**DE NOVO CLASSIFICATION REQUEST FOR**
**$FFR_{CT}$ V. 1.4**

## REGULATORY INFORMATION

FDA identifies this generic type of device as:

**Coronary Physiologic Simulation Software Device –** A coronary vascular physiologic simulation software device is a prescription device that provides simulated functional assessment of blood flow in the coronary vascular system using data extracted from medical device imaging to solve algorithms and yield simulated metrics of physiologic information (e.g., blood flow, coronary flow reserve, fractional flow reserve, myocardial perfusion). A coronary vascular physiologic simulation software device is intended to generate results for use and review by a qualified clinician.

**NEW REGULATION NUMBER: 870.1415**

**CLASSIFICATION:** II

**PRODUCT CODE: PJA**

## BACKGROUND

**DEVICE NAME:** $FFR_{CT}$ V. 1.4

**SUBMISSION NUMBER:** DEN130045

**DATE OF DE NOVO:** November 6, 2013

**CONTACT:** HeartFlow, Inc.
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**REQUESTER'S RECOMMENDED CLASSIFICATION:** II

### INDICATIONS FOR USE

HeartFlow $FFR_{CT}$ is a post-processing software for the clinical quantitative and qualitative analysis of previously acquired Computed Tomography (CT) DICOM[1] data for clinically stable symptomatic patients with coronary artery disease. It provides $FFR_{CT}$, a mathematically derived quantity, computed from simulated pressure, velocity and blood flow information obtained from a 3D computer model generated from static coronary CT

[1] Digital Imaging and Communications in Medicine (standard for the communication and management of medical imaging information and related data)

images. $FFR_{CT}$ analysis is intended to support the functional evaluation of coronary artery disease.

The results of this analysis are provided to support qualified clinicians to aid in the evaluation and assessment of coronary arteries. The results of HeartFlow $FFR_{CT}$ are intended to be used by qualified clinicians in conjunction with the patient's clinical history, symptoms, and other diagnostic tests, as well as the clinician's professional judgment.

The device is only for prescription use.

**LIMITATIONS**

The safety and effectiveness of the FFRCT analysis has not been evaluated for the following populations:

1. Suspicion of acute coronary syndrome (where acute myocardial infarction or unstable angina have not been ruled out)
2. Recent prior myocardial infarction within 30 days
3. Complex congenital heart disease
4. Prior coronary artery bypass graft (CABG) surgery
5. Patients with a Body Mass Index >35
6. Patients who require emergent procedures or have any evidence of ongoing or active clinical instability, including acute chest pain (sudden onset), cardiogenic shock, unstable blood pressure with systolic blood pressure <90 mmHg, severe congestive heart failure (New York Heart Association [NYHA] III or IV) or acute pulmonary edema

Due to the potential for artifacts in the CT data or degradation of CT data quality, the safety and effectiveness of the $FFR_{CT}$ analysis has not been evaluated for the following populations:

1. Patients with intracoronary metallic stents
2. Patients with prior pacemaker or internal defibrillator lead implantation
3. Patients with prosthetic heart valves
4. Patients with significant arrhythmias or tachycardia (uncontrolled by medication) that would preclude CT acquisition
5. Coronary vessels with excessive calcification

$FFR_{CT}$ has been studied in patients with prior PCI but the results have only been validated in vessels without metallic stents.

The diagnostic performance of $FFR_{CT}$ has been validated in patients who are candidates for invasive coronary angiography based on clinical presentation and/or non-invasive testing.

The performance of $FFR_{CT}$ has not been fully characterized in small vessels. Vessels smaller than 1.8mm, determined from the static CT images, are grayed out and marked

"unavailable" on the FFRCT anatomy model.

$FFR_{CT}$ has been clinically validated using DICOM data acquired from the following CT scanner manufacturers: Siemens, Toshiba, General Electric, and Phillips. $FFR_{CT}$ performance using DICOM data acquired from scanners for which it has not been clinically validated is unknown, and therefore safety and effectiveness of its use has not been established.

