National Institute for Health and Care Excellence

External Assessment Centre correspondence

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

The purpose of this table is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the sponsors' original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the sponsor
b) need to check "real world" assumptions with NICE's expert advisers, or
c) need to ask the sponsor for additional information or data not included in the original submission, or
d) need to correspond with an organisation or individual outside of NICE

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is made available to MTAC. The table is presented to MTAC in the Assessment Report Overview, and is made available at public consultation.

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2 & 3	**Teleconference with Sponsor on 30.03.15**	Multiple Questions –Teleconference notes & sponsor's written response included in *Appendix 1*.	No further action required.
3	**Email from Sponsor on 02.04.15**	Raw data from meta-analysis attached (*Appendix 2*).	No further action required.
2 & 3	**Email to Expert Advisers on 17.04.15:** **1.** In studies on HeartFlow, exclusion criteria tend to include: • Previous CABG; • Previous PCI; • Acute coronary syndrome at presentation. Does this effectively limit the study population to people who have never been diagnosed with CAD, or might it also include people who have been diagnosed with CAD, but are treated with medication only? **2.** Does a previous history of CAD (including previous PCI or CABG) in a patient presenting with stable chest pain mean that they will automatically be categorised as having a high pre-test likelihood of CAD (defined according to NICE CG95 pathway)?	**Reply from <u>Keith Oldroyd</u> received on 19.04.15:** **1.** Well first of all one might ask how you know anyone has definite CHD without some form of angiography? Typical angina?? Anyway can certainly be used in patients with known CHD on medical therapy but generally if they have worsening symptoms I would go straight to invasive angiography. **2.** As above – YES. **3.** Vessel based as will potentially influence decision on need for revasc. **4.** Yes but then they should clearly get follow on PCI if appropriate to avoid multiple procedures. **5.** Yes there is a grey-zone between 0.75-0.80. Using FFR 0.80 gives the patient the benefit of the doubt and means that there is over-treatment. However because of FAME and FAME 2 there is currently no going back from 080 to 0.75. They may change in future.	No further action required.

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	3. What is the clinical importance of choosing patient-based rather than vessel-based FFRct analysis? Which one is preferred for assessments of the diagnostic accuracy of FFRct? **4.** If vessel-based diagnostic accuracy is low (or not higher than patient-based) then a patient will need to be referred for invasive FFR in order to confirm the FFRct findings before a decision is made regarding which coronary artery should be treated. Do you agree with this statement? **5.** The established cut-off for an abnormal FFR varies in the literature between <0.8 and <0.75. What is the clinical significance of an FFR<0.75 versus an FFR<0.8? Is there a 'grey area' for FFR values and, if so, how does this impact upon patient management? **6.** Is there a percentage of luminal stenosis (as measured by CCTA or ICA) above and below which you would not proceed to perform invasive FFR measurements? Is it true that in clinical practice you will only measure FFR in vessels with intermediate stenosis and that a vessel with >75% stenosis is considered a priori severe enough to cause ischaemia?	**6.** NO – DEFINITELY NOT. What does 75% mean anyway. That's the whole point. CTCA over-reads %DS. Even invasively 75% is meaningless unless we all use high quality QCA which we don't. Even some lesions with > 90%DS can have negative FFR's. We are nowhere near being able to send a patient for CABG on the basis of CTCA plus ctFFR. The value of ctFFR would be in a stenosis thought to be "significant" on CTCA with a clearly negative ctFFR. Even then I suspect most people will still do ICA and invasive FFR until they become confident about concordance. **7.** This is mixing up the presence of CHD with the presence of myocardial ischaemia. CHD without ischaemia is extremely common and requires medical therapy but not revascularisation. **Reply from <u>Nick Curzen</u> received on 20.04.15:** **1.** There will be a significant minority of patients who will not be suitable for FFRCT… certainly it will not be ALL patients with previous CABG or PCI and is not likely to be all with ACS. But probably at least 10% will not be suitable for some reason such as fast AF/ extensive previous surgery/ inability to receive beta blockers etc. **2.** Yes. but, ultimately, FFRCT will be tested in all comers and will not be restricted to low pre-test likelihood groups. **3.** FFRCT will only be useful if it allows both patient- and lesion-based assessment. It will be able to do this… I am presenting the FFRCT RIPCORD study that does this at EuroPCR in May 15.	

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	7. A number of studies (prospective and retrospective) have not used the pre-test likelihood of CAD as an inclusion criterion for patient enrolment. Instead, some of them use the percentage of luminal narrowing (for example 50-70% or 30-90%). Do you consider there to be an association between luminal narrowing and pre-test likelihood of CAD given that previous studies have shown that there is a mismatch between degree of narrowing and functional significance (Kern et al. 2006, Christou et al. 2007)?	**4.** In the near future, I agree with this statement, but I fully expect further research to change this in the future. **5.** The grey area is a much talked about, but seldom relevant entity. The current recommended cut off is 0.8 and very few patients actually fall close to this level. The issue of the grey area is to treat patients according to their clinical history etc. **6.** No… the clinical trials are clearly showing that you cannot judge lesions in 1/3 of cases from an angiogram as to whether they are causing ischaemia. See data in *Appendix 3*. There is now a very strong case that all vessels require assessment of physiology unless >90% **7.** See above. If further validated appropriately, FFRCT should allow for almost universal assessment of suitable patients for anatomy and physiology, and thereby make many of our current tests obsolete. **Reply from <u>Andreas Baumbach</u> received on 21.04.15:** **1.** There could be a role for CABG and previous PCI patients, however, this would need to be verified. **2.** Yes **3.** FFR is vessel based **4.** Yes	

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		5. There is a grey zone. For now the relevant cutoff is 0.8 **6.** Only subtotal lesions in symptomatic patients **7.** Strictly speaking if there is a lesion then patients have CAD, although they may be asymptomatic **Reply from <u>Ian Purcell</u> received on 17.05.15:** **1.** CABG and PCI (stented) treated arteries cannot be analysed by HeartFlow yet due to technical limitations of the fluid dynamic model. Stents may be overcome by next generation software. Medically treated patients with known CAD possible. ACS excluded as not yet tested in this population but should be the same in principle comparing HeartFlow with invasive assessment in ACS patients when/if done. **2.** Yes but tautological since 100% likelihood of CAD as known CAD and may not help with predicting whether pain is cardiac or non-cardiac. Known treated CAD is different group so prevalence risk score not helpful in determining likelihood of obstructive CAD. Studying this group has impact on test accuracy by altering Bayes' theorem. **3.** Vessel based better since we using data to plan revascularisation strategy. **4.** Broadly yes. In terms of planned PCI not as issue since the invasive assessment can be carried out at the same time as PCI but a significant barrier to planning CABG without confirmation of vessels	

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		to be treated by conventional invasive assessment. I would not proceed to revascularisation at present using FFRct alone without invasive confirmation. **5.** FFR<0.80 currently adopted cut off for invasive FFR. This will reduce false negatives in comparison with <0.75 used in earlier studies. **6.** No absolute cut off since FFR tells us that diameter stenosis is a poor guide to physiological significance. However in practice FFR most used for intermediate stenoses 30-80%. It should be noted that only stenosis of >30% in CT angiography were analysed by HeartFlow in the main published studies and in Platform. **7.** The predictive accuracy of a new method of analysis will be influenced by whether subjects enrolled by pre-test likelihood versus lumen data by altering disease (coronary stenosis) prevalence. Many patients with a high pre-test likelihood will still not have a lumen narrowing.	
2 & 3	**Email to Sponsor on 23.04.15:** **1.** Would you be able to provide KiTEC with the criteria used for the methodological quality assessment of the 22 studies included in the meta-analysis? In this context, KiTEC is referring to the requirements needed to be fulfilled by each study in order to score positive,	**Reply received 29.04.15** **1.** Please find attached the QUADAS-2 criteria and a background document on how to use the QUADAS-2 scoring system to define a study as positive, negative or unsure for risk of bias. (Attached documents: 'Background information QUADAS-2' and 'QUADAS-2 scoring system' – *Appendix 4*) The criteria used for scoring risk of bias in each study were in accord with the guidelines provided in the Background Document.	No further action required.

