of HeartFlow, the proportion of patients getting cardiac CT as a first line investigations	Newcastle NICE publication Also provided

						increased (by ~20%), while other first line functional and invasive investigations decreased • HeartFlow use led to reduced requirement for and provision of other non-invasive functional tests (DSE, stress cMRI, NMPS) • 13/15 (86.7%) patients who had invasive angiography following HeartFlow assessment were re-vascularised compared with 8 of 16 patients (50%) following cardiac CT alone prior to HeartFlow availability • There was better adherence to guidelines and cath lab utilisation without	as an attachment

					• delays in care or increase in clinic appointments • Initial results from patient survey (n=25) indicate positive feedback across dimensions rating: time from clinical appointment to CT scan, maintaining dignity, discomfort during test, willingness to have test again	
		Hudson et al.	Royal United Hospitals, Bath	49	• FFR_{CT} changed multidisciplinary consensus management in 67% of patients • 43% of ICAs avoided • 14 patients referred for ICA, and all 14 required Percutaneous Coronary Intervention (PCI) (Ratio: 100%)	Bath NICE publication Bath Poster Also provided as attachments

					• There was a significant reduction in waiting time to next investigation and definitive treatment • No adverse events were observed in patients deferred from ICA based on FFR_{CT}	
		Fitzpatrick et al.	Bristol Heart Institute	20	• Following the HeartFlow Analysis, 70% patients were discharged without additional invasive and/or non-invasive testing • 5 (25%) patients were referred for ICA, and all 5 required PCI (Ratio: 100%)	Bristol JCCT Abstract Bristol Poster Also provided as attachments

4	Does the company have a list of NHS users? If so, could you please append a list to this	Across 56 NHSE hospitals, there are 742 clinicians that have a HeartFlow account to interact with the

	submission, this can be kept commercial-in-confidence as required	HeartFlow Analysis. We are happy to provide the full list of clinicians, upon request. Linked is a list of key clinician contacts for all NHSE sites currently or interested in using HeartFlow. Also provided as an attachment titled List of key clinician contacts for all NHSE sites currently or interested in using HeartFlow *pdf*
5	Has the technology added new indications or is now used in new applications not covered by the original guidance? If so, please give details.	At this time there are no new indications or applications not covered by the original guidance. However, there is an increasing body of published data, which HeartFlow hopes to leverage in the future, demonstrating applicability for several previously unevaluated and expanded populations, e.g., patients with BMI > 35 and Cardiac clearance for peripheral vascular disease patients.

Additional information

6	Any other relevant information supporting the use of the technology.	The innovative unique clinical value of the HeartFlow Analysis means that significant investments must be made to advance the capabilities of healthcare providers across the country. The introduction of the HeartFlow Analysis means enhancing the whole diagnostic pathway for stable chest pain, from increasing the quality of every single cardiac CT scan all the way to building a better patient experience. This requires strong regular partnership between NHSE hospitals and the HeartFlow team to provide ongoing support and education. When an NHS facility begins to build a CCTA + HeartFlow program, our team partners with hospital teams via field-based District Managers, CT Applications Specialists, Technical Solutions Engineers and other team members. These team members provide experience, resources, and expertise to train sites and enable program implementation during each site's 90-day onboarding and beyond. These include: ● **Initial Clinical Implementation Support**: Site-customised best-in-class protocols, didactics, and proctoring are delivered on topics ranging from clinical standards to CCTA standards to patient workflows. Additionally, world-renowned

		clinicians with deep experience using the HeartFlow Analysis are available to serve as mentors during this clinical implementation. ● **Initial Technical Implementation Support**: Throughout the IT and IG approval and installation process, HeartFlow Technical Solutions Engineers partner to ensure successful integration of secure, custom IT tools within the hospital system that enable safe data transmission to HeartFlow's cloud infrastructure across England. ● **Ongoing CT Applications and Case Support**: HeartFlow CT Applications team members are assigned to each NHSE hospital and provide ongoing clinical support to facilitate high processing rates for those CCTA submitted for a HeartFlow Analysis. Customer Case Support team members are available to resolve concerns and ensure clinician satisfaction. ● **Ongoing Technical Support**: HeartFlow continuously monitors all technical connection points within NHSE hospitals on a 24/7/365 basis. Whether occurring within the NHSE facility's system or related to HeartFlow's regular software improvements, any concerns are investigated without delay to ensure consistent availability and security. *Note: Typically, imaging vendors can charge up to £15,000 per site and £2,000 per day for implementation and on-site support. Currently, HeartFlow provides these services at no-cost to NHSE Hospitals.* Beyond the on-site support at each NHSE facility, HeartFlow delivers training to clinicians across the country, whether independently, in partnership with AHSNs, or in conjunction with clinical societies such as the British Society of Cardiovascular Imaging (BSCI), the British Cardiovascular Intervention Society (BCIS) and others national and global societies. Educational events in 2019 have reached hundreds of interventional cardiologists, cardiac imagers (both cardiologists and radiologists), and radiographers with a focus on