$FFR_{CT}$ results may be adversely affected by the following:

1. Marginal quality of the submitted imaging data (motion, blooming, misregistration, etc.)
2. Grossly incorrect brachial pressure (like cath measured FFR, $FFR_{CT}$ is somewhat insensitive to pressure but wide discrepancies will effect the $FFR_{CT}$ results)
3. Regionalized or global myocardial dysfunction
4. Myocardial mass abnormalities (Hypertrophic right ventricle for example)
5. Abnormal patient physiology (e.g., severe congenital disease or excess calcification)

$FFR_{CT}$ simulates maximal hyperemia, which results in vasodilation of the epicardial coronary arteries. This condition is commonly induced using nitrates. Therefore, HeartFlow recommends following SCCT guidelines for CCTA acquisition, which recommends the use of sublingual nitrates at the time of image acquisition unless contraindicated. Absence of nitrates during CCTA may adversely affect the results of the FFRCT analysis.

$FFR_{CT}$ Results provision timeframes are contractually defined, results are subject to delay. $FFR_{CT}$ should not be used for patients with unstable coronary syndromes, or in patients where urgent and timely workup and evaluation is critical.

The specificity of $FFR_{CT}$ may decrease in patients with Agatston scores greater than1000.

Due to the possible variability in the $FFR_{CT}$ results, the results should be reviewed as one of several clinical data points to be used in conjunction with the patient's original CT images, clinical history, symptoms and other diagnostic tests, as well as an appropriately trained clinician's clinical judgment, to evaluate the patient.

Qualitative anatomical information presented on the 3D/2D computer generated anatomical models is for orientation purposes only. Quantitative lumen diameter is representative of the geometric model and the accuracy is dependent on the quality of the CT data provided. It does not represent artery diameter, and should not be used for treatment decisions.

The $FFR_{CT}$ analysis process is dependent on the quality of the imaging data provided by the ordering physician. In some cases, the image data quality will necessitate clarification or instruction from the providing physician. FFRCT results may be affected by assumptions needed to resolve anatomy in areas of uncertainty, whether provided by the

physician or made by HeartFlow case analysts. All assumptions used in the generation of the HeartFlow FFRCT results will be listed in the PDF results in English. Certified translation of case assumptions may be requested via email (care@heartflow.com) and will take 5 – 7 business days.

$FFR_{CT}$ results represent patient conditions at the time of CT acquisition. The duration of time and changes to patient health after CT acquisition must be assessed when interpreting the FFRCT results. Clinical validation that supports FFRCT was limited to subjects whose CT acquisition occurred within 60 days of invasive FFR (mean 18 +/- 13 days).

PLEASE REFER TO THE LABELING FOR A COMPLETE LIST OF WARNINGS AND PRECAUTIONS.

## DEVICE DESCRIPTION

$FFR_{CT}$ v1.4 is post-processing image analysis software developed for the clinical quantitative and qualitative analysis of previously physician-acquired DICOM-compliant cardiac CT images and data, to assess the anatomy and function of the coronary arteries. The software displays the resulting coronary anatomy combined with functional information using graphics and text, including a computed and derived quantification of blood flow, termed $FFR_{CT}$ to aid the clinician in the assessment of coronary artery disease.

The HeartFlow $FFR_{CT}$ software is housed at Heart Flow, Inc. The health care provider electronically sends the patient's CT scan data to HeartFlow, Inc. where a 3D computer model of the coronary arteries is developed and simulates blood flow in the models using computational fluid dynamics. A resulting report is electronically sent to the physician with the estimated fractional flow reserve (FFR) values (called $FFR_{CT}$ values) displayed as color images of the patient's heart (Figure 1) and an associated color interpretation table (Table 1)Table 1: Error from the HFNXT Study Population. Not indicative of all patient populations. Please refer to the summary of clinical data to determine the population in which the $FFR_{CT}$ technology has been validated. indicating the error associated with each measurement range in the HFNXT clinical study.