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	negative or unsure for risk of bias. KiTEC is aware that the sponsor has already provided the scoring for the methodological quality assessment in their document *MT252_Questions to Sponsor - 20150331 Final (Appendix D)*, however, this document does not include the criteria used. **2.** As part of their methodological quality assessment *(Appendix D)* the sponsor has categorised the studies included in their systematic review as intermediate or high pre-test likelihood. Given that most of the studies did not explicitly report that they have recruited patients based on their pre-test likelihood of CAD, would the sponsor be able to provide KiTEC with the information used to categorise these studies? **3.** We notice that the raw data for the meta-analysis (sent by the sponsor on 02/04/2015) only includes patient-level data for 11 of the listed studies. The original clinical submission states that the meta-analysis pools data from 22 studies. Can the sponsor please clarify	Specifically, signalling questions were used in each of the 4 domains and included: (1) Patient selection: (prospective/retrospective, consecutive patients, FFR only for intermediate lesions, small subsample of "difficult to diagnose" intermediate lesions, exclusion of patients with <50% or >90%, etc); (2) Index test: was index test interpreted without knowledge of reference standard (blinding), was index test done after angiography, was threshold of test result pre-specified or selected after angiography/FFR was known, did index test methods vary – ie Tesla 1.5 vs 3.0 for MRI, new experimental technique used; (3) Reference standard: was FFR interpreted with pre-knowledge of results of index test, was decision to perform FFR dictated by index test, was reference standard FFR value of 0.75 or 0.80 pre-specified? Was index test performed after angiography/FFR? (4) Flow and timing: was there an appropriate interval between index and reference test? Did all patients have the same reference standard 0.75 vs 0.80, did index test influence decision to perform reference standard? Were all patients included in the analysis or was this a sub-selected group of patients? **2.** While most studies did not explicitly report pre-test likelihood of disease, all included patients underwent invasive angiography with measurement of FFR as the reference standard. As such, each patient was determined, on the basis of clinical assessment, to be in need of invasive angiography and thus was deemed to be of intermediate risk or higher. There was only one study by Stuijfzand et al with an intermediate pre-test likelihood study cohort. This study employed no pre-selection criteria based on scan findings and had no patients included with a prior cardiac history.	

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	whether the meta-analysis was based on the results of 11 studies, or if data is missing from the raw data spreadsheet? **4.** Would the sponsor be able to provide their reasoning for not performing a vessel-based meta-analysis? The raw data for the meta-analysis contains both vessel and patient-level values, however, the sponsor appear to have only conducted a patient-level meta-analysis. **5.** Can the sponsor provide the following technical details regarding their meta-analysis? a. the statistical package that was used (in their reply the sponsor mention that they used Meta-Disc 1.4 for performing meta-regression, was the same software used for all the analyses presented in the sponsor's submission?), b. the model approach used, c. the specific commands used.	**3.** Only 11 studies provided enough information to create a patient-based 2x2 table and be included in the per-patient analysis. However, all 22 studies are included in the meta-analysis and were described either in the patient or vessel-based analysis. We have provided the results of both analyses in Appendix A (*see Appendix 4*) of this submission. **4.** The per-vessel meta-analysis was done and a summary is included in Appendix A. We did not include the per-vessel analysis with our original submission because it does not fit within the scope, which looks at decisions on a per-patient level. **5.** All analyses were performed in Meta-Disc 1.4. We have attached a document ('Meta-DiSc pubmed article' (*Appendix 4*)) that describes the meta-analysis software as well as its public obtainability. A second document ('Meta-DiSc 1.4 background information on employed methods' (*Appendix 4*)) describes the statistical methods Meta-Disc uses to calculate pooled sensitivities, specificities, likelihood ratios, and diagnostic odds ratios.	

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4	**Email to Sponsor on 11.05.15:** **1. Inputs Sheet** a. Test accuracy – different % with disease rates(20%,45%, 75% and 95%) along with sensitivity & specificity have been used for different pre-test likelihoods to estimate TP, FP, TN, FN. Whilst we think this is a reasonable approach, could you please advise us of the source for % with disease rates (i.e 20%,45%, 75% and 95%). **2. Additional Calculations for PCI rates following PCI** The TP, FP, TN & FN probabilities have been used to estimate the treatment volumes (PCI and OMT) in the model. The following questions relate to these estimations:	**Reply received 13.05.15:** **1.** The source for % with disease rates (i.e. 20%, 45%, 75% and 95%) is 2012-2013 data from the Rapid Access Chest Pain Centre at St. Thomas Hospital as published in 2015 by Dr. Rajani1. We realize that the mix of disease will vary from centre to centre. For this reason we broke down the health and economic impact by disease burden on the Summary tab of the model (rows 5-22). **2.** a. Rows 72-88 on the Inputs tab takes data from the cohort numbers in the cost model and then calculates the results (TP, FP, TN, FN) of performing a diagnostic angiogram on those patients, taking into account the disease burden. C86 as you pointed out should be 41. Thank you for identifying this. The results of the model, however, are dependent upon the calculated % of patients that test TP, FP, TN, or FN (columns F-I). Thus changing the number from 33 to 41 does not change the model output. We would be happy to discuss this via conference call, while sharing screens, if helpful.	

