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KiTEC

RX114 – HeartFlow Technical Evaluation

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Project Details

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Abbreviations

BPM	Beats per minute
CCTA	Coronary Computed Tomography Angiography
CI	Confidence Intervals
CT	Computed Tomography
CTQ	Computed tomography Quality
DICOM	Digital Imaging and Communication in Medicine
DOB	Date of Birth
FFR	Fractional Flow Reserve
FFR_{CT}	Device name
FOV	Field of vision
HDP	High Density Plaque
HU	Hounsfield Unit
IDP	Intermediate Density Plaque
IFU	Instructions for Use
LAD	Left Anterior Descending
LCX	Left Circumflex artery
LM	Left Main artery
LDP	Low Density Plaque
LOA	Limits of agreement
MTAC	Medical Technologies Advisory Committee
NIST	National Institute of Standards and Technology
PACS	Picture Archiving and Communication System
PHI	Protected Health Information
R&R	Repeatability & Reproducibility
RCA	Right Coronary Artery
ROU	Region of Un-Interpretability
SCCT	Society of Cardiovascular Computed Tomography
SD	Standard Deviation
SOP	Standard Operating Procedure
QA/QC	Quality Assurance/Quality Control

1. Summary

HeartFlow FFR_{CT} was selected by the NICE MTAC as a technology suitable for guidance production on the 18th of December 2014. The MTAC, however, raised the following concerns about the technology.

- The reproducibility of the results. Specifically, this related to the role of a Case Analyst in the mathematical modelling on which the HeartFlow FFR_{CT} results are based.
- Information governance arrangements for the remote processing of data.

In response to these concerns, KiTEC, in collaboration with the sponsor, has provided an outline of the procedure and listed available evidence on reproducibility. Furthermore, using publicly available information and information provided by the sponsor, issues related to Analyst training and workload, risk analysis and security have been addressed. KiTEC concluded the following.

- There is a QA/QC process in place that ensures only data that fulfil the quality requirements are processed. To further increase the quality assurance and minimise risk, different members of the team are responsible for performing different parts of the analysis.
- The majority of the analysis is automated; however, the Analyst can manually edit any part of the analysis. These edits can affect FFR_{CT} estimation. Despite this, according to Gaur et al. (2014), who published the only available data on FFR_{CT} reproducibility, the complete process results in acceptable 95% CI limits of agreement of -0.06 to 0.08.
- Lumen extraction reproducibility, one step in the process of FFR_{CT} computation, decreases in the distal portion of the vessel (Gage R&R = 29.4%). This could be a result of multiple variables including lower contrast perfusion/CT quality at the distal end of the vessel, lower CT resolution, smaller vessel diameter, and disease burden. FFR_{CT} reproducibility was found to be equivalent to invasive FFR reproducibility.
- According to published evidence, FFR_{CT} slightly underestimates values in comparison with FFR (Koo et al. 2011, Min et al. 2012, Norgaard et al. 2014).
- As part of a continuous monitoring program, HeartFlow monitors FFR_{CT} reproducibility by re-processing 5% of its commercial case volume on a weekly basis (currently 206 vessels from 60 cases are processed twice). According to the sponsor, reproducibility is consistent with the published literature (Gaur et al. 2014).

- The sponsor fulfils all the requirements for protecting data confidentiality and integrity for remote processing. Furthermore, the ability to process fully anonymised DICOM data enables NHS customers to adopt this approach for extra security.

2. Intended Use

HeartFlow FFR_{CT} is a post-processing image analysis software package that non-invasively estimates FFR using previously acquired CCTA studies for clinically stable symptomatic patients with coronary artery disease. The safety and effectiveness of the FFR_{CT} analysis has not been evaluated for the following populations (HeartFlow 2015).

- Suspicion of acute coronary syndrome
- Myocardial infarction within the last month (30 days)
- Complex congenital heart disease
- Prior coronary artery bypass graft surgery
- Patients with a Body Mass Index >35
- Patients who require emergency 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 III or IV) or acute pulmonary oedema

In addition, due to the potential for artefacts 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 (HeartFlow 2015).