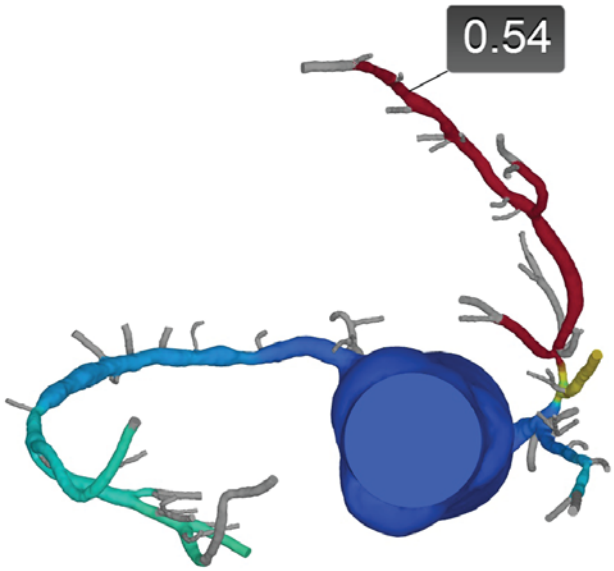



**Figure 1: Example color mapped diagram of coronary vessels from $FFR_{CT}$ Results**

| $FFR_{CT}$ is | Color | Average Error to $FFR_{CATH}$* +/- 1SD |
|---|---|---|
| ≤0.70 | Red | -0.05 +/- 0.11 |
| 0.70 - 0.75 | Red to Orange | -0.04 +/- 0.12 |
| 0.76 - 0.80 | Orange to Yellow | -0.03 +/- 0.08 |
| 0.81 - 0.84 | Yellow to Green | -0.04 +/- 0.07 |
| 0.85 - 0.90 | Green to Cyan | -0.03 +/- 0.06 |
| 0.91 - 1.0 | Cyan to Blue | -0.01 +/- 0.04 |
| ALL | | -0.03 +/- 0.07 |

**Table 1: Error from the HFNXT Study Population. Not indicative of all patient populations. Please refer to the summary of clinical data to determine the population in which the $FFR_{CT}$ technology has been validated.**

See the $FFR_{CT}$ v1.4 Instructions for Use for further details.

## SUMMARY OF NONCLINICAL/BENCH STUDIES

The following nonclinical testing was presented to demonstrate the appropriate functionality of the software and the basis of the computational methods. Some testing (e.g., biocompatibility, shelf life, etc.) was not applicable for this software only device.

### SOFTWARE

The sponsor provided detailed documentation of their proprietary software based on a moderate Level of Concern (LOC) according to the FDA guidance document "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices". The documentation included a detailed description of the computational modeling processes and algorithms used to develop the 3D model of the coronary anatomy.

A comprehensive risk analysis was provided for the software with detailed description of the hazards, their causes and severity as well as acceptable methods for control of the identified hazards. They provided a description, with test protocols including pass/fail criteria and report of results, of acceptable verification and validation activities at the unit, integration and system level. A justification was provided for the use of CT scans from various image acquisition systems by the software. The expected impact of various hardware features on performance was assessed and minimum specifications for acceptable CT images for analysis were specified. Performance stratified by scanner models used in the clinical study was also reported to help demonstrate that essential scanner features and characteristics did not significantly impact performance. Stress testing and repeatability testing were also performed.

The cybersecurity considerations of data confidentiality, data integrity, data availability, denial of service attacks, and malware were adequately addressed using platform controls, application controls and procedure controls and evidence was provided that the controls perform as intended. Risks related to failure of various software components and their potential impact on patient reports and operator failures were also adequately addressed in the risk analysis.

Additional verification and validation testing was provided to demonstrate the functionality and accuracy of specific modules and components such as automatic and semi-automatic image analysis and segmentation tools. This testing assessed accuracy compared to ground truth data sets. Several tests also assessed reproducibility.

**PERFORMANCE TESTING – BENCH**

Some pre-clinical bench studies of the computational methods underlying HeartFlow's $FFR_{CT}$ technology were referenced in the submission. These studies characterized the solver technology during development that was ultimately licensed to HeartFlow. Tests included comparing computational flow velocity solutions to Laser Doppler Anemometry and phase-contrast MRI flow data in an *in vitro* model under steady-state and pulsatile flow conditions. This testing provided quantitative evidence of the validity of the computational modeling measurement methods used by the device.

**PERFORMANCE TESTING – ANIMAL**

Several prior published *in vivo* animal model validation studies were referenced to support the validity of the technological methods used by the device. However, because animal models do not permit evaluation of the technology in relevant anatomic or physiologic models reflecting diseased human coronary vessels, animal testing was

deemed insufficient to further support clinical utility of the HeartFlow $FFR_{CT}$ technology.