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

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	a. We are unable to follow how the positives, negatives, total and disease % was calculated and how this was used in the model? We could assume from cell C87 that it has been linked to the cohort numbers in the cost model ('FFR-CT'!X23). Is this the case for all the calculations? For instance in cell C86, the total is 33.4 but if you look at the corresponding cohort number (Y21), it is 41. Is this an error? Please clarify. b. The numbers do not tally in some of the calculations. For example, Cells A72 + B72 should give a total of 81 and not 41. c. Could you please explain how the 1 year death from MI was incorporated into the model more clearly? Could you please be specific about how the costs have been assigned to death MI? d. Why was no cost for OMT assigned? Is this because you assume there will be no associated cost during the first	b. This row (72) was left in error. In reviewing the model now we confirmed that no calculations are dependent on inputs in this row. However, thank you for calling this error to our attention. We have corrected this and other errors in our updated excel model, which is attached. We double checked calculations and did not find other errors. In rows 77 and 87 we realize that we were inconsistent in the formulas used to determine the sum of columns A & B, but the resulting numbers were correct. c. The death and MI rate is based on whether each patient is appropriately or inappropriately diagnosed to receive PCI. We then referred to literature to estimate the likelihood of an event based on the appropriate or inappropriate diagnosis. The assumptions used are: • True Positive (TP) – Patient correctly diagnosed to receive PCI: 3% One year Death and/or MI Rate • False Positive (FP) – Patient incorrectly diagnosed to receive PCI: 3% One year Death and/or MI Rate • True Negative (TN) – Patient correctly diagnosed to receive medical therapy (no PCI): 1% One year Death and/or MI Rate • False Negative (FN) – Patient incorrectly diagnosed to receive medical therapy (no PCI): 5% One year Death and/or MI Rate	

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	year? **3. NICE Model** a. 10-29% - why are cells Y40 and Y43 multiplied by 0.5? b. 61-90% - why are cells Y80 & Y83 multiplied by 0.5? **4. FFRCT Model** a. 10-29% - why are cells AO38 & AO41 multiplied by 0.5? b. 61-90% - why are cells AO78 & AO 81 multiplied by 0.5? c. 61-90% Functional imaging (AV 77, 78, 80, 81) is multiplied by 20% disease (E 29 – H29). Shouldn't it be M29 – P29 from the inputs sheet? d. In the patient volumes for 10-29%, why is cell AO41(functional imaging)	The primary reference that we used in assigning these event rates was a publication by Nico Pijls2. Dr. Pijls reaches these conclusions through the review of other studies as outlined in the table below: Even though FFRCT resulted in a lower death and MI rate, we did not include any monetary costs associated with these health states in the model. d. No cost was assigned for OMT because it was assumed that the cost of OMT would be applied both to patients undergoing PCI and those not needing PCI (identified as OMT patients in the model). The cost of usual OMT (statins, b-blockers, aspirin, and	

Sources for Pijls, JACC 2012, Functional measure of Coronary Stenosis	TN 1%	TP or FP 3%	FN 5%
COURAGE, Shaw J Nucl Cardiol 2006		X	X
Pijls, Fearon, 2 Year FAME follow-up, JACC 2010	X		X
Pijls, 5 year follow-up DEFER, JACC 2007	X		
Boden, Optimal medical therapy w or w/o PCI, NEJM 2007	X		
Nam, Functional SYNTAX score for risk assessment in multiessel CAD, JACC 2011	X		
Stone, Prospective study of natural history, NEJM, 2011		X	X

[2] Pijls, N. H. e. a. (2012). "Functional Measurement of Coronary Stenosis." Journal of American College of Cardiology **59**(12): 1045-1057.

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	excluded from the volumes? e. Similarly for patient volumes for 61-90%, why are cells AI 84 & AO81 (functional imaging) excluded from the volumes?	other antiplatelet agents) is low, and inclusion of these costs would not significantly affect the model. There is the potential for a small cost savings in the CT/FFRCT pathway by not using OMT in patients with no evidence of coronary atherosclerosis (normal CTA) that is not accounted for in the model. **3.** a. NICE guideline CG95 for Chest Pain of Recent Onset indicates that patients with 10-29% probability of disease who test positive for significant CAD by CT should be treated as stable angina patients3. Nice guideline CG126 for Management of Stable Angina states that ICA be used to "guide treatment strategy for people with stable angina whose symptoms are not satisfactorily controlled with optimal medical treatment." If stable angina symptoms are satisfactorily controlled with OMT the guidelines recommend a functional or non-invasive anatomical test4. We assumed a 50/50 split between these two patient pathways; 50% receive a functional test and 50% receive ICA. b. Similar to above, NICE guideline CG126 for Management of Stable Angina suggests that this population should be treated as stable angina patients. Following the logic in our answer to question 3a we assume that half of the patients will go on to ICA and the other half will receive non-invasive functional testing.	

[3] http://www.nice.org.uk/guidance/cg95
[4] http://www.nice.org.uk/guidance/cg126

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		4. a. The answer here is the same as that in 3a. We kept the model consistent for both the current NICE pathway and the proposed FFRCT pathway. b. Similar to above, the answer here is the same as that in 3b. We kept the model consistent for both the current NICE pathway and the proposed FFRCT pathway. c. Thank you for finding and pointing out this inconsistency. As you noted, since this in the 61-90% pre-test likelihood pathway, the appropriate disease burden is in cells M29 – P29. We have updated the model and included the results in the tables (*see Appendix 5*) at the end of this document. d. The 1.5 patients in cell AO41 were counted as medical therapy patients. Upon further consideration, we split these patients into PCI and Medical Therapy groups (using appropriate disease burden and SPECT SN & SP). The patient volumes and results have been updated and are reflected in the tables at the end of this document. e. The patients in cells AI 84 are split by those that have reversible ischemia (AO 84) and those without ischemia (AO 90). These two groups are then included in the volumes. Likewise, the patients in cell AO 81 are split by those that have reversible ischemia (AS	

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		78) and those without ischemia (AS 81). These two groups are then included in the volumes.	
3	**Email to Sponsor on 12.05.15:** The EAC couldn't replicate the sponsor's meta-analysis results for SPECT. According to the sponsor's submission 3 SPECT studies were included but only 2 seem to have been analysed. Nevertheless no combination of 2 out of the 3 studies provides the results reported in the sponsor's submission. Can the sponsor provide some more information on this?	**Reply received 13.05.15:** We suspect that the problem is the result of an inaccuracy in of one of the two studies included in the meta-analysis: Melikian, JACC Intv 2010 (attached (*Appendix 6*)). In the results section on page 310, for MPI, per-patient Se is 76%,Sp is 38%, PPV is 66% and NPV is 50%. However, in the 2x2 table (Figure 2A) we see that TP=31, TN=10, FP = 10 and FN=16, which would result in a Se of 66%, Sp 50%, PPV 76% and NPV 38%. If we interchange the number of FPs and the number of FNs, sensitivity indeed becomes 76%, and Sp is 38%, PPV is 66% and NPV is 50%. We therefore think there is a typo in the 2x2 table with reversal of the numbers 10 and 16 in the table. - The Takx 2014 meta-analysis which also included the Melikian study reports the TP, FP, FN and TN as they appear in Figure 2A and reports a Se of 66% and Sp of 50%, see supplemental eTable 5 (attached (*Appendix 6*). - However, Zhou (Eur J Radiol 2014) in his meta-analysis of SPECT (attached (*Appendix 6*)) uses TP 31, FP 16, TN 10 and FN 10 which result in the same Se and Sp values as in the text (76% and 38%), see Table 1 on the manuscript. In reviewing our submission, we note that for the Melikian 2010 study, we have incorrectly entered the per-patient FP as 10 rather than 16, and the	