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

3. Scanners and Scanning Guidelines

The CCTA imaging data for HeartFlow analysis must be acquired by scanners designed for coronary imaging applications (≥64 slices). Scanners from all major vendors including GE, Siemens, Phillips and Toshiba, have been successfully used for HeartFlow analysis. HeartFlow's scanning protocol follows the SCCT guideline (Abbara et al. 2009). According to this guideline the CCTA acquisition parameters are as follows.

1. Patient specific inclusion: Heart Rate, < 65 bpm, ideally < 60 bpm
2. Coronary CT acquisition
    - Minimum number of slices: 64,
    - Tube voltage: 100-120kV,
    - Tube current: adjust for patient size/weight and desired image noise,
    - Minimum slice thickness: < 1mm,
    - Minimum axial resolution: 0.35mm or 14.2 lp/cm,
    - Cardiac gating
        i. Prospective,
        ii. Retrospective,
        iii. Flash
    - Scan range: tracheal bifurcation or the mid-level of the left pulmonary artery to just below the lower cardiac border.
3. Image reconstruction and post processing
    - Reconstruction kernel: FFR_{CT} was validated with datasets from multiple CT platform vendors and reconstruction algorithms and techniques, including iterative reconstruction algorithms. HeartFlow has no recommendation on reconstruction algorithms or techniques. HeartFlow is able to generate anatomic models in all cases where there is sufficient contrast-to-noise such that lumen boundaries can be visualized, irrespective of specific parameters.
    - Cardiac phase
        i. Diastolic 100%
        ii. Systolic
    - FOV: < 25.0 cm
4. Pre-acquisition medications
    - Beta blockers

i. Administration: administer to achieve short-term heart rate reduction for the purpose of CCTA
ii. Route: oral and intravenous

- Nitrates
  i. Dosage / route: 400–800mg (1–2 tablets, and preferably the latter) of sublingual nitroglycerin a few minutes before the initiation of the scan protocol.

4. Software Version

The original CE mark was granted for FFR_{CT} version 1.x. The technical file has been updated to support subsequent releases including HeartFlow's most recent commercial release, version 1.7. According to the sponsor there were only minor differences between versions, all of which were intended to address usability and support issues. The sponsor claims that none of these changes impacted upon the intended use or principles of operation. However, the EAC notes that different versions of the software can have a significant impact on diagnostic accuracy. For example in the NXT trial (Norgaard et al. 2014) changes in the automated image processing methods to more accurately identify the luminal boundary and changes in the physiological models (models of microcirculatory resistance) were implemented. This resulted in a substantial improvement in diagnostic performance when evaluated retrospectively by using data from the DISCOVER-FLOW (Koo et al. 2011) and DeFACTO studies (Min et al. 2012).

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5. Analysis Workflow

5.1 Data Upload

The clinician uploads the data on HeartFlow servers using HeartFlow Connect, a network application that enables the CCTA data to be transmitted via a secure connection to the HeartFlow core laboratory for analysis. Data can be uploaded from any device capable of sending DICOM data including PACS, workstations or directly from CT scanners.

5.2 Quality Check

[redacted]

5.3 Anatomy Extraction

5.4 Identification of Regions of Un-Interpretability

[redacted]

5.5 Plaque Removal

[redacted]