## HUMAN FACTORS TESTING

Two human factors validation tests were performed: one assessing customers and the other assessing software operators. Customer human factors testing assessed the process of submitting image data and downloading results. The results of the testing found acceptable user satisfaction for the usability objectives. No exceptions to safe behavior (as derived from the risk analysis) were noted during the testing. Operator testing assessed the ability of analysts to consistently and effectively use the software for each individual procedure required for developing accurate output reports. This testing found the software to be adequately safe and effective for use by the intended internal users for case processing and quality control with acceptable user satisfaction. Acceptable mitigations were also identified for user errors and other observations during both of the studies.

## CONSISTENCY (REPRODUCIBILITY/ REPEATABILITY) EVALUATION

Reproducibility (variability between case analysts) and repeatability (variability between results from the same case analyst) of measurements were both assessed using prior clinical CT scans under challenge conditions (including worst-case image quality, minimal case analyst training and experience, and disease burden) as well as normal controlled conditions. Resulting variability was found to be acceptable.

## SUMMARY OF CLINICAL INFORMATION

HeartFlow conducted three clinical studies involving validation of $FFR_{CT}$. Two of these studies, Discover-FLOW and DeFACTO, were conducted with prior versions of the software v1.0 and v1.2, not commercially available in the United States. The DeFACTO study provided supportive data for the *de novo* submission. The final study, HeartFlowNXT (HFNXT), is the basis for the clinical validation of the current version 1.4.

### *DeFACTO Study*

DeFACTO (Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography Study) (NCT01233518) was a prospective, international, multicenter study designed to assess the diagnostic performance of $FFR_{CT}$ for diagnosis of hemodynamically significant coronary artery stenosis. The study involved 252 stable patients with suspected or known CAD from 17 centers in 5 countries who underwent CT, invasive coronary angiography (ICA), FFR and $FFR_{CT}$ between October 2010, and October 2011. All CT, FFR and angiographic data were interpreted in a blinded fashion by independent core laboratories. Accuracy of $FFR_{CT}$ for diagnosis of ischemia was compared with an invasive FFR reference standard. Ischemia was defined by an FFR or $FFR_{CT} \leq 0.80$ while anatomically obstructive CAD was defined by visual stenosis of ≥50% on CT and ICA.

The primary study endpoint was improvement in per-patient diagnostic accuracy (sensitivity and specificity) such that the lower boundary of the one-sided 95% confidence interval exceeded 70%. The results of this study were published by Min, et.al.[2] Because the DeFACTO trial assessed performance of a previous version of the device, it provided supportive data but was not central to the review of $FFR_{CT}$ v. 1.4.

### *HeartFlowNXT*

HeartFlow analysis of coronary blood flow using coronary CT angiography: NeXt sTeps (the HeartFlowNXT or HFNXT study) (NCT01757678) was a prospective, multicenter, non-randomized study. The overall objective of the HFNXT study was to determine the diagnostic performance of $FFR_{CT}$, as compared to cCTA alone (according to Society of Cardiovascular Computed Tomography (SCCT) guidelines and within 60 days of ICA), for the non-invasive determination of the presence of hemodynamically significant coronary lesions using direct measurement of FFR (≤0.80) during cardiac catheterization as the reference standard. The study reflected improvements in $FFR_{CT}$ technology (software version v1.4) and a focus on quantitative image-quality analysis.

[2] Min, J.K., et. al., *Diagnostic accuracy of fractional flow reserve from anatomic CT angiography.* JAMA, 2012. 308(12): p. 1237-45.

The study was conducted at 11 sites in 8 countries in Canada, Europe and Asia from September 2012 to August 2013, with 276 subjects enrolled. A total of 254 adult subjects with known or suspected coronary artery disease who were scheduled for clinically indicated invasive coronary angiography comprised the intention-to-diagnose (ITD) population. Subjects had an overall mean age of 63.7 years and 63.8% were men. Similar to many interventional cardiology trials, few minority patients were enrolled in HFNXT. Only 1.2% of patients were Hispanic and there were no Black patients. Because higher calcium scores could be expected among these patients due to higher incidence of high body mass index (BMI), hypertension and diabetes, $FFR_{CT}$ performance across calcium scores was compared that in US patients in the DeFACTO study (comprised with 11% Hispanic and 4% Black patients). Performance was maintained at all levels of calcium scores below 1000. No significant differences in diagnostic accuracy were observed in subjects with or without high BMI, hypertension, or diabetes.