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		TN value as 16 rather than 10, resulting in a "correct" value for Se of 76%, but an incorrect value for Sp (62%) according to the values presented in the manuscript text. We believe that the correct per patient values for SPECT in the Melikian study should be as follows: TP=31, FP=16, TN=10, FN=10 with Sensitivity 76% and Specificity 38%. We are in agreement with Zhou and plan to make this correction in our meta-analysis.	
3 & 4	**Email to Expert Advisers on 12.05.15:** **1.** The aim of the PLATFORM Study is to compare clinical outcomes, resource utilization, and quality of life (QOL) of FFRCT-guided evaluation versus standard practice evaluation in patients with suspected CAD. All outcomes are evaluated at 90 days (+30/-15 days), 180 days (+/- 30 days) and 365 days (+/- 30 days). For NICE submission, the sponsor has submitted preliminary results from the 90 days only. Will you consider a time frame of 90 days post-diagnostic test to be adequate for assessing Major Adverse Coronary Events rate? **2.** Some patients who are diagnosed with CAD do not undergo	**Reply from <u>Ronak Rajani</u> received on 12.05.15:** **1.** No. A 90-day time frame is not sufficient to adequately assess whether FFRct has any impact on major adverse coronary events. This time frame is too short for a meaningful comparison since the event rate would be expected to be small within the time frame. **2.** It is generally accepted that patients who have a diagnosis of angina with coronary disease should be treated with medical therapy in the first instance, if there is no evidence of prognostic disease. This comes from the Courage trial, which showed that patients treated with medical therapy were not disadvantaged by having medical therapy vs. revascularisation. This was based on patients being on optimal medical management and on at least two antianginal agents. The FAME trials showed that patients with an invasive FFR <0.8 did better if they received revascularisation compared with medical therapy. Revascularisation is currently indicated for patients therefore who have unstable coronary disease (unstable angina, myocardial	

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	revascularisation but receive optimal medical treatment. Could you please provide some information on: a. Who these patients will be? b. If the optimal treatment is usually a single or multi-agent? **3.** The RIPCORD study has shown that there isn't an agreement between FFR and DS% as measured by ICA. Nevertheless in clinical practice the interventional cardiologist will not measure FFR in all coronary arteries but will use a cut-off >50%, or a range 30-70% etc (the EAC noted a lack of consensus on this matter in the included studies). Could you outline the reasons why in clinical practice not all vessel are assessed with FFR? **4.** The sponsor has proposed the following diagnostic pathway for HeartFlow: a. CT calcium scoring is the first diagnostic tests used for all patients with intermediate pre-	infarction) or where a lesion has been evaluated and the invasive FFR <0.8. Patients with stable symptoms on medical therapy do not usually require revascularisation. **3.** It is well accepted that there is discordance between diameter stenosis and physiological significance as evaluated by invasive FFR. It is however more unusual to have a positive FFR for a mild stenosis <50%. Therefore interventional cardiologists use their clinical judgement in deciding whether or not to perform invasive FFR and generally do this if there is uncertainty as to whether a lesion could be accounting for a patient's symptoms. It would be hard to sell to interventional cardiologists the prospect of performing invasive FFR on all patients with a range 30-70%. We must bear in mind that coronary CTA is not the same as invasive angiography. Coronary CTA has a tendency to report stenoses to be one grade higher than what is visually seen on invasive angiography. The reason for the low use of invasive FFR is multifactorial. Firstly it is expensive and costs up to £3000. Secondly not all interventional cardiologists perform invasive FFR routinely. This is especially the case in the DGH setting. Lack of experience, time, equipment etc. Secondly patients usually have undergone some other functional test in advance of the invasive angiogram which provides information as to where ischaemia is likely to be and where stenting should be performed. In these cases there would be no need to perform invasive FFR (even though this may be considered to be the gold standard) unless there was uncertainty. **4.**	

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	test likelihood (10-90%), b. If between 1-400 Agatston units then CCTA is performed. c. If CCTA shows evidence of coronary artery stenosis based on pre-specified cut-offs then the data are send for HeartFlow analysis Do you consider the new clinical pathway proposed by the sponsor to be appropriate?	a. This is difficult and is not supported by any current international guidelines. This is also out of keeping with current NICE guidelines, which sees calcium scoring as being for low risk to low-intermediate risk patients. b. If between 1-400 Agatston units then CCTA is performed. On the whole the approach is reasonable to individuals aware of the cardiac CT literature. It is however not one that is likely to be accepted by practising clinicians nor experts in cardiac CT. The sponsors are proposing an algorithm for the evaluation of patients with stable chest pain. This is something that I personally feel is beyond their remit and is currently being evaluated by NICE. Cardiac CTA is still believed to be a test for the exclusion of coronary disease and for those patients at low risk. The current algorithm proposes an extension of this to higher risk groups. This is outside of current appropriate use criteria. Although current risk estimates grossly overestimate the prevalence of coronary disease, an algorithm that automatically proposes FFRct to be in essence the first line test for almost all categories of patients (except in those where the data in unsuitable) is not one that will be accepted by cardiologists. It neglects to consider other tests currently available such as stress echo, stress MRI which are in current NICE guidelines and are likely to remain so in the next iteration. The sponsor has data to support their algorithm and believe FFRct to be superior to these existing technologies but there is not as yet the body of evidence to support this. The algorithm is a massive deviation to what is currently in existence and there has to be care in what is proposed to what real world data exists for this and what will be accepted as reasonable practice by cardiologists.	

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		The algorithm in my opinion is overstretched. I think FFRct is a good technology and one with potential but it will need to find its place against the existing technologies and within current accepted guidelines. The current algorithm suggests cardiac CT as the first test for the assessment of all patients with stable chest pain with a risk 10-90%. They don't have at present enough trial data to support this. Significant disease also needs to be defined. To perform FFRct on patients with a minor stenosis is not one that will be accepted. This will have huge cost implications to the NHS as a whole. Patients who are currently referred for cardiac CT are those who have atypical symptoms and who are low risk. The sponsors propose a huge change to this in that their algorithm will evaluate patients with typical angina and at high risk. One could argue that patients with chest pain that is typical should be treated with optimal medical therapy in the first instance. Maybe have one test to confirm the diagnosis. A functional test such as SPECT or dobutamine stress echo or MRI perfusion. It is too idealistic for the sponsor to suggest that every patient with chest pain should have a measure of FFRct. This is not performed anywhere in the world. I personally for example would not use FFRct in a patient with a low grade stenosis on a CT scan who had atypical symptoms. This algorithm would propose this. In unpublished data. The rate of a positive FFRct in patients with a stenosis <50% is relatively low. Approximately 15%. Even with this – I am not certain an interventional cardiologist would necessarily stent a lesion with only mild stenosis irrespective of trial data if the patient was not on optimal medical therapy. A better use of the algorithm perhaps would have been to propose FFRct as an alternative test to functional testing with MPS and DSE and stress MRI which may be superior in defining lesion specific ischaemia. Or indeed as an optional adjunct to a coronary CTA where	

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		there is a question as to whether a coronary plaque may be physiologically significant or accounting for a patient's symptoms. I don't think it is the sponsor's role to redefine current practice in the UK for the evaluation of patients with stable chest pain. **Reply from <u>Andreas Baumbach</u> received on 13.05.15:** **1.** No. 90 days cover procedural complications rather than spontaneous events. **2.** a. Pts with moderate coronary lesions not causing angina, or mild angina b. OMT comprises Aspirin, Statin, Mostly a nitrate and beta blockers **3.** FFR is an invasive measurement which takes time to do and comes with small risk of complications. In the majority of cases one can make a good clinical decision based on the angiogram. **4.** I don't understand why CaScore 0 rules out an angiogram. There are some patients with soft plaques and no calcium. Also, of course this shows the limitations. A lot of older patients will have higher Ca Score and hence CTA is not feasible. **Reply from <u>Ian Purcell</u> received on 17.05.15:** **1.** 30 days adequate only to measure complications directly resulting from the diagnostic test itself. 30 days too short to identify events in a cohort with stable CAD. 365 days or more	