5.6 Lumen Extraction

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

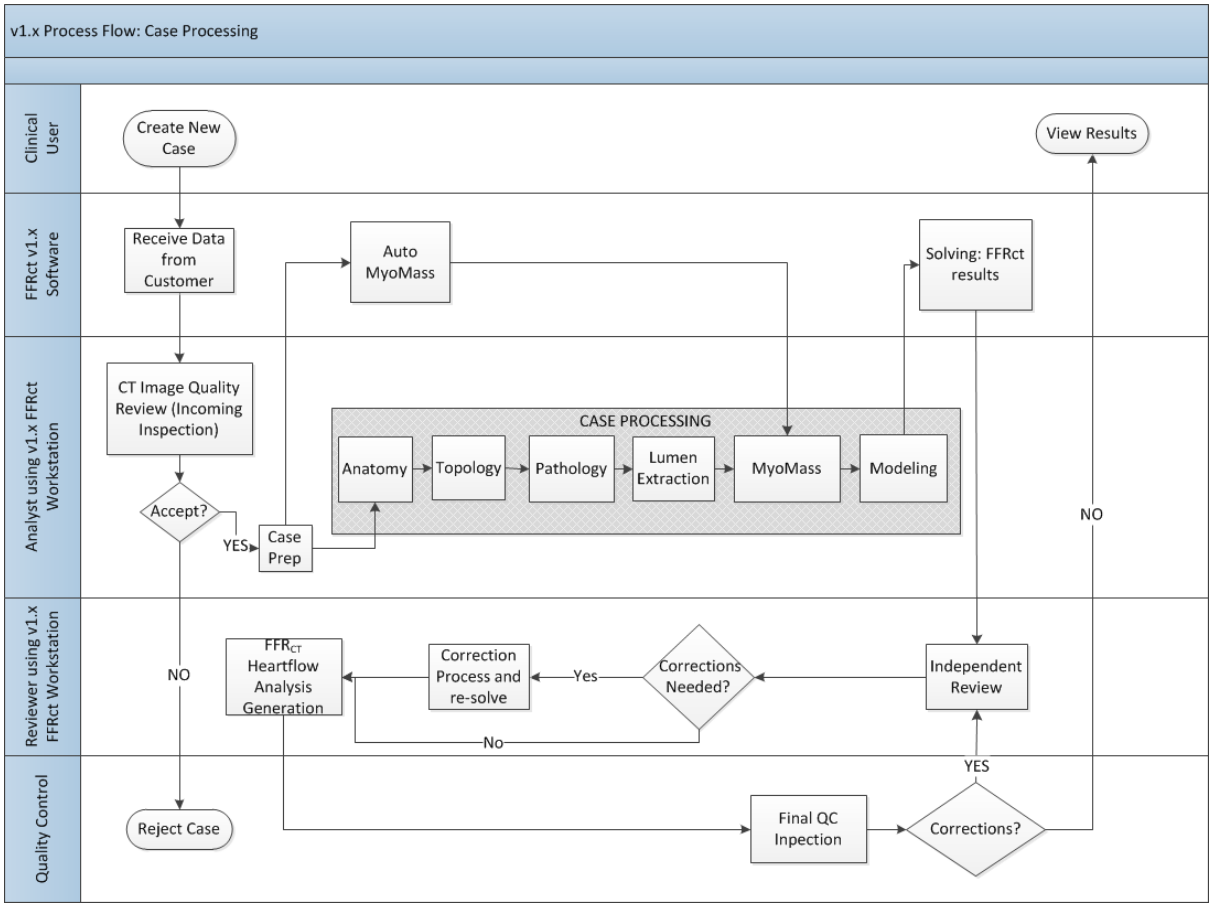
5.7 Case preparation

[redacted]

5.8 Review

[redacted]

[redacted]



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6. Reproducibility

[redacted]

Table 3: Summary of reproducibility assessments performed by the manufacturer

[redacted]	

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The EAC retrieved one study which discussed the reproducibility of the HeartFlow analysis (Gaur et al. 2014). The data provided in this publication was the initial reproducibility data submitted to the FDA and was not required for CE mark approval. The variation of repeated FFR_{CT} analyses was shown to be non-inferior to the variation of repeated FFR measurements (Gaur et al. 2014). However, the FFR_{CT} measurements were performed in patients with mean FFR of 0.89 (SD=0.067), well above the cut-off of 0.8 that is considered as diagnostic of lesion-specific ischaemia (Tonino et al. 2009, Serruys et al. 2012). FFR was ≤0.80 in only 12 out of 58 vessel measurements (21%). As highlighted by the authors, because of the relatively small sample size in this study, they were not able to determine the reproducibility of FFR_{CT} analyses in vessels with FFR in a narrower and more clinically relevant range (e.g. 0.75–0.85).

