NICE National Institute for Health and Care Excellence

QAngio XA 3D/ QFR and CAAS vFFR imaging software for assessing the functional significance of coronary obstructions during invasive coronary angiography

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Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
Medis Medical Imaging Systems	1	14		Definition QFR: QFR is a registered trademark, therefore cannot be used as a general name for angio-based physiologic assessment of coronary obstructions. Registered in EU, Brazil, Hong Kong, Australia, Canada, China,India, Israel, Japan, Mexico, Republic of Korea, USA. Include ® please.	None of the included studies use a trademark when referring to QFR, so it is unclear why this is requested. We have made no change at present but we can update this at the copy-editing stage if required.
Medis Medical Imaging Systems	2	15		Definition PCI: insert “catheter” following “uses a .....””	This has been amended (see erratum)
Medis Medical Imaging Systems	3	26	1st paragraph	AngioPlus is registered in China and has CFDA approval; not CE-marked	This has been amended (see erratum)
Medis Medical Imaging Systems	4	26	Under QFR description	The QAngio software also provides anatomic information along the entire segment for stent sizing purposes, as is also described for CAAS.	This has been clarified (see erratum)
Medis Medical Imaging Systems	5	29	3rd line from bottom	I believe that there is no objective evidence for that statement by Pie Medical	This was a comment received from Pie Medial. We are not suggesting that there is objective evidence to support it. No change needed.
Medis Medical Imaging Systems	6	43	1st line	I appreciate that NICE has done a thorough search through the literature, but our list includes many more papers and abstracts until Jan 2020 in which QFR was mentioned. Where is the difference coming from? I guess the excluded articles are based on the reasons as mentioned in the block diagram on p. 44?	We screened all the studies given to us by Medis for inclusion. All included studies match the protocol specified selection criteria. The list of studies excluded at full text stage with reasons is provided

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					in Appendix 2, Table 68 and was checked and updated, as it did not contain reasons for exclusions of 5 references submitted by Pie Medical during the course of this assessment (all excludes). Figure 2 (PRISMA flow diagram) was edited accordingly. (See new tables and figures in erratum)
Medis Medical Imaging Systems	7	89	2nd paragraph under 4.10.3	QFR is a registered trademark for Medis, therefore cannot be used in association with CAAS software	We have corrected incorrect usage of QFR relating to CAAS throughout.
Medis Medical Imaging Systems	8	92	3rd paragraph, 1st line	FRR should be FFR	This has been corrected (see erratum)
Medis Medical Imaging Systems	9	185	Table 62, strategy 4	NHB rank should be 3 in stead of 4	This has been amended in Table 62 (see erratum)
Medis Medical Imaging Systems	10			As a general remark, every tool must have a region of uncertainty, which should apply to CAAS as well. They only problem is that they do not know how to calculate it.	No response needed
Pie Medical Imaging	11	Several		At a number of locations, it states QFR where it should state vFFR (and vice versa)	We have checked and corrected incorrect usage of QFR relating to CAAS throughout.

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Pie Medical Imaging	12	20	1.3.1	Inclusion criteria. Here it states: *Empirical studies of QFR or vFFR (with or without invasive FFR) that reported relevant clinical outcomes (including morbidity and mortality) or issues related to implementation of QFR or vFFR and their use in clinical practice were also eligible.* Why was the FAST OUTCOME study excluded? This NICE assessment focusses on the measuring in patients for need for revascularisation comparing performance with invasive FFR. However, there is substantial evidence that there is a clinical impact (and as such economic effect) of measuring FFR after stenting. E.g. these two publications show that an FFR measurement after stenting is an independent predictor of long-term outcomes • Impact of Post-Percutaneous Coronary Intervention Fractional Flow Reserve Measurement on Procedural Management and Clinical Outcomes: The REPEAT-FFR Study by Azzalini et al (Journal of Invasive Cardiology 2019) • Role of Postintervention Fractional Flow Reserve to Improve Procedural and Clinical Outcomes by Hakeem and Uretsky (Circulation 2019) In the FAST POST study (also submitted for this review) already the correlation of vFFR with FFR post-stent and accuracy to predict a post-stent FFR < 0.9 was validated and presented. The FAST OUTCOME study showed in > 800 patients that a post-stent vFFR (using cut-off of 0.9) has shown to be a significant predictor of target vessel revascularization rates at 1 year.	The protocol-specified population selection criteria state that patients with intermediate stenosis who are referred for ICA to assess coronary stenosis and the need for revascularisation were eligible for inclusion. Post-intervention assessment of revascularized vessels (whether using QFR, vFFR or FFR) was beyond the scope of this DAR. Therefore, it was not considered in the systematic review or economic analysis. This has now been clarified in the population section of the inclusion criteria in Section 4.1.3. (see erratum) We note that that use of pre-intervention QFR or vFFR does not prevent post-intervention use of FFR (or any other test), so it is not relevant to the economic assessment of QFR or vFFR within the scope of this DAR.

