ADVANCE-ED

Assessing **D**iagnostic **VA**lue of **N**on-invasive FFR_{CT} in **C**oronary car**E** in the **E**mergency **D**epartment

Study Objective	The primary objective of the ADVANCE-ED study is to compare decision plans prior to FFR_{CT} with the actual decision made after FFR_{CT}.
Study Design	This is a prospective multi-center study. All clinically stable, symptomatic patients who present to the emergency department (ED) or observation unit with suspected CAD and who have at least one ≥40% lesion and no lesion >90% confirmed by CCTA are eligible for enrollment once their CCTA has been completed and their FFR_{CT} (if applicable) has been ordered. All enrolling sites will have CCTA incorporated into their standard evaluation of chest pain in the ED/observation unit. Non-control sites will have CCTA and FFR_{CT} analysis incorporated into their standard evaluation of chest pain in the ED/observation unit.
Sponsor	HeartFlow, Inc 1400 Seaport Blvd., Building B Redwood City, CA 94063

Investigator Protocol Signature Page

I have read and understand the protocol and agree that it contains all the ethical, legal, and scientific information necessary to conduct this study. I will personally conduct the study as described. I will provide copies of the protocol to all assigned physicians, nurses, and other professional personnel who will be involved per the delegation of authority log, and I will be responsible for their compliance and adherence to the study protocol. I am aware that this protocol must be approved by the Institutional Review Board. I agree to adhere strictly to the attached protocol. I agree that clinical data entered on case report forms by me, and my staff, will be supplied to HeartFlow and may be utilized by HeartFlow in various ways, such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow HeartFlow monitors and auditors and their designees full access to all medical records at the research facility for subjects screened or randomized in the study. I agree to provide all subjects with informed consent forms and will ensure adequate informed consent is obtained, as required by government regulations and International Conference on Harmonization guidelines