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		necessary to detect differences in clinical outcomes in this low risk cohort. **2.** a. Patient with symptoms controlled to their satisfaction on medical therapy and without prognostically threatening CAD. The definition of "prognostically threatening CAD" is controversial but would exclude left main stenosis, most 3 vessel CAD and proximal LAD stenosis. b. Up to 2 anti-anginal agents. More than this is usually considered an indication for revascularisation. **3.** The reasons are multi-factorial. 1. For decades % stenosis on invasive coronary angiography has been used to determine need for revascularisation with good outcomes in studies and clinical practice. This experience will not be abandoned by cardiologists overnight. 2. Most cath labs and cardiologists outside PCI centres cannot and, in my view, should not provide FFR. 3. Resource and time. The yield of FFR in changing decision making outside a chosen angiographic range (not consistent but often 30-80% diameter stenosis) lower than concentrating resource on equivocal lesions. 4. Decision to revascularise is not purely angiographic. History, ECG, non-invasive imaging data taken into account to support decision without FFR. 5. FFR not relevant in culprit vessel PPCI. Fewer data for FFR in ACS. **4.** The pathways are more complicated than you have summarised	

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		and differ depending on pre-test likelihood. They are a reasonable starting point for analysis. I am concerned by false negatives at higher likelihood scores ie >80%.	
4	**Email to Sponsor on 15.05.15:** The scope specifies the population to be included as 10-90%. However, the electronic model also included <10% and >90% to estimate per patient costs. We understand that to simulate the cohort, 1000 patients are required but to arrive at the final per patient cost, the <10% and >90% has to be excluded. Can you please explain why these are not excluded?	**Reply received 15.05.15:** In the economic model we have created two pathways, one according to the current NICE guidelines and one according to the scope, which includes HeartFlow technology in the treatment pathway for those patients with a pre-test likelihood of CAD of 10-90%. Although the model includes the economic and clinical outcomes for patients with all PTLs, the pathway for patients with a PTL of <10% or >90% is exactly the same in both the NICE pathway and the HeartFlow pathway. On the summary tab of the economic model we have broken down the clinical and economic benefits by PTL in rows 5 - 22. Here you can see that there is no change in either cost per patient or event rate for patients with a PTL of <10% or >90%. Although these patients are included in the model, their presence does not alter the results. Looking only at the subpopulation of patients with a PTL of 10-90% results in a further improvement in average cost savings (-£207.31) and a greater reduction in the 1-year MACE rate (-0.08%). We have included the updated results in the table below (*see Appendix 7*) as well as on the Summary tab of the economic model, attached (Columns H-J).	
3	**Email to Sponsor on 08.06.15:** **1**. For the PLATFORM study the	**Reply received 10.06.15:** **1.** The usage of noninvasive tests in each cohort during the	

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	committee is interested to know what tests were available in the 2 cohorts, how they fitted into the CG95 pathway, and how they compare to the model applied in your economic submission. From the study protocol submitted to KiTEC cohort 1A can include stress EKG, stress Echo, SPECT, CMR, CCTA. Do you have data on the percentage use of these modalities for the evidence submitted so far for all cohorts analysed in the study? Do you know whether the clinical centres participating in the study followed the CG95 guideline for selection of these tests ie. selected these tests based on the intermediate pre-test likelihood, for example this would be 10-30% for CCTA but not 60-90%. Finally is the decision model used for the PLATFORM study similar to the one submitted for your economic analysis as outlined in figure C2.2 of the submission? **2**. For the Radiation FFRCT poster by Dr Bilbey the committee requested further information if possible. Unfortunately the poster does not provide contact information for the corresponding	initial period following enrollment is listed in the table below. Note that some subjects required more than one test, so the data are presented as number of tests, rather than % of patients. **Test** / **Overall** / **Cohort 1A** / **Cohort 1B** / **Cohort 2A** / **Cohort 2B** Exercise treadmill test: 14 / 6 / 0 / 3 / 5 Stress Echo: 29 / 29 / 0 / 0 / 0 SPECT: 19 / 15 / 1 / 3 / 0 CMR: 9 / 2 / 3 / 1 / 3 CCTA: 358 / 60 / 1 / 104 / 193 Other: 2 / 2 / 0 / 0 / 0 Physicians participating in the PLATFORM study were not required to follow any set of prescribed guidelines for non-invasive test selection. Eleven sites across northern Europe participated in the study, including two sites in the UK. While it may be that the UK sites practice followed CG95, it was not required as part of the study. PLATFORM investigators were not given a decision model to guide them in their practice except that Cohort 1B patients received a CCTA as a first line test and Cohort 2B patients (originally referred for ICA) received a CCTA instead of initial ICA. The investigator could then request an FFRCT analysis for patients as needed (the recommendation was that FFRCT analysis be performed in cases where the CCTA showed a	

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	author. Do you have further info regarding the authors corresponding email?	stenosis > 30%), order another non-invasive test, proceed to ICA, or define treatment planning without further testing. This trial design enabled a true assessment of utility without constraining physicians to specific prescribed pathways. **2.** We have the contact information for Jonathan Leipsic, who was a contributing author and could provide additional information: Jonathon Leipsic Cell: 778-886-0895 Office: 604-806-8283 Email: JLeipsic@providencehealth.bc.ca	
3	**Teleconference with Jonathon Leipsic (contributing author to PLATFORM study) on 16.06.15:**	**Main Points from TC (Minuted by KiTEC and approved by Jonathon Leipsic on 23.06.15)** 1. This simulation study used patients from the CONFIRM registry5 . A sample size of 100 patients was used for the abstract included in the assessment report but a higher sample of 1000 patients has been analysed for the full text publication. The use of a higher sample size confirmed the authors findings reported in the abstract. 2. The prevalence of CAD as defined by CCTA is 18% in the registry. Using the Diamond-Forester criteria the majority of the patients had an intermediate pre-test likelihood of CAD. 3. The authors used radiation doses from their centre as parameters for their modelling (3-5mSv for CCTA according to 2010 values).	

[5] https://clinicaltrials.gov/ct2/show/NCT01443637

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		A GE Discovery 64-slice high definition scanner was used for CCTA acquisition with the use of ECG-prospective triggering (most commonly). 4. The authors used a pathway that had included only one of the tests for each arm and a binary result (positive or negative test). A positive test (for example positive SPECT) would lead to ICA and a positive ICA would lead to revascularisation. As a result their pathway is different from CG95 where uncertain test results will lead to other diagnostic tests. 5. A cut-off of 50% was used to determine intermediate stenosis with CCTA. Only patients with intermediate stenosis had FFRCT. 6. The authors did not include MRI in the non-invasive functional imaging tests group. 7. The reduction of radiation dose achieved with the FFRCT pathway is attributed to the lower rate of false positives with the addition of FFRCT in CCTA.	