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				Preventing revascularization has a proven economic impact, and as such we believe this should be included in this economic model. Especially because this is part of the current work-up of these patients in PCI centers	
Pie Medical Imaging	13	22	1.4.1	*Also applicable to other sections where validation data on correlation of vFFR to FFR is used.* The FAST POST study was excluded. While not reporting diagnostic accuracy towards the FFR cut-off of 0.8 it does report correlation of vFFR to FFR and reproducibility in an independent cohort of 100 patients. The method of measuring vFFR or FFR does not differ between patients pre- or post-stenting. Also, in the pre-stenting group, patients who had stents previously implanted are available. So, we believe this data should be included in this analysis.	As above, post-intervention use of the index and reference standard tests in revascularised vessels was not within the scope of this DAR.
Pie Medical Imaging	14	22	1.4.1	A reference is made to the conference abstract from the Barts Hospital in London (reference 22). This abstract has used the vFFR software outside of its official instructions for use (so off-label) as stated in the user manual. The instructions for use state that a frame rate of at least 12,5 fps should be used, in this abstract 7.5 fps was used which is lower. The accuracy results from this paper must not be used. Additionally, a reference is made to the study of Pizzato (Reference 16). Also, in this study the software was used outside its instructions for use.	As per protocol-specified selection criteria, all versions of CAAS vFFR were eligible for inclusion. Table 8 specified that Jin et al (2019) used a lower frame rate of 7.5 fps. We have made an additional note of this in section 4.8 and 4.8.1. We have now clarified that these studies may not represent the manufacturer-intended use of vFFR. (see erratum)

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					We evaluated the applicability of Pizzato et al (2019) as part of the quality assessment (see table 2 and appendix 10.3). We note that despite possible deviations from instructions, the index test users in this study reported they were trained by Pie Medical and referred to the manufacturer training manual.
Pie Medical Imaging	15	17	Abstract	There was very little data on other clinical and implementation outcomes, although QAngio appears feasible as part of ICA examination. What is the definition of 'appears', which objective criteria were used?	"Appears" given the limited data available (rather than conclusive). We think the usage here is clear and reasonable.
Pie Medical Imaging	16	17	Abstract	Data on the diagnostic accuracy of CAAS vFFR was limited and a full meta-analysis was not feasible. Overall comment and question: At a number of sections in the document the statement is made regarding the limited availability of data on CAAS vFFR. However nowhere are objective criteria are provided how much data the authors expect to judge this as 'enough' data.	We think describing three retrospective studies of around 500 patients (or 303 in 1 study if the two non-manufacturer trials are discounted) as "limited" evidence is reasonable, particularly when compared to 26 studies, involving 5440 patients for QAngio QFR technology. (We note, for example that >3 studies are needed for reliable diagnostic meta-analysis)

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Pie Medical Imaging	17	18	Abstract	RCT evidence evaluating the effect of QFR on clinical and patient-centred outcomes is needed. We assume it incorrectly states QFR here.	QFR is correct, but we have moved the sentence to avoid confusion. (see erratum)
Pie Medical Imaging	18	20	1.3.1	and clinical effectiveness and implementation outcomes were synthesised narratively. Data from figures reported in studies were digitized to simulate the accuracy of a 'grey-zone strategy', whereby confirmatory FFR is only performed in patients with a QFR between 0.78 and 0.84. How is this 0.78 and 0.84 defined? As these cut-of values are not stated in the QFR publications.	This is to comply with the original NICE scope.
Pie Medical Imaging	19	39	4.1.6.3	**4.1.6.3 "Grey zone" analysis** Extracted figure data was used to conduct an analysis where testing includes a "grey-zone" of intermediate QFR values for which an FFR would be performed as a confirmatory test. The "grey-zone" diagnostic procedure considered, following the QAngio instructions, was: 1. Perform QFR 2. If QFR >0.84 continue without stenting/bypass [test negative] 3. If QFR ≤0.78 proceed to stenting/bypass [test positive] 4. If QFR is between 0.78 and 0.84, perform an FFR test and proceed to stenting/bypass if FFR≤0.80 [the grey zone] For the grey zone analysis, it was assumed that anyone within the grey zone has perfect diagnostic accuracy (because all received a 'gold-standard' FFR test), therefore false positive and negatives are only present in patients outside the grey zone. The impact of using the grey zone on the diagnostic accuracy of QAngio was assessed. The effect of using different FFR thresholds on the diagnostic accuracy of QAngio was also assessed. Due to lack of guidance on CAAS vFFR grey-zone cut-offs no such analyses were performed for this technology. It states lack of guidance on CAAS vFFR grey-zone cut off, however we provided that information as is also stated by the authors on page 29.	This has been amended to there being insufficient data in publications (i.e. figures of CAAS vFFR vs FFR) for the analysis to be feasible. We also note that, given the similar pattern of data for CAAS and QFR, results of any "grey-zone" application are likely to be similar for CAAS vFFR. (see erratum)

