Title: **The HeartFlow ADVANCE Registry: Assessing Diagnostic Value of Non-invasive FFR_{CT} in Coronary CarE**

Registry Objective The objective of the HeartFlow ADVANCE Registry is to evaluate utility, clinical outcomes, and resource utilization of FFR_{CT}-guided evaluation in clinically stable, symptomatic patients with coronary artery disease (CAD), in order to further inform patients, health care providers, and other stakeholders about which technologies are most effective and efficient in the diagnosis and management of CAD.

Registry Design

Principal Investigators

Sponsor HeartFlow, Inc.

Data Analysis HeartFlow, Inc. or designee

Monitoring

Clinical Events Committee (CEC) & Endpoint Review Committee

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III. REGISTRY OBJECTIVE

The objective of the HeartFlow ADVANCE Registry is to evaluate utility, clinical outcomes, and resource utilization of FFR_{CT}-guided evaluation in clinically stable, symptomatic patients with CAD in order to further inform patients, health care providers, and other stakeholders about which technologies are most effective and efficient in the diagnosis and management of CAD.

SPECIFIC OBJECTIVES:

1. To determine if the availability of FFR_{CT}, in addition to coronary anatomy from the cCTA, will lead to a significant change in the coronary management plan.

2. To assess the real world outcomes of utilizing FFR_{CT} to guide invasive management and/or medical treatment.

3. To assess resource utilization, following standard practice for diagnostic and treatment pathways incorporating FFR_{CT} as the preferred CAD diagnostic test.

4. To provide society including patients, health care providers, and other stakeholders with information about which diagnostic technologies are most effective and efficient in managing patients with CAD.

IV. REGISTRY ENDPOINTS

IV. A. Primary Endpoints

The primary endpoint of the ADVANCE Registry is the reclassification rate between the coronary management plan based on the review of the cCTA compared to the management plan based on FFR_{CT} when obtained, as assessed by an independent review committee.

IV. B. Secondary Endpoints

The secondary endpoints of the ADVANCE Registry include the following:

a. Rate of reclassification between Investigator management plan based on cCTA alone compared to actual clinical management within 90 days.
b. Rate of invasive catheterization without obstructive disease at 90 days.
c. Percent of patients undergoing revascularization within 90 days for whom functional data are available prior to revascularization.
d. Major Adverse Coronary Event (MACE) rates at 90 days, 180 days, 1 year, and 3 years. MACE is defined as the composite rate of all cause death, non-fatal myocardial infarction (MI) and unplanned hospitalization for acute coronary syndrome (ACS) leading to urgent revascularization.

e. Individual components of MACE (all cause death, non-fatal MI, unplanned hospitalization for ACS leading to urgent revascularization) at 90 days, 180 days, 1 year, and 3 years.
f. Estimated cumulative medical radiation exposure at 1 year.
g. Resource utilization composite at 90 days, 180 days, 1 year, and 3 years:
    a) Invasive diagnostic and therapeutic coronary procedures
    b) Treatment of MACE events
    c) Noninvasive cardiac testing

V. C. Subject Selection

All clinically stable, symptomatic patients diagnosed with CAD by cCTA, that meet eligibility criteria, and are able and willing to participate are candidates for the ADVANCE Registry. Those patients that meet all inclusion/exclusion criteria and who sign the EC/IRB approved informed consent will be enrolled in the registry. FFR_{CT} shall be used in accordance with the current Instructions for Use document.

V. D. General Inclusion & Exclusion Criteria

Inclusion Criteria:

1. Provide written informed consent
2. Clinically stable, symptomatic patients who undergo cCTA and are diagnosed with CAD and meet eligibility criteria for $FFR_{CT.}$

Exclusion Criteria:

1. cCTA showing no CAD
2. Uninterpretable cCTA by site assessment, in which severe artifacts prevent angiographic evaluation
3. Any active, serious, life-threatening disease with a life expectancy of less than 1 year
4. Inability to comply with follow-up requirements

VI. H. Invasive Catheterization without Obstructive Disease

Invasive catheterization without obstructive disease will be measured by either site read coronary angiogram showing no stenosis of ≥ 50% or no invasively-measured FFR ≤ 0.80 in a segment distal to a stenosis.