A total of 22.8% of patients in the trial had diabetes mellitus, 68.5% had hypertension, 78.7% had hyperlipidemia, 57.1% were current or former smokers. Also, 77.6% presented with angina in the 30 days prior to enrollment; 77.7% of subjects with angina had stable angina and 22.3% had unstable angina. Only 2% had documented prior history of myocardial infarction and no patients had renal dysfunction, defined as creatinine >1.5 mg/dL. The mean body mass index for enrolled subjects was 25.6 ± 3.7 kg/m2. Left ventricular ejection fraction was reported for 76% of the enrolled subjects with a mean value of 61.8%. The time from the cCTA scan to the ICA procedure was between 1 to 30 days in 87% of the ITD patients with a mean of 18.1 days. Sublingual or intravenous nitrates were administered in 99.6% of subjects undergoing coronary artery CT scanning. In 78% of the subjects beta blockers were administered to reduce heart rate prior to scan. The mean calcium score for ITD subjects was 302 (±468) Agatston units. A calcium score was reported for 84.3% of subjects, and of these, 25.7% had a calcium score > 400 Agatston units.

Direct comparison of invasive FFR and $FFR_{CT}$ was performed in 484 vessels. At least one invasive FFR measurement was collected in all ITD subjects with an average of 1.9 measurements per subject. All invasive FFR data was reviewed by an independent FFR/QCA core laboratory.

The primary endpoint was the per-vessel sensitivity and specificity of $FFR_{CT}$ to detect hemodynamically significant obstruction when FFR was used as the reference standard. The pre-specified target goals identified by the sponsor for sensitivity and specificity were 65% and 55%, respectively. As this study was conducted OUS, these target goals were not agreed upon by the FDA.

Primary endpoint success required both sensitivity and specificity hypotheses to be met. The per-vessel sensitivity of $FFR_{CT}$ in the ITD population was 83.5% with a lower one-sided 95% CI of 75.3%. The per-vessel specificity of $FFR_{CT}$ in the ITD population was 85.8% with a lower one-sided 95% CI of 81.5%. Both of the lower one-sided confidence limits for sensitivity and specificity were significantly above the pre-specified target goals of 65% and 55%, respectively, and were considered acceptable. The results are shown in Table 2 below.

**Table 2: Primary Endpoint Results: Per-Vessel Sensitivity and Specificity of FFRCT Intent to Diagnose Population**

| | ESTIMATE, % | LOWER ONE-SIDED 95% CONFIDENCE BOUND | TARGET RATE | MET[1] NOT MET |
|---|---|---|---|---|
| Sensitivity | 83.5% | 75.3% | 65% | MET |
| Specificity | 85.8% | 81.5% | 55% | MET |
| FFR is used as the reference standard<br>$FFR_{CT}$: Diseased if hemodynamically-significant obstruction is ≤ 0.80<br>FFR: Diseased if hemodynamically-significant obstruction is ≤ 0.80<br>[1]MET if 95% LCL > Target Rate | | | | |

Per-subject $FFR_{CT}$ specificity compared to site-read cCTA demonstrated superior diagnostic ability ($p$<0.001) in the intent to diagnose (ITD) subjects in one or more major epicardial coronary artery segments, using invasive FFR as the reference standard and defining hemodynamically-significant obstruction of a coronary artery (positive result) as an FFR ≤ 0.80 for both FFR and $FFR_{CT}$ and as > 50% stenosis severity for site-read cCTA. Diagnostic performance of $FFR_{CT}$ compared to site-read cCTA on the subject level is shown in Table 3 below.