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Pie Medical Imaging	20	83	4.9.3	One study found high inter-rater repeatability for QAngio (fQFR: 0.001 (SD0.036) and cQFR: 0.001 (SD0.049)) as well as CAAS vFFR (0.005 (SD0.037)) and no statistically significant differences between raters' measurements. Which study is referred to? We assume reference 22. Key inter-rater variability measures are reported in the FAST and FAST POST study showing constant inter-observability in a total of 200 patients.	As discussed in response to comment 13, FAST POST did not meet the systematic review selection criteria.
Pie Medical Imaging	21	107	6.3	The strategy: ICA with vFFR , followed by confirmatory FFR/IFR if vFFR is inconclusive is missing, while these grey zone data haven been provided on specific request of the committee. While on page 108 it is stated: Note that it is not possible to consider a sixth strategy using CAAS vFFR, followed by confirmatory FFR/iFR when vFFR is inconclusive because there is no diagnostic accuracy data available to inform this strategy. On what basis is decided that for QFR this data is available as the reported grey zone (exact definition of why 0.78 or 0.84 is not reported in publications, just in their manual. And for vFFR	We considered that the data to support this analysis (essentially Figure 5 of Masjedi et al) was insufficient to make this a reliable or meaningful analysis. This has been clarified in Section 4.1.6.3 (see erratum, see also response to Comment 19) The EAG notes that the data provided is also insufficient to parameterise the strategy 'ICA with vFFR , followed by confirmatory FFR/IFR if vFFR', as stated in Section 6.5.3.1 and reproduced below: *"The diagnostic accuracy of an equivalent hybrid diagnostic approach for vFFR was not*

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					possible due to data limitations. The diagnostic accuracy data for vFFR is very scarce (see Section 4.8), and only 81 data points for the joint FFR and vFFR distribution were available from one single study.53 Furthermore, the underlying distribution of FFR values in this single study was considerably different from that of the data extracted for QFR (probability of FFR ≤0.80 was 0.296 in the single vFFR study compared to 0.402 across 3,194 data points in the QFR studies).”
Pie Medical Imaging	22	195	7.3	Current evidence on CAAS vFFR is very limited, so its diagnostic accuracy,clinical value and cost-effectiveness are highly uncertain. Here it states very limited, while in other paragraphs it states limited or too limited. What is the authors definition of limited and very limited?	See response to comment 16 above
Pie Medical Imaging	23	General		We have an ongoing prospective multicenter clinical trial called FAST II which is almost finished including patients. Are these additionally data sufficient for this committee and when can we submit them for an updated calculation / assessment?	A matter for DAR committee/NICE to consider. No response from EAG
Abbott Medical UK Ltd	24	General		Abbott do not consider the directionality of the DAR appropriate and expect the draft guidance to be balanced and evidence based.	It is not clear what is meant by “directionality” in this context. We assume it relates to comment numbers 26 and 35.

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					If this is the case, please refer to the response to comments 26 and 35, which appear to misinterpret the analyses presented in the report.
Abbott Medical UK Ltd	25	General		Abbott would like to remind that QFR and/or vFFR should not be compared with PressureWire measurement as this is not part of the published scope. The scope says that "*The comparator is clinical decision making based on the visual interpretation of the angiographic images done during invasive coronary angiography (ICA), alongside clinical judgement.*". A change of comparator is likely to be considered as a breach of process.	The scope clearly discusses the potential for QFR to replace FFR with pressure wire (e.g. Section 2.2.1 of scope). The scope also clearly states in Table 1, scope of the assessment, under comparator that the reference standard is invasive FFR or iFR measurement. We note that the analyses reported follow the NICE-approved protocol, and that comparing a novel diagnostic tool to all other existing alternative tools is standard practice in DAR assessments.
Abbott Medical UK Ltd	26	General		Abbott are concerned that the assessment depends on the assumption that outcome data shown to apply to PressureWire could be assumed to apply to QFR and vFFR on the basis that there is good agreement between the numerical thresholds (that is, QFR/FFR numbers and outcomes after QFR/FFR are different. A correlation between FFR and QFR numbers cannot be taken to mean that events can be predicted). This does not appear to be a valid assumption. It is noted that in the	This DAR has **not** assumed that "data shown to apply to PressureWire could be assumed to apply to QFR and vFFR"