VII. A. Rules for Subject Withdrawal

Each subject is free to withdraw from the registry at any time. Investigator(s) also have the right to withdraw subjects from the registry in the event of illness, death or serious injury, other reasons concerning the health or wellbeing of the subject, or in the case of lack of cooperation. Should a subject decide to withdraw or should the investigator(s) decide to withdraw the subject, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the subject's withdrawal should be made and an explanation given as to why the subject is withdrawing or being withdrawn from the registry. All data collected up to the point of

withdrawal will remain in the study database and will be included in the analysis.

The reason for withdrawal must be noted in the eCRFs.

VII. B. Rules for terminating the registry

There are no formal termination criteria for this registry. The sponsor reserves the right to terminate the registry at any time. Investigators have the responsibility to comply with all applicable regulatory guidelines and regulations. The sponsor, the Institutional Review Board/Ethics Committee, or the FDA/local regulatory authorities may terminate a center for the following (but not limited to) reasons:

1) Failure of the investigator to comply with investigator agreement, protocol, guidelines and/or regulations.
2) Serious protocol violations
3) Submission of knowingly false information from the research facility to the sponsor, clinical monitor, or other party involved in the registry.

VIII. Safety Assessments and Recording Reportable Events

For the purposes of this registry, once HeartFlow becomes aware of an alleged complaint, HeartFlow will report per FDA Medical Device Reporting requirements, or local regulatory requirements. Such reportable events will include any MACE-related death or serious injury related to an FFR_{CT} result where the investigator alleges that the FFR_{CT} result is incorrect.

Additionally, for the purposes of this registry, it will be required to record all MACE in the eCRFs. MACE is defined as the composite rate of:

- all cause death
- non-fatal myocardial infarction
- unplanned hospitalization for acute coronary syndrome leading to urgent revascularization

Please refer to section XIII.L, Clinical Events Committee (CEC), for further details.

IX. RATIONALE AND ETHICAL CONSIDERATIONS

This on-label, post-market, multi-center, prospective registry will enable evaluation of utility, clinical outcomes, and resource utilization following FFR_{CT}-guided treatment in clinically stable, symptomatic patients with CAD diagnosed by cCTA.

The potential risks to subjects participating in the HeartFlow ADVANCE Registry are solely and directly related to the performance of the registry procedures.

Anticipated risks

FFR_{CT} utilizing cCTA data, is a commercially available technology in the locations where the registry will be conducted, and will be used in the manner in which the product has been authorized for marketing and within the authorized intended use and subject population. FFR_{CT} analysis will be performed using the required cCTA data-set for these subjects. The FFR_{CT} analysis does not require additional imaging or image acquisition protocols, therefore is not expected to present any additional clinical risks to subjects.

X. STATISTICAL CONSIDERATIONS

X. A. General Considerations

Tabulations of summary statistics, graphical presentations, and statistical analyses will be performed using SAS® software or an equivalent. Data obtained from clinical records and entered into the eCRF database will be provided in separate data listings showing individual subject values. The Steering Committee will work on the planning and reporting of statistical analyses by preparing a fully defined statistical analysis plan.

X. B. Subject Characteristics

Subject accountability will be described, including number of subjects enrolled, the number included in the analysis, and reasons for any subjects discontinued from the study or not included in the analysis. Demographic information will be summarized using descriptive statistics. Gender will be summarized by counts and percentages. Medical histories will be summarized by counts and percentages.

X. C. Endpoint Analysis

X. C. 1. Analysis of Primary Endpoint

The primary endpoint is the reclassification rate between the coronary management plan based on the review of the cCTA alone compared to the management based on FFR_{CT} when obtained, as assessed by an independent review committee.

X. C. 2. Analysis of Secondary Endpoints

Descriptive statistics for the secondary endpoints will be provided. Rates of MACE and each component of MACE, at each follow-up (90 days, 180 days, 1 year, and 3 years) post-procedure and annually thereafter) will be estimated.

X. D. Analysis Populations

Intent-to-Diagnosis (ITD): All patients who meet the registry criteria, sign the written informed consent, and are enrolled in the registry, will be counted in the ITD set, which will be the primary analysis set.

Per-Protocol (PP): The ITD sample excluding patients who are "deregistered" or do not meet certain key entry criteria.