Appendix 1

Questions posed to sponsor in introductory tele-conference (between KiTEC, NICE and sponsor) held on the 30th of March, 2015.

Present in the Teleconference:

NICE – Bernice Dillon
Sponsor – Campbell Rogers and colleagues (Daniel Clark and Ben xx)
KiTEC – Murali Kartha, Anastasia Chalkidou, Naomi Herz, Kate Goddard, Fiona Reid.

Please find KiTEC's questions in black, replies provided by the sponsor at the teleconference (minuted by KiTEC) in red and the sponsor's written replies (provided on 01.04.15) in blue.

1. KiTEC has found some discrepancies between the number of studies listed in the PRISMA flowchart and the number of studies retrieved by re-running the sponsor's search strategies.

    a. Can the sponsor please clarify the exact search strategy and any limits they used for their SR?

    b. Are the keywords provided in Appendix 1 representative of the full search strategy or were there additional modifications that are not listed in the submission?

    CD – there were a few more filters, but same search terms. They will send this directly to KiTEC.

    The keywords and filters indicated in Appendix A: Diagnostic Accuracy Literature Search and Appendix B: Clinical Outcomes Literature Search are representative of the full search strategy.

2. According to section 10.1.1 of the clinical submission, the range of databases searched for the systematic review should include as a minimum:

    - Medline
    - Embase
    - Medline (R) In-Process
    - The Cochrane Library

    a. Can the sponsor clarify which databases they searched, as only PubMed and Web of Science are listed in their submission?

CD – Pubmed/medline and WoS search only.

We completed an extensive literature search in both PubMed and the Web of Science. HeartFlow discussed this plan with NICE via email and confirmed that it was acceptable.

b. Can the sponsor please explain their reasons for choosing to search Web of Science instead of Embase?

We do not have access to Embase. Separately, it is our understanding that Embase has a primary focus on pharmacological literature.

3. On page 14 of the clinical submission, the sponsor states:

'It is proposed that HeartFlow's noninvasive FFRCT technology (please see red boxes added above) in conjunction with CCTA would replace: "CT coronary angiography" in the pathway for Likelihood of Disease 10-29%.'

Can the sponsor confirm that they propose FFRct be used in addition to standard CCTA for patients with a 10-29% likelihood of disease?

KiTEC's interpretation is correct, it was just a wording issue.

Yes, HeartFlow proposes that FFRCT be used in addition to standard CCTA for patients with a 10-29% likelihood of disease.

4. In regards to the unpublished results of the PLATFORM study:

a. KiTEC will require a copy of the PLATFORM study protocol. This will help us to understand the study design that was adopted and, subsequently, to evaluate any methodological shortcomings.

Yes – they will send this IN CONFIDENCE tomorrow.

The Protocol is being sent as separate document (). Please note that the PLATFORM design has not been published and the protocol is shared in confidence.

HeartFlow
PLATFORM Protocol.p

b. Can the sponsor clarify what the primary outcome of this study was?

Cohort 2b and 1b End point is in 90 days. Outcome is – the rate at with angiography can be shown to not have obstructive disease in stenosis >50 in >2mm.

As described in the protocol: "The primary endpoint of the PLATFORM Study is 90-day (+30/-15 days) rate of coronary angiogram showing no stenosis ≥ 50% in a vessel ≥ 2.0 mm by QCA, or no invasively-measured FFR ≤ 0.80 in a segment distal to a stenosis in a vessel ≥ 2.0 mm by QCA."
In Cohort 1B this rate was 75%. In Cohort 2B this rate was 11%.

c. Was the study powered for the primary outcome only?

The study was powered for both the primary outcome (described above) as well as the secondary outcome of 90-day Major Adverse Coronary Event rates.

d. How was the selection of patients for Cohort 1 or Cohort 2 done (e.g. clinicians judgement? other?)

Participating clinicians selected patients to participate in the trial in accord with inclusion and exclusion criteria of the study. The inclusion criteria for PLATFORM were as follow:

Consecutive subjects who meet the inclusion criteria and none of the exclusion criteria will be asked to participate in the study.

Inclusion Criteria:

1. Age ≥18 years
2. Providing written informed consent
3. Subjects with intermediate likelihood of obstructive CAD with an Updated Diamond-Forrester (UDF) risk score 20-80% with symptomatic, suspected CAD who:

a. ***In Cohort 1A & 2A only*** are scheduled to undergo initial clinically-indicated non-invasive coronary evaluation and have not undergone non-invasive coronary evaluation, including exercise tolerance testing, stress echocardiography, SPECT or MRI, or cCTA, within the past 90 days OR ICA at any time; or

b. ***In Cohort 1B & 2B only*** have been referred to invasive coronary angiography (ICA) and have not undergone ICA within the past 90 days

4. Ability to undergo cCTA

NOTE: cCTA will not be required for Cohort 1, but the exclusion applies to both Cohorts 1 and 2 for subject poolability.

Exclusion Criteria

1. Suspicion of acute coronary syndrome. Subjects experiencing unstable angina are not excluded where clinical documentation has ruled out a myocardial infarction.
2. Prior, clinically documented myocardial infarction
3. PCI prior to first test

4. CABG prior to first test
5. Contraindications for cCTA such as:
    a. Presence of pacemaker or internal defibrillator leads
    b. Atrial Fibrillation
    c. Known anaphylactic allergy to iodinated contrast
    d. Pregnancy or unknown pregnancy status in women of childbearing potential
    e. Body mass index >35 kg/m^2
    f. Contraindication to acute beta blockade
    g. Contraindication to acute sublingual nitrate administration
    h. Prosthetic heart valve
6. Contraindications to FFR_{CT}
    a. Complex Congenital Heart disease other than anomalous coronary origins alone
    b. Ventricular septal defect with known Qp/Qs>1.4

    NOTE: FFR_{CT} will not be performed for Cohort 1, but the exclusions apply to both Cohorts 1 and 2 for subject poolability.
7. Requiring an emergent procedure within 48 hours of presentation
8. Evidence of active clinical instability, including cardiogenic shock, unstable blood pressure with systolic blood pressure <90 mmHg, or NYHA Grade III or IV congestive heart failure or acute pulmonary edema
9. Any active, serious, life-threatening disease with a life expectancy of less than 2 years
10. Inability to comply with study follow-up requirements

Current participation in any other clinical trial involving an investigational device or dictating care pathways at the time of enrollment

e. One of the exclusion criteria for this study is ‘Contraindications to FFRCT’. Can the sponsor explain what these contraindications might be?

Contraindications to FFR_{CT} as described in the Protocol are as follow:

a. Complex Congenital Heart disease other than anomalous coronary origins alone
b. Ventricular septal defect with known Qp/Qs>1.4

5. On page 148 of the clinical submission, the sponsor states:

'Moreover, both noninvasive and invasive Comparators cannot reliably identify those patients who either do not have CAD, or have CAD that can be most effectively managed conservatively with medication, lifestyle changes, and risk factor modification.'

Is the sponsor including invasive-FFR in the definition of 'invasive comparators' in this instance?