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				assessment of implantable cardiac monitors for atrial fibrillation detection after cryptogenic stroke, the Diagnostics Advisory Committee did not think it appropriate to apply data from one device to others.	We have **not** assumed that good correlation between pressure wire FFR and QFR / vFFR leads to a good prediction of outcomes. This is exactly why formal bivariate meta-analysis of accuracy is used. We have used the pressure wire FFR values that were derived from patients who **also** had QFR measurements. We did not impose a correlation between FFR and QFR nor did we assume that the QFR values derived from QAngio are a proxy for pressure wire FFR values. Please also see our response to comment 35.
Abbott Medical UK Ltd	27	18	Abstract conclusion	The comment that QFR could entirely replace FFR goes beyond the remit of the DAR in that it is the expression of a judgement. It is only the committee that makes judgements on the data in the context of guidance formation and thus such an opinion in the DAR is frankly, speculative and inappropriate. Abbott would respectfully request that the committee disregard this opinion and draw an independent conclusion.	We consider this to be a reasonable conclusion when it is taken in the full context of the evidence available. It is not a recommendation for practice. Hence the use of “suggests that” and “could potentially”. The NICE Appraisal Committee will draw their own conclusion.

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Abbott Medical UK Ltd	28	18	Abstract conclusion	We note that the opinion that QFR could replace FFR is dependent upon *"…further evidence on general clinical benefits and specific subgroups.*".	No response required. This is an issue for committee discussion.
Abbott Medical UK Ltd	29	40	4.1.6.5	We note that it is stated that *"The systematic review identified very little published data on the clinical impact of using QFR and QAngio screening. In particular, very little data was found on the impact QFR (with or without a grey zone) might have on future incidence and prevention of coronary events."* This lack of outcome data is concerning.	No response required. This is an issue for committee discussion.
Abbott Medical UK Ltd	30	45	4.2.1	It is noted that most of the studies were conducted in Asia. This means that most of the patients in these studies were non-Caucasian, hence the overall results may not be generalisable to the NHS.	No response required. This is an issue for committee discussion.
Abbott Medical UK Ltd	31	66	4.6.2.1	QAngio results are uncertain when microvascular resistance (IMR) is high. There may therefore be a substantial proportion of patients in whom QAngio results are unreliable. How is it known in which patient the result is unreliable unless IMR is measured? As it is stated in the same section that IMR is measured by pressure wire, the proposed financial benefit of QAngio cannot be realised as a pressure wire has to be taken and a procedure performed to measure IMR.	We note that the claim made, (QAngio results are uncertain when microvascular resistance (IMR) is high) was not clearly supported by the evidence. This is an issue for committee discussion.
Abbott Medical UK Ltd	32	66	4.6.2.1	Small vessel disease has a mixed effect on the diagnostic accuracy of QFR. In other words, there is uncertainty over the diagnostic accuracy of QFR in small vessel disease. This uncertainty does not provide a sound basis for QFR adoption within the NHS.	We note that the claim made, (Small vessel disease has a mixed effect on the diagnostic accuracy of QFR) was not clearly supported by the evidence. This is an issue for committee discussion.

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Abbott Medical UK Ltd	33	67	4.6.2.1	It is noted that *"There was also limited evidence on the impact of patient comorbidities on the accuracy of QAngio."*. Abbott note that the comment that there was limited evidence on the impact of patient co-morbidities and are aware that many patients with coronary artery disease have other co-morbidities so there is limited evidence in the impact of these on QFR.	No response required. This is an issue for committee discussion.
Abbott Medical UK Ltd	34	84	4.9.6	It is noted within the DAR that "*No evidence was reported in QAngio and CAAS vFFR studies for any of the following protocol specified outcomes ….*" Abbott notices that there was a simulation study of clinical effectiveness. Abbott is extremely worried about the lack of outcome data for both QFR and vFFR techniques. A lack of outcome data is not the basis for adoption of a new technology.	No response required. This is an issue for committee discussion.
Abbott Medical UK Ltd	35	85	4.9.7	IRIS-FFR sought to evaluate the prognosis of deferred & revascularised coronary stenoses after FFR measurement. For QFR, all that exists are correlations with FFR – no data have yet demonstrated that just because there is a numerical correlation between QFR and FFR, that the same relationship in terms of event prediction will also occur, and this is by no means certain and is an absolutely critical flaw. If there was a systematic QFR error in estimating FFR in a particular lesion or patient subset, this would be missed by this analysis altogether, and invalidates the comparison and the use of the well-characterised IRIS-FFR cohort. A large prospective study examining the utility of QFR vs. FFR in an all-comers population is needed, then a direct comparison could be made.	We note that we recommend that a study of QFR similar to IRIS-FFR is desirable in our recommendations for research, precisely to address this issue. We note that in Section 4.9.7 we are **NOT** using any correlation between QFR and FFR. The simulation study uses the **known** FFR values from the patients to simulate later outcomes (based on IRIS-FFR), and then evaluating the resulting clinical consequences of using the **known** QFR values to guide decisions.