[redacted]

According to published evidence, there is good correlation between FFR_{CT} and FFR; however, FFR_{CT} systematically underestimates FFR values, as outlined below (Koo et al. 2011, Min et al. 2012, Norgaard et al. 2014).

- Mean difference ±SD 0.022 ±0.116, p=0.016 (Koo et al. 2011)
- Mean difference 0.058; 95% CI, 0.05-0.07 (Min et al. 2012)
- Mean difference ±SD 0.03±0.074, p<0.001 (Norgaard et al. 2014)

In addition a recent conference abstract by (Gaur et al. 2015) has shown moderate agreement between FFR_{CT} and FFR).

Finally, as noted in the sponsor's IFU, because of the variability in FFR_{CT} results, they should be reviewed by an appropriately trained clinician alongside clinical data, including the patient's original CT images, clinical history, symptoms and other diagnostic tests, before any decisions about treatment are made.

7. Analyst Training and Workload

[redacted] Prior to requesting this information from HeartFlow, the EAC informally approached a cardiologist to ascertain the time they thought would be required to train someone in basic cardiac anatomy to the level required of a Case Analyst. They confirmed that 3-4 months would be adequate.

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8. Risk Analysis

According to the sponsor, risk analysis is conducted continuously, throughout the process lifecycle. For risks where software error is mitigated through design, the applicable design requirement(s) is referenced in the risk mitigation.

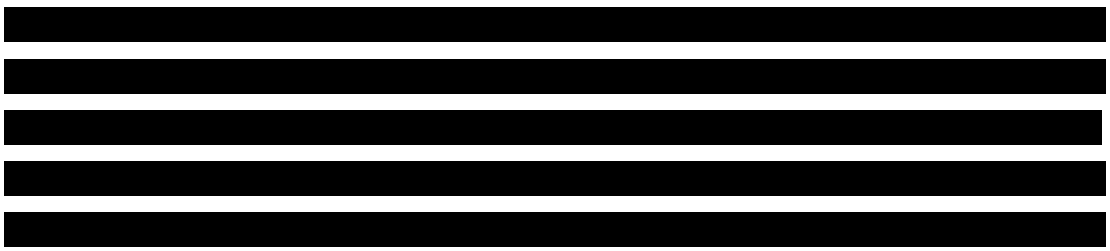

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Table 4: A summary of the tasks each individual can perform for each case

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9. Security

The DICOM data used for HeartFlow analysis often contain PHI (such as patient name, NHS number, DOB etc. HeartFlow can also process completely anonymised data, if this is preferred by the customer site, without compromising the results. If PHI is included, controls are implemented to ensure data protection. Data confidentiality measures are addressed through business associate agreements for PHI data.

Access to HeartFlow's data centre in San Jose, California is very restricted and HeartFlow accesses this data using password protected workstations. To ensure data integrity, all data is validated upon receipt at HeartFlow using a checksum. To avoid malicious attacks HeartFlow

performs constant monitoring and load balancing. To gain FDA approval (FDA 2013), the sponsor submitted platform, application and procedure controls to address the following considerations.

- data confidentiality
- data integrity
- data availability
- denial of service attacks
- malware

A number of security protocols have been implemented to ensure the security of data that is sent to HeartFlow. All FDA and CE questions regarding data security were addressed to their satisfaction, resulting in FDA product clearance and TUV CE-mark. The security protocols include the following.