X. E. Procedures for Reporting Deviations from Original Statistical Plan

A formal statistical analysis plan encompassing all primary, secondary, and pre-specified analyses will be developed with input from the Steering Committee prior to locking the database. Any deviations from the statistical analysis (outlined in this protocol,) will be described, with reasons for the deviations listed, in the final study report.

XI. DATA HANDLING AND QUALITY ASSURANCE

XI. A. Completing and Signing Case Report Forms

This registry will utilize eCRFs for the collection of all data. Required data will be recorded on the appropriate electronic eCRF at the time of or as soon as possible after the subject visit. Data changes and corrections for any errors should be corrected within the eCRF. The audit trail will record all changes made, the date and time of the correction, the person making the change, and a reason for the change. The appropriate electronic signature will be provided by the investigator as indicated.

XI. B. Clinical Data Management

The sponsor or designee will be responsible for the processing and quality control of the data. The handling of data, including data quality control, will comply with all applicable regulatory guidelines.

The training of clinical site personnel in eCRF completion will be the responsibility of the sponsor or designee. To ensure uniform data collection, a Case Report Form Guide will be created to assist with eCRF completion. All clinical site research coordinators will undergo site initiation training to become thoroughly familiar with the protocol, case report forms, and with methods of data verification.

XI. C. Archiving of Data

All registry data collected at the investigator site and sponsor site will be archived in accordance with local guidelines and regulations. Clinical sites will be asked to retain the data for 2 years following completion of the registry. If local country guidelines require longer data storage, data will be kept according to that country's guidelines.

All data obtained through this protocol will be securely handled and stored by the research site and by Heartflow, Inc., its designee, and/or other research entities that are listed in this protocol. Trained investigational site staff will keep a record of what data is electronically transferred and to whom. These details are also described in the informed consent form and explained to each subject appropriately.

XIII. SPECIAL REQUIREMENTS AND PROCEDURES

XIII. A. Institutional Review

Before starting this registry, the protocol approved by the sponsor will be submitted to the regulatory bodies/local health authorities, as required, in accordance with local regulations and to the EC/IRB. The registry will not start before the EC/IRB gives written approval or a favorable opinion in accordance with all applicable regulatory bodies/local health authorities.

No changes from the final approved protocol will be initiated without the EC/IRB's prior written approval or favorable opinion except when necessary to eliminate immediate hazards to the subjects or when the change involves only logistics or administration. The sponsor will authorize any protocol amendments if necessary. Significant protocol amendments should be submitted to the EC/IRB without delay.

XIII. B. Guidelines for Obtaining Subject Informed Consent

Written informed consent approved by HeartFlow and the IRB/EC will be obtained from each subject or their legal guardian.

XIII. C. Site Initiation/Training

Prior to enrolling in the registry, the sponsor or its designee will contact the Investigator and Research Coordinator to discuss the protocol and review the data requirements of the registry, including eCRF completion instructions.

XIII. D. Registry Monitoring

A monitoring plan will be created at the outset of the registry and will describe the minimum monitoring standard to be applied, which may include a combination of on-site and remote monitoring activities.

XIII. E. Registry Close Out

Upon completion of the registry (when all subjects enrolled have completed the follow-up contacts and the eCRFs and queries have been completed), the sponsor and/or its designees will notify the site that the registry is complete and a closeout visit (on site or virtual) will be performed. All unused study materials will be returned to the sponsor and/or appropriately discarded as per instruction by the sponsor and/or its designee.

XIII. G. Clinical Events Committee (CEC)

The Clinical Events Committee (CEC) will adjudicate clinical events that occur during the conduct of the registry to make the determination as to whether particular individual events meet the protocol-specified endpoints. The events that will be adjudicated in this registry include the following:

- Death
- Non-fatal myocardial infarction
- Unplanned hospitalization for ACS leading to urgent revascularization

The eCRF captures some of the data critical to the event adjudication. However, there will still be a need for supporting documentation from the sites in order to render an adjudicated result. The eCRF data and supporting documentation are completely anonymized by each site and identified only with the subject ID.
Events will be adjudicated by the CEC according to pre-specified criteria. The CEC adjudicated data will be used in the analyses unless otherwise stated.