It is just ICA, not including invasive FFR.

No. We did not intend to include invasive-FFR in the definition of 'invasive comparators' in this instance.

6. On page 149b the sponsor states:

'*FFRCT provides noninvasively information on fractional flow reserve, and can help with clinical decision making by accurately distinguishing those patients who may benefit for coronary revascularization from those patients who can be safely treated medically without revascularization.'*

The sponsor is referencing evidence associated with the effect of invasive FFR in rates of revascularisation by PCI and CABG. Is there any evidence for FFRct?

Evidence for FFRCT derives from 3 places – PLATFORM data, RIPCORD trial (retrospective simulation?), third bit of evidence will be sent [in confidence] and will have NPV and PPV answers.

The evidence for FFR_{CT} is in two forms.
The first is clinical utility data from PLATFORM [O17], FFR_{CT} RIPCORD [O20], and Noninvasive fractional flow reserve derived from coronary computed tomography angiography: experiences from real-world clinical practice [O19]. These studies reflect real world usage in distinguishing patients who may benefit from coronary revascularization [O17] and [O19], and expected clinical impact in a retrospective manner [O20].
The second is what accuracy FFR_{CT} vis a vis invasive FFR should be considered in applying FFR clinical studies to FFR_{CT} utility. The per-vessel SN for FFR_{CT} is 84%, and the per-vessel SP is 86%. Furthermore, not yet published analyses demonstrate that:
1) If FFRct is > 0.80, the likelihood that FFR is ≤ 0.75 is 1.1%
2) If FFRct is > 0.85, the likelihood that FFR is ≤ 0.75 is 1.0%
3) If FFRct is > 0.85, the likelihood that FFR is ≤ 0.80 is 1.4%.

7. On page 149c the sponsor refers to a model constructed for extrapolating data on radiation exposure. Is all the evidence listed in this section from the [O18] ACC Poster, 'Potential impact of non-invasive FFRCT on radiation dose exposure and downstream clinical event rate'?

Yes – all from that poster. The manuscript for full publication is being prepared. They can provide more evidence from the investigators.

Yes. All evidence listed in this section is from the [O18] Poster.

8. Could the sponsor please provide a full list of references for all studies they have included in their submission? Could they also provide the full reference list (all 63 studies) read in full as part of their meta-analysis (as per figure B4)?

CD – yes, will do that.

Please see list of references in Appendix C. Appendix C1 contains the full list of references for studies included in the submission. Appendix C2 contains the full reference list (63 studies) for studies read for the meta-analysis.

9. In regards to the meta-analysis:

The sponsor is working with a third party and a lot of the information about the meta-analysis will need to come from them.

a. Did the sponsor use QUADAS for the methodological quality assessment to determine which studies to include/exclude from their meta-analysis?

Yes, QUADAS was used for the methodological quality assessment.

b. Please provide access to the criteria used for methodological quality assessment of the 22 studies included in the meta-analysis.

Please see Appendix D for the criteria used for methodological quality assessment.

c. There are some discrepancies between tables B14.5 and table B14.6 in terms of the total number of patients listed. Can the sponsor clarify why these discrepancies exist?

There are two causes for the apparent discrepancies seen between tables B14.5 and B14.6. The first cause is that some studies included more than one comparator test. For example, the Norgaard 2014 study included CCTA, FFRCT, and ICA and thus the 254 patients in that study were counted in the analysis for each comparator. Thus the total number of patients shown on B14.5 is greater than the number of patients in the 22 studies. The second cause is that Table B14.6 only includes studies that reported per patient analysis, not the total number of patients included for each diagnostic test. For example, there are two MRI studies included in Table B14.5, one with 37 patients and one with 34 patients. Only the study with 34 patients (Bernhardt 2012) included data on patient based analysis and is reflected in Table B14.6. The other MRI study (Costa 2007) included only per-vessel analysis.

d. Has the sponsor performed a statistical comparison of the diagnostic accuracy outcomes for the different comparators in table B14.6? Can the sponsor please provide this to KiTEC? The table currently lists the diagnostic accuracy values (sensitivity, specificity etc.) and the confidence intervals but not p-values.

At present the answer is no. We expect that we will have access to and provide this statistical comparison when we submit the raw data referenced in question 9f.

e. Did the sponsor have access to individual patient data for performing the meta-analysis? If not, how was the meta-regression performed?

The sponsor does not have access to individual patient data, but will send all raw data from pooled values from publications.

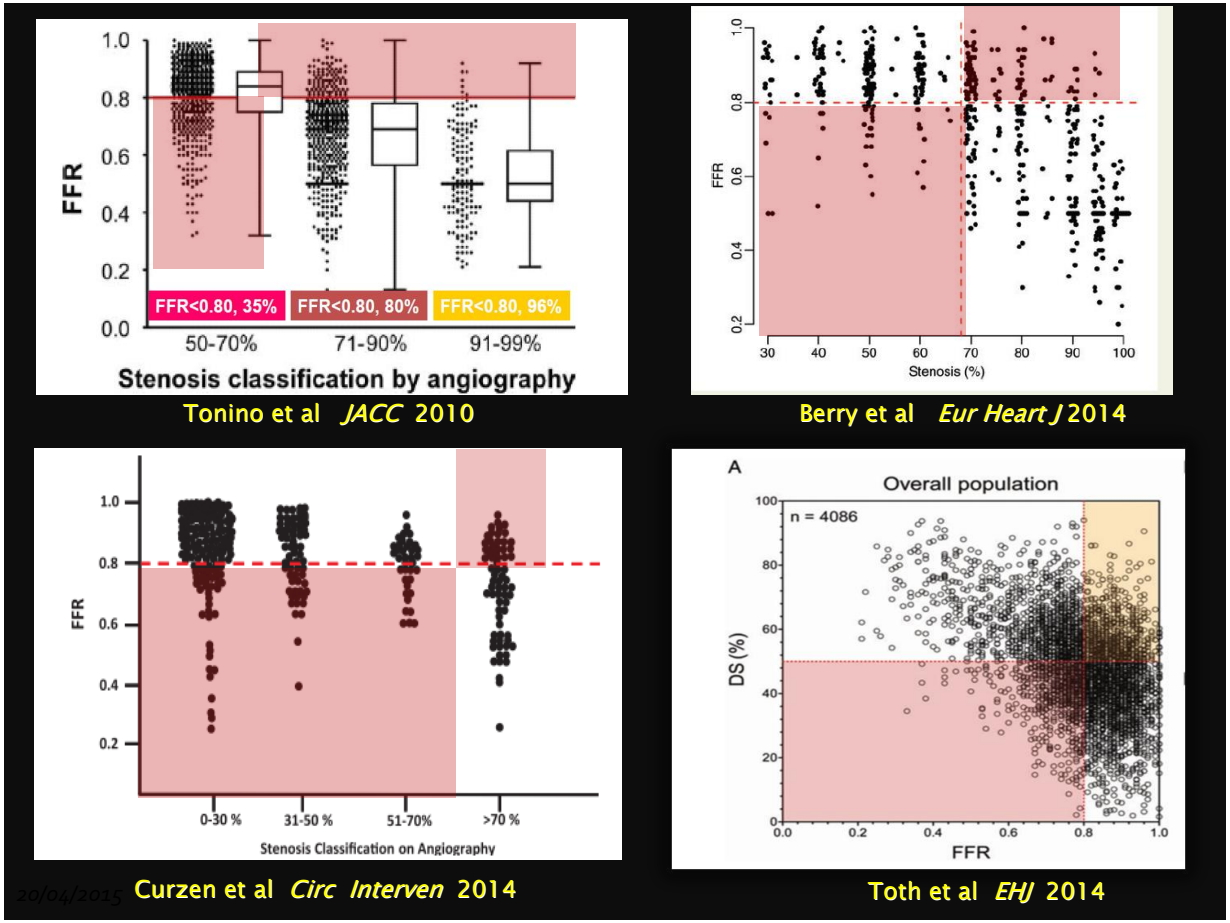
No, we did not have access to individual patient data.