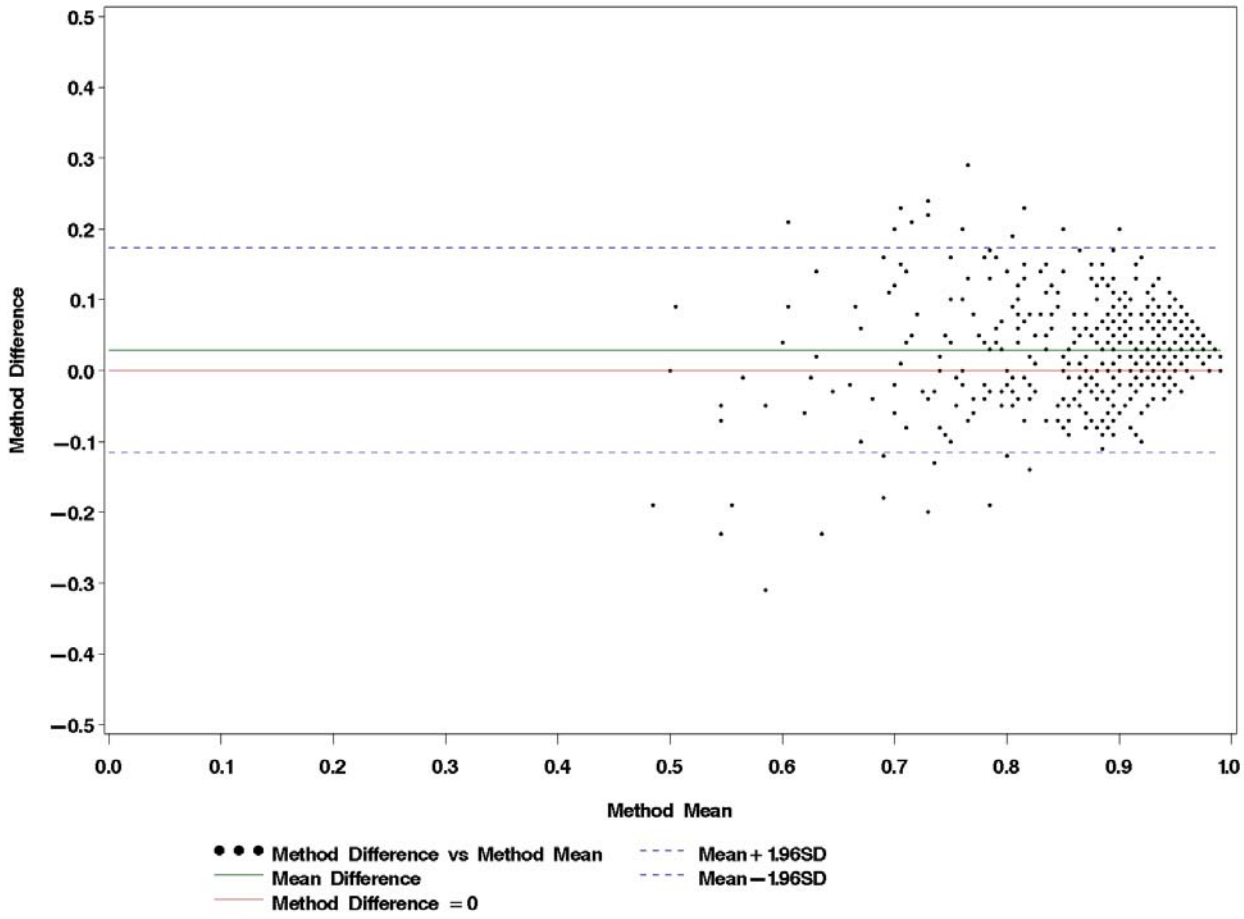
**Table 3: Per-Subject Diagnostic Performance Analysis with FFR ≤ 0.80 as the Reference Standard. Intent to Diagnose Population.**

| | $FFR_{CT}$ ≤ 0.80 ESTIMATE % (95% Wilson CI) | SITE-READ cCTA > 50% ESTIMATE % (95% Wilson CI) |
|---|---|---|
| Diagnostic Accuracy | 81.1% (95.8%-85.4%) | 52.8% (46.6%-58.8%) |
| Sensitivity | 86.3% (77.0%-92.1%) | 93.8% (86.2%-97.3%) |
| Specificity | 78.7% (72.1%-84.2%) | 33.9% (27.3%-41.2%) |
| PPV | 65.1% (55.6%-73.5%) | 39.5% (32.8%-46.6%) |
| NPV | 92.6% (87.2%-95.8%) | 92.2% (83.0%-96.6%) |

$FFR_{CT}$ values were not found to be precisely correlated with the FFR value across the range of measurement. The Bland-Altman plot of FFR vs. FFRCT for all measurements is shown in Figure 2.

The HeartFlowNXT study demonstrated good diagnostic performance for $FFR_{CT}$ when all vessels were included, irrespective of size, location, or territory, and across a range of cCTA image quality measures.