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					We think this is clearly set out in section 4.1.6.5 (where the word correlation does not appear). The same approach is used in the economic model. The baseline risk of MACE is conditional on FFR value as derived from the IRIS-FFR study, which evaluated the prognosis of deferred & revascularised coronary stenoses after pressure wire FFR measurement. It is the distribution of FFR values that differs by diagnostic strategy (and hence MACE outcomes differ by strategy), and this distribution is based on **known** (pressure wire) FFR values from the same patients who have **known** QFR values so that expected outcomes can be derived for the different strategies. In the context of this DAR, we have to make reasonable assumptions about how QFR might behave, in the absence of

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					better evidence. The above approach seems reasonable without an IRIS-FFR-type study, which evaluates the prognosis of deferred & revascularised coronary stenoses after QFR measurement. "If there was a systematic QFR error...". We note that we have found no evidence of such an error: there is no such error for the overall population
Abbott Medical UK Ltd	36	90	4.10.3	It is observed that "*One CAAS study noted that careful adaptations in image acquisition will be required to reduce the risk of test failures if used in daily clinical practice*". This raises concerns over the ability of vFFR to be used in routine practice.	No response required. This is an issue for committee discussion.
Abbott Medical UK Ltd	37	91	4.11	It is noted that "*Diagnostic accuracy data for CAAS vFFR was limited to only three studies. Results from the studies were heterogeneous limiting meta-analysis and a full evaluation of CAAS vFFR. Hence its diagnostic value is currently uncertain, but it may be potential alternative to QAngio*.". There is considerable uncertainty as to the diagnostic accuracy of vFFR. Abbott are of the view that this technology should not be adopted within the NHS given such uncertainty.	No response required. This is an issue for committee discussion.
Abbott Medical UK Ltd	38	92	4.11	The comment "*Data on CAAS vFFR are currently too limited and heterogeneous to draw any useful conclusions on its clinical value*" supports Abbott's view that vFFR should not be adopted within the NHS.	No response required. This is an issue for committee discussion.
Abbott Medical UK Ltd	39	105	6	As the clinical data feed into the economic model, the economic results rely upon the assumption that outcome data from one modality can be	As noted in response to comments 26 and 35, the EAG did not assume that outcome

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				assumed to apply to a different modality. The economic results thus rely upon an assumption rather than fact.	data collected for patients tested with FFR was directly applicable when using different test modalities (namely, QFR and vFFR). It is important to understand that the key mechanism by which tests accrue value is an indirect one that arises from the tailoring of treatment decisions to patient characteristics (e.g., test results). This indirect mechanism can be characterised by explicitly linking the test results to how individuals are classified in accordance to the results, how they are clinically managed and their outcomes, which are conditional on classification and choice of clinical management (Soares et al., 2018) [1]. The economic modelling relies on a linked evidence approach to characterise this mechanism of value accrual, and, therefore, does not assume *"that outcome data from one modality can be*

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					assumed to apply to a different modality". Instead, it captures the impact of differences in diagnostic performance on the classification of individuals and their subsequent clinical management, and links it to clinical outcomes based on the individuals' underlying FFR distribution (which is known) and the treatment effect of the optimal medical treatment with or without revascularisation. The EAG notes that the use of linked evidence is a common approach and one that is recognised by the NICE Diagnostics Assessment Programme manual (Section 13.2): *"If, as is likely, there are no end-to-end studies available for a diagnostic technology, then different types of evidence are collected and a linked evidence approach taken."*

[1] Soares MO, Walker S, Palmer SJ, Sculpher MJ. Establishing the value of diagnostic and prognostic tests in Health Technology Assessment. Medical Decision Making. 2018 May;38(4):495-508.