[redacted]

f. Please provide access to all the raw data related to the meta-analysis performed by the sponsor. This should include the sponsor's answers to the methodological quality assessment.

We are still in the process of gathering raw data from the third-party who performed the meta-analysis. All data will be supplied as soon as it is available.

database NICE - raw data.xlsx


FFR
1.0
0.8
0.6
0.4
0.2
0.0
FFR<0.80, 35%
FFR<0.80, 80%
FFR<0.80, 96%
50-70%
71-90%
91-99%
Stenosis classification by angiography
Tonino et al JACC 2010
FFR
Stenosis (%)
Berry et al Eur Heart J 2014
FFR
0-30 %
31-50 %
51-70%
>70 %
Stenosis Classification on Angiography
20/04/2015
Curzen et al Circ Interven 2014
A
Overall population
n = 4086
DS (%)
FFR
Toth et al EHJ 2014


Backgound information QUADAS-


QUADAS-2 scoring system.pdf


Meta-DiSc 1.4 background informati


Meta-DiSc pubmed article.pdf

Diagnostic performance of CCTA, ECHO, FFRct, ICA, 3.0 T MRI, and SPECT for the detection of hemodynamic significant coronary stenosis.

Index test	N	Sensitivity (95% CI)	Specificity (95% CI)	PLR (95% CI)	NLR (95% CI)	DOR (95% CI)
Patient based analysis						
CCTA	694	0.90 (0.86 – 0.93)	0.39 (0.34 – 0.44)	1.54 (1.25 – 1.90)	0.22 (0.10 – 0.50)	6.91 (2.80 – 17.03)
ECHO	115	0.77 (0.61 – 0.88)	0.75 (0.63 – 0.85)	3.00 (1.94 – 4.65)	0.34 (0.17 – 0.66)	9.51 (3.87 – 23.38)
FFRct	609	0.90 (0.85 – 0.93)	0.71 (0.65 – 0.75)	3.34 (1.78 – 6.25)	0.16 (0.11 – 0.23)	21.94 (9.07 – 53.07)
ICA	954	0.69 (0.65 – 0.75)	0.67 (0.63 – 0.71)	2.54 (1.25 – 5.13)	0.46 (0.39 – 0.55)	5.46 (2.54 – 11.76)
MRI	34	.91	1	-	-	-
SPECT	110	0.74 (0.60 – 0.85)	0.75 (0.62 – 0.86)	2.91 (1.41 – 7.43)	0.38 (0.23 – 0.63)	7.23 (2.63 – 19.85)
Vessel based analysis						
CCTA	2085	0.91 (0.88 – 0.93)	0.58 (0.55 – 0.61)	2.09 (1.74 – 2.49)	0.17 (0.12 – 0.24)	13.15 (8.47 – 20.41)
ECHO	NA	0.50	0.90	-	-	-
FFRct	1050	0.83 (0.78 – 0.87)	0.78 (0.75 – 0.81)	4.02 (1.84 – 8.80)	0.22 (0.13 – 0.35)	19.15 (5.73 – 64.95)
ICA	3196	0.71 (0.69 – 0.74)	0.66 (0.64 – 0.68)	2,26 (1.71 – 2.99)	0.45 (0.36 – 0.56)	5.34 (3.38 – 8.45)
MRI	219	0.90	0.82	5.17	0.14	44.77

		(0.81 – 0.96)	(0.74 – 0.88)	(1.44 – 18.54)	(0.08 – 0.26)	(8.48 – 236.34)
SPECT	470	0.59	0.76	2.76	0.49	6.39
		(0.52 – 0.66)	(0.71 – 0.81)	(1.77 – 4.31)	(0.35 – 0.67)	(3.29 – 12.42)

Table 1: Updated Model Economic Outputs based on KiTEC corrections

Prevalence of Disease	Cost Intervention: NICE Guideline	Cost Comparator: FFR_{CT} (old)	Cost Comparator: FFR_{CT} (updated)	Incremental cost/saving
<10%	£0	£0	£0	£0
10-29%	£1,385	£1,361	£1,375	-£10
30-60%	£2,125	£2,095	£2,095	-£30
61-90%	£3,402	£2,875	£2,880	-£522
>90%	£2,769	£2,769	£2,769	£0
Total	**£2,239**	**£2,080**	**£2,084**	**-£154.97**

Table 2: Updated Model Clinical Outputs based on KiTEC corrections

Prevalence of Disease	Event Rate: NICE Guideline	Event Rate HeartFlow (old)	Event Rate HeartFlow (updated)	Increment
<10%	1.20%	1.20%	1.20%	0.00%
10-29%	1.63%	1.57%	1.58%	-0.05%
30-60%	2.53%	2.37%	2.37%	-0.17%
61-90%	3.20%	3.17%	3.18%	-0.01%
>90%	3.48%	3.48%	3.48%	0.00%
Overall	**2.57%**	**2.50%**	**2.51%**	**-0.06%**

Appendix 6 (Attachments included in sponsor's email on 13.05.15 re. meta-analysis)


Melikian JACC interventions 2010.pd


supplement Takx.pdf


Zhou 2014 meta SPECT.pdf

Cost / Patient

	NICE	HeartFlow	Change	% of sample population	% of PTL 10-90%	Change
<10%	£0	£0	£0	9.6%	NA	NA
10-29%	£1,385	£1,375	-£10	18.6%	25%	-£10
30-60%	£2,125	£2,095	-£30	28.4%	38%	-£30
61-90%	£3,402	£2,880	-£522	27.7%	37%	-£522
>90%	£2,769	£2,769	£0	15.7%	NA	NA
Overall	**£2,239**	**£2,084**	**-£154.97**	**100%**	**100%**	**-£207.31**

Event Rate

	NICE	HeartFlow	Change	% of sample population	% of PTL 10-90%	Change
<10%	1.20%	1.20%	0.00%	9.6%	NA	NA
10-29%	1.63%	1.58%	-0.05%	18.6%	25%	-0.05%
30-60%	2.53%	2.37%	-0.17%	28.4%	38%	-0.17%
61-90%	3.20%	3.18%	-0.01%	27.7%	37%	-0.01%
>90%	3.48%	3.48%	0.00%	15.7%	NA	NA
Overall	**2.57%**	**2.51%**	**-0.06%**	**100%**	**100%**	**-0.08%**