		delivering better clinical care through the adoption of NICE CG95.These include: ● **Professional Education Programs** ○ **Case Review with Multi-disciplinary team**- Upon completion of the first 20 FFR_{CT} cases, HeartFlow will meet with the Trust to review the cases. During this time, the team will go through and review the quality of CT scans and discuss if there are opportunities to improve or change CT acquisition protocols. The case review session enables all stakeholders involved in the care of patients to better understand how the HeartFlow Analysis fits into their pathway and fosters stronger collaboration between members of the entire Heart Team ○ **Radiographer Education Programs** ■ Physician-led videos and live / archived webinars, or on-site instructor-led education programs providing an overview of $FFR_{CT,}$ as well as CCTA preparation, acquisition, and post-processing techniques. Physicians can receive SOR 2.5 or 5 credits category A ASRT through attending webinars. ■ HeartFlow also offers a National Radiographer Training Day, which includes an overview of CT quality, the importance of heart rate control and imaging techniques. ○ **Radiologist and Cardiologist Education Programs** ■ HeartFlow conducts training to all clinical users at the time of onboarding and on an ongoing basis.

		■ All users registered with HeartFlow receive invitations to FFR_{CT} seminars held at educational symposia (European Society of Cardiology annual meeting, SCCT annual meeting, etc.) Note: registration is required for use of the technology. ■ HeartFlow routinely schedules and offers peer led conference calls and discussions as part of a user group initiative. User groups will be established in the UK to facilitate clinicians sharing of best practices around the use of technology in decision making and patient care. ■ HeartFlow webinars are eligible for physicians to receive Royal College of Radiologist (RCR) credit ● **Peer-to-Peer Programs** ○ **Regional Meetings** ■ HeartFlow works with key clinical leaders in Trusts to organise regional meetings. These meetings serve to bring together clinicians across multiple trusts to engage in peer-to-peer discussions on topics such as CT quality, training, and case interpretation. During the regional meetings, clinicians often share cases together and share best practices. ○ **Hospital "mentors"** ■ When a hospital is considering adopting HeartFlow, there are often questions that are best answered by a hospital that has already adopted HeartFlow. As such, we often pair up hospitals that are considering adopting HeartFlow with a more experienced hospital

		as a “mentor”. The experienced hospital can provide perspective on their implementation process, any changes they had to make to workflow, training of heart team and any tips or tricks which may make the adoption process smoother. ● **Patient Education** ○ As part of the HeartFlow training, physicians are encouraged to share the HeartFlow Analysis with their patients. Being able to see the 3D model helps a patient better understand their diagnosis and helps with compliance or adherence to recommended treatment or lifestyle changes

Declaration

Company representative:	Campbell Rogers
Position:	Chief Medical Officer
Date:	3 September 2020

Appendix 1

Unpublished study details	
Should this study be seen as: publicly available, academic-in-confidence, commercial-in-confidence? Is there a planned publication date?	
Study details [e.g. Trial code if registered as a clinical trial, authors, title, details of funding]	
Design [e.g. was it randomised, was there a control group or comparator technology, was it a post-marketing study]	

Assigned interventions [how was the technology used, how often]	
Participants [how many people were in the study, how were they selected, which indication did they have, which setting were they in e.g. hospital, GP etc]	
Follow-up period	
Primary outcome [what was the main symptom or parameter measuring the effect of the technology]	
Secondary outcome(s) [any other symptoms, parameters measured]	
Key results – efficacy	
Key results – safety [were there any side effects or adverse events]	
Information source [e.g. webpage or link to details of the study, if available]	
Any other comments	

Thank you. Please return the completed form by NICE Docs

For more information about how we process your data please see our privacy notice.

Appendix 2 – supporting information

Relevant Institute work

In progress

None identified

Appendix 5 – Initial review

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Health Technology Evaluation

MTG Review – Initial information

Review of MTG32 HeartFlow FFRCT for estimating fractional flow reserve from coronary CT angiography

This guidance was issued in February 2017.

The review date for this guidance is August 2020.

Current guidance

1.1 The case for adopting HeartFlow FFRCT for estimating fractional flow reserve from coronary CT angiography (CCTA) is supported by the evidence. The technology is non-invasive and safe, and has a high level of diagnostic accuracy.