**Figure 2: FFRCT Bland-Altman Plot**




## LABELING

The device is labeled for clinically stable symptomatic patients with coronary artery disease that have a previously-collected DICOM CT scan. Several product warnings are included in the labeling that carefully specify the intended patient population, identify anatomy and image acquisition factors that may impact $FFR_{CT}$ results, and provide cautionary guidance for interpretation of the $FFR_{CT}$. These warnings were found to be appropriate.

The labeling also provided a detailed summary of the clinical trial procedures, patient population, and results. Per-vessel measurement performance of $FFR_{CT}$ with respect to invasive FFR was reported, including a localized performance summary by vessel and segment. A PDF $FFR_{CT}$ Results summary is provided to the physician for each patient scan. This summary includes prominent warnings regarding interpretation of the output as well as a representation of average error observed in the clinical data for various ranges of $FFR_{CT}$ measurement.

Labeling intended for internal case analysts was also provided, which adequately described detailed data processing steps and data features that could affect accuracy of results.

## RISKS TO HEALTH

Table 4 below identifies the risks to health that may be associated with use of a Coronary Physiologic Simulation Software Device and the measures necessary to mitigate these risks.

**TABLE 4: RISK/MITIGATION MEASURES**

| Identified Risk | Mitigation Measures |
|---|---|
| False negative results improperly indicating diseased vessel as low probability for significant disease leads to delay of further evaluation/treatment | Software Verification, Validation, and Hazard Analysis<br>Non-clinical Performance Testing<br>Clinical Testing<br>Consistency (Repeatability/Reproducibility) Evaluation<br>Labeling |
| False positive results improperly indicating diseased vessel as high probability for significant disease leads to incorrect patient management | |
| Delayed delivery of results leading to delay of further evaluation/treatment | |
| Failure to properly interpret device results leads to incorrect patient management | Human Factors Testing<br>Labeling |

## SPECIAL CONTROLS:

In combination with the general controls of the FD&C Act, the Coronary Physiologic Simulation Software Device is subject to the following special controls:

1. Adequate software verification & validation based on comprehensive hazard analysis with identification of appropriate mitigations must be performed including:
   a. Full characterization of technical parameters of the software, including any proprietary algorithm(s) used to model the vascular anatomy.
      i. Adequate description of the expected impact of all applicable image acquisition hardware features and characteristics on performance and any associated minimum specifications.
   b. Adequate consideration of privacy and security issues in the system design.
      i. Adequate mitigation of impact of failure of any subsystem components (signal detection and analysis, data storage, system communications and cybersecurity) with respect to incorrect patient reports and operator failures.

2. Adequate non-clinical performance testing must be provided to demonstrate the validity of computational modeling methods for flow measurement.

3. Clinical data supporting the proposed intended use must be provided, including the following:

a. Output measure(s) must be compared to a clinically acceptable method and must adequately represent the simulated measure(s) the device provides in an accurate and reproducible manner.
b. Clinical utility of the device measurement accuracy must be demonstrated by comparison to that of other available diagnostic tests (from literature analysis).
c. Statistical performance of the device within clinical risk strata (e.g., age, relevant comorbidities, disease stability) must be reported.
d. The data set must be adequately representative of the intended use population for the device (e.g., patients, range of vessel sizes, imaging device models). Any selection criteria or limitations of the samples must be fully described and justified.
e. Statistical methods must consider the pre-defined endpoints.
    i. Estimates of probabilities of incorrect results must be provided for each endpoint.
    ii. Where multiple samples from the same patient are used, statistical analysis must not assume statistical independence without adequate justification.
    iii. Report must provide appropriate confidence intervals for each performance metric.
f. Sensitivity and specificity must be characterized across the range of available measurements.
g. Agreement of the simulated measure(s) with clinically acceptable measure(s) must be assessed across the full range of measurements.
h. Comparison of the measurement performance must be provided across the range of intended image acquisition hardware.
i. If the device uses a cut-off threshold or operates across a spectrum of disease, it must be established prior to validation and it must be justified as to how it was determined and clinically validated.