XIII. H. Endpoint Review Committee

An Endpoint Review Committee, consisting of independent physicians not participating in the diagnosing, planning, or treatment of subjects in the registry will be used to adjudicate the primary endpoint. The Committee will document the treatment management plan following review of the cCTA and again, following review of the enrolling FFR_{CT} for all patients in whom cCTAs and FFR_{CT}s are available.

XIV. FINAL REPORT

Following conclusion of the registry, a final report shall be written by HeartFlow or its designee and distributed to all investigators. This final report shall account for all enrolled subjects.

Appendix 1 - REGISTRY DEFINITIONS

Appendix 2 – REFERENCES

Appendix 3 – PROTOCOL SIGNATURE PAGE, ADVANCE Registry

SPONSOR APPROVAL
This protocol has been reviewed and is approved by HeartFlow.

_____ _____
. Date

HeartFlow, Inc.

SITE APPROVAL
Site Number: _____ **Site Name:** _____

I have read and understood the HeartFlow Registry Protocol titled "The HeartFlow ADVANCE Registry: Assessing Diagnostic Value of Non-invasive FFR_{CT} in Coronary CarE" and agree to follow the procedures and requirements.

Print Name	***Signature***	***Date***

Statistical Analysis Plan for Heartflow ADVANCE Registry

By signing this document, I am confirming that I have reviewed and approve the analysis plan referenced above.

Principal Investigator

Signature Date (mm/dd/yyyy)

Principal Investigator

Signature Date (mm/dd/yyyy)

Heartflow

Signature Date (mm/dd/yyyy)

Statistical Analysis Plan: <u>Heartflow ADVANCE Registry</u>

I. Study Overview

cCTA is a non-invasive test used to diagnose the severity of coronary artery disease. FFR_{CT} is a non-invasive test that can be added to cCTA. This study seeks to describe the findings of each test and describe how adding FFR_{CT} would change the management plan indicated by cCTA. The study also seeks to describe subject outcomes, radiation exposure, and additional cardiac testing needs for subjects by whether they were planned for medication only, PCI, or CABG.

II. Study Objectives

A. Summarize baseline demographics and subject characteristics overall and by whether FFR_{CT} results were available
B. Summarize the extent of disease in each vessel measured by cCTA and FFR_{CT}
C. Summarize the changes in coronary therapeutic management strategy before and after considering both cCTA and FFR_{CT} and report the proportion of intended strategies that were changed.
D. Compare invasive catheterization (ICA) and revascularization rates between enrollment and the 90 day assessment based on the findings from cCTA and FFR_{CT}
E. Determine whether major adverse coronary event rates during follow-up differ according to treatment plan and testing findings
F. Summarize the estimated cumulative radiation exposure
G. Determine whether the time to first cardiovascular test during follow-up differs according to management strategy

IV. General Methodology

Most of the analyses will be descriptive. Unless noted otherwise, categorical variables will be presented as number and percentage and continuous variables will be presented as median (25^{th}, 75^{th} percentile). Kaplan-Meier methods will be used to report event rates that occur during follow-up. The key objectives that will involve statistical testing are the relationships between having an invasive procedure or revascularization and the findings from cCTA and FFR_{CT}.

V. Subject Accountability and Characteristics

VI. Sample Size Determination

VII. Definitions

VIII. Endpoint Analyses

A. Primary Endpoint: The proportion of coronary management plans that were changed when core lab FFR_{CT} coronary anatomy findings were added to the core lab cCTA findings

B. Secondary Endpoints

i. Secondary Endpoint 1: The proportion of coronary management plans that were changed when site reported lab FFR_{CT} coronary anatomy findings were added to the site reported lab cCTA findings

ii. Secondary Endpoint 2: Vessel level findings from cCTA and FFR_{CT}

iii. Secondary Endpoint 3: Invasive catheterization and revascularization rates 90 days post enrollment

iv. Secondary Endpoint 4: Major adverse coronary event (MACE) rates during follow-up

v. Secondary Endpoint 5: Estimated cumulative radiation exposure

vi. Secondary Endpoint 6: Cardiovascular testing rates during follow-up

vii. Secondary Endpoint 7: Result from first post-baseline ICA

IX. Safety Analyses

Not applicable

XI. Changes from the Study Protocol Reflected in this Analysis Plan

None