- HeartFlow web service architecture has been designed to provide business continuity, with limited exposure. According to the sponsor the service does not have any single point of failure
- All data transmission is encrypted (SSL, TLS1.0, 1.1, 1.2)
- A firewall server controls all incoming traffic
- All data is stored at data centres with restricted and audited access
- The NIST cybersecurity guidance is followed[1]
- A disaster recovery plan is in place
- System and application logs are collected

The sponsor informed KiTEC that HeartFlow has employed a 3rd party to monitor cyber-security. This group is performing a risk analysis and will attempt to hack into HeartFlow's system to ensure all security measures are addressed. The sponsor has provided a white paper on cybersecurity that provides additional details on the security protocols used by HeartFlow (Appendix 2).

[1] http://www.nist.gov/cyberframework/upload/cybersecurity-framework-021214.pdf

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Appendix 1

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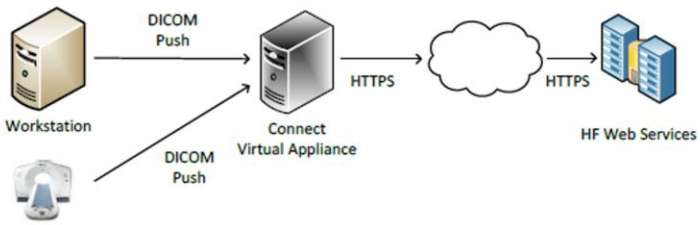
Appendix 2

Introduction

At HeartFlow, we understand the need to protect your data. Our company understands the risks posed by transferring and storing sensitive Protected Health Information (PHI), and has implemented technologies and processes at every step of the HeartFlow FFR_{CT} Analysis to mitigate those risks.

System Overview

HeartFlow has designed the HeartFlow Connect Virtual Appliance to integrate into radiology workflows common in many clinical settings around the world. The HeartFlow Connect device is responsible for receiving DICOM data from any customer device that is capable of sending DICOM data (PACS, workstations, scanners, etc.), creating a case for each received study, and uploading the DICOM files associated with the study to HeartFlow.



The HeartFlow Connect device is installed on the customer network, behind any firewalls and security policies that a customer already has in place. DICOM data is sent to HeartFlow over a secure, encrypted protocol and port (HTTPS, port 443). HeartFlow needs no remote access to Connect for maintenance or updates, and inbound connections to HeartFlow Connect are protected by the customer's own firewall. Clinical users access the case list and view the HeartFlow FFR_{CT} Analysis results at the HeartFlow website via authenticated sessions that are secure and encrypted. The authentication and authorization processes are only a subset of the security measures in place to protect our assets. In addition, the HeartFlow networks are monitored for known vulnerabilities and suspicious activities, and a response team is in place to react to any potential incident.

Our security management team periodically conducts a comprehensive risk analysis. It assesses the potential impact of risks and the adequacy of our security controls. Finally, because HeartFlow is a business associate to its customers, all HeartFlow staff

is trained to follow requirements of the Health Insurance Portability and Accountability Act (HIPAA) and best practices for data security in general.

System Controls

Below is a summary of the current control measures that HeartFlow has implemented to protect customer data that is transferred, used and stored by HeartFlow. These systems are redundant, and provide a solution to mitigate the risks that HeartFlow has identified. These risks can change, and HeartFlow regularly assesses its systems and implements the tools and procedures to meet new challenges.

Platform Controls

- HeartFlow's web service architecture does not have any single point of failure, and has been designed to provide business continuity, with limited exposure.
- All data transmission is encrypted (SSL, TLS1.0, 1.1, 1.2).
- A firewall server controls all incoming traffic.
- All data is stored at data centers with restricted and audited access.
- HeartFlow follows NIST cybersecurity guidance.
- HeartFlow has a disaster recovery plan in place and trains all relevant personnel on corresponding procedures.
- HeartFlow system and application logs are collected.

Application Controls

- Access to PHI is restricted to necessary personnel.
- Authentication is required to access the systems, and access is audited.
- Authorization design uses principles of least privilege and separation of duties.
- Session management includes automatic timed user session log-offs, and strong passwords are enforced for user accounts.
- HeartFlow validates user inputs and data integrity after each transfer.
- Systems hosting e-PHI are not permitted outbound connections to the Internet.