4. Adequate validation must be performed and controls implemented to characterize and ensure consistency (repeatability and reproducibility) of measurement outputs.
    a. Acceptable incoming image quality control measures and the resulting image rejection rate for the clinical data must be specified.
    b. Data must be provided within the clinical validation study or using equivalent datasets demonstrating the consistency (i.e., repeatability/reproducibility) of the output that is representative of the range of data quality likely to be encountered in the intended use population and relevant use conditions in the intended use environment.
        i. Testing must be performed using multiple operators meeting planned qualification criteria and using the procedure that will be implemented in the production use of the device.
        ii. The factors (e.g., medical imaging data set, operator) must be identified regarding which were held constant and which were varied during the evaluation, and a description must be provided for the computations and statistical analyses used to evaluate the data.

5. Human factors evaluation and validation must be provided to demonstrate adequate performance of the user interface to allow for users to accurately measure intended

parameters, particularly where parameter settings that have impact on measurements require significant user intervention.

6. Device labeling must be provided that adequately describes the following:
   a. The device's intended use, including the type of imaging data used, what the device measures and outputs to the user, whether the measure is qualitative and/or quantitative, the clinical indications for which it is to be used, and the specific population for which the device use is intended.
   b. Appropriate warnings specifying the intended patient population, identifying anatomy and image acquisition factors that may impact measurement results, and providing cautionary guidance for interpretation of the provided measurements.
   c. Key assumptions made in the calculation and determination of simulated measurements.
   d. The measurement performance of the device for all presented parameters, with appropriate confidence intervals, and the supporting evidence for this performance. Per-vessel clinical performance, including where applicable localized performance according to vessel and segment, must be included as well as a characterization of the measurement error across the expected range of measurement for key parameters based on the clinical data.
   e. A detailed description of the patients studied in the clinical validation (e.g., age, gender, race/ethnicity, clinical stability, current treatment regimen) as well as procedural details of the clinical study (e.g., scanner representation, calcium scores, use of beta-blockers/nitrates).
   f. Where significant human interface is necessary for accurate analysis, adequately detailed description of the analysis procedure using the device and any data features that could affect accuracy of results.

## BENEFIT/RISK DETERMINATION

The probable risks of the device are based on data collected in clinical studies described above. Because the device uses a previously-obtained CT scan (<60 days old) that would have been obtained anyway for analysis, no additional intervention to the patient is required in order to perform the analysis. Therefore, the device only poses risks associated with the diagnostic decisions made based on the report provided by the device. In cases of a false positive reported by the device, an unnecessary angiogram and/or revascularization may occur, resulting in associated procedural risks, the most serious of which include heart attack, heart failure, stroke, the need for surgical intervention, and death. In cases of a false negative, there is risk of failure to diagnose and properly treat a significant lesion, which could also be associated with adverse events such as heart attack, heart failure, or death. The HFNXT study did not specifically quantify the likelihood of such events because the device results were blinded during the study.

The probable benefits of the device are also based on data collected in the clinical studies as described above. These include improved per-vessel sensitivity and specificity for detecting hemodynamically-significant obstruction of the coronary arteries compared to other available non-invasive methods. The HFNXT study did determine the likelihood of false positives and false negatives in the intended use population. Per vessel-sensitivity was 85.8% compared to

FFR (Lower 95% CI 73.5%). Per vessel-specificity was 83.5% compared to FFR (Lower 95% CI 81.5%).

Additional factors to be considered in determining probable risks and benefits for the $FFR_{CT}$ include the quality of the study design and conduct, the robustness of the study result, patient tolerance for risk, and availability of alternative diagnostics. The HFNXT study was well designed and conducted. There are several other diagnostic methods available for identifying functional significance of coronary lesions. However, the results of the HFNXT study indicated that the device performed favorably compared to other available technologies. It is not clear that these results can be generalized to a broader population than that studied, namely those with symptoms of coronary artery disease who have had a CT scan and are planned for a diagnostic angiogram. Patients are likely to be willing to accept the risks associated with the device because of its non-invasive nature.

In conclusion, given the available information above, the data support that for quantitative and qualitative analysis of previously-acquired CT scans to support functional evaluation of coronary artery disease by qualified professionals, the probable benefits outweigh the probable risks for the FFRCT v. 1.4. The device provides substantial benefits and the risks can be mitigated by the use of general and the identified special controls.

## CONCLUSION

The de novo for the $FFR_{CT}$ v. 1.4 is granted and the device is classified under the following:

Product Code: PJA
Device Type: Coronary Physiologic Simulation Software Device
Class: II
Regulation: 21 CFR 870.1415