1.2 HeartFlow FFRCT should be considered as an option for patients with stable, recent onset chest pain who are offered CCTA as part of the NICE pathway on chest pain. Using HeartFlow FFRCT may avoid the need for invasive coronary angiography and revascularisation. For correct use, HeartFlow FFRCT requires access to 64-slice (or above) CCTA facilities.

1.3 Based on the current evidence and assuming there is access to appropriate CCTA facilities, using HeartFlow FFRCT may lead to cost savings of £214 per patient. By adopting this technology, the NHS in England may save a minimum of £9.1 million by 2022 through avoiding invasive investigation and treatment**Summary of company update (see Appendix 1)**

Changes in the technology: The technology has undergone incremental software updates. The current version of the technology is HeartFlow FFRCT version 2.56 which was released in August 2020. The company state the current version 2.56 is not significantly different from version 1.7. The changes made primarily address security updates, compatibility updates and user experience improvements based on user feedback. New features of the technology include:

Faster turnaround time from 48 hours to 6 hours

Providing left coronary artery system analysis only when motion or artefact in the right coronary artery would otherwise prohibit case processing
Providing analysis for vessels without stents, when there is a stent present in another vessel
User features: use of HeartFlow FFRCT on mobile ISO provider, treatment planning features, integration with electronic health records and shared patient management updates, increased options of model viewing

There have been no changes to the function and mode of action of the technology. The CE mark of the technology has been updated to include the above changes.

Proposed expansion of the scope : No changes to the scope proposed.

Changes to the care pathway or comparator

The NICE pathway is chest pain.

There have been no changes to the NICE clinical guideline recent-onset chest pain of suspected cardiac origin: assessment and diagnosis (CG95) since the publication of MTG32 HeartFlow FFRCT.

Evidence

a. Other new evidence

In response to NICE's request for information, the company submitted 63 studies in total. The studies are listed in a supplementary excel document included in the company submission titled MTG32 Publication update 9.20 final. The study publication dates range from 2016 to 2020. The company also included details of 3 non-peer-reviewed single centre experiences including 158 participants, abstracts are available online and links are accessible through the company submission in Appendix 1.

Five clinical experts that NICE approached as part of the guidance review process reported that new evidence was available. One expert stated that there are approximately 150 manuscripts since 2017 on the use of FFRCT. One expert reported unpublished audit data from 2018 reporting data from before and after the introduction of FFRCT. The

data reports that the introduction of FFRCT did not impact the proportion of patients that received invasive angiography.

The search strategy used in the original guidance for HeartFlow FFRCT was re-run by information services with dates ranging from February 2017 to September 2020. The searches found 3617 results.

b. Results from MTEP research commissioning

Not applicable. No research was commissioned.

Cost case

There has been no change to the cost of the technology since the publication of MTG32, however, changes in comparator costs mean the cost case is no longer valid. Costs were updated for cardiac catheterisation and the following imaging modalities:

Complex CT
Complex Echocardiogram
Single photon emission CT (SPECT)
Cardiac magnetic resonance (CMR)

Additional information

The company's updated information states that 56 NHS England hospitals use HeartFlow FFTCT. An additional 28 hospitals in NHS England are implementing the technology. In 2018, HeartFlow FFRCT was selected to be included in the Innovation and Technology payment (ITP) programme, as a result trusts have adopted FFRCT at no cost. The ITP funding was extended for 2019 and 2020. In 2020, eligibility criteria ruled that trusts needed to complete more than 300 CCTAs pre year to secure funding for Heartflow FFTCR.

Six clinical experts responded to NICE's request for information. Four of clinical experts have direct involvement in the use of HeartFlow FFTCR or refer patients for its use. The experts had conflicting opinions about the adoption and usefulness of the technology. All experts agree that the technology is used in a secondary care cardiology setting, however two experts believe the technology is being widely used across the NHS, one believes that only a small number of centres use the technology and 2 experts do not have access to the technology locally. Two experts indicate that a range of different imaging modalities are available to cardiologists and the choice of imaging investigations is at the discretion of the reporting radiologist or cardiologist. All of the experts agree that there may be enough new evidence to

impact the recommendation, four of the experts specially reference the cost case and want to see more evidence to support the cost savings reported in the guidance.

Recommendation

There is a substantial amount of new evidence since the publication of MTG32 HeartFlow FFRCT. Changes to comparator costs invalidate the cost case reported in the original guidance. Due to these updates, MTEP technical team recommend that the GE proposal is prepared by an EAC.

Contributors to this paper:

Technical Lead:	Rebecca Owens	
Technical Adviser:	Christopher Pomfrett	date: 12/10/20

References

Please see the supplementary excel document attached titled MTG32 Publication update 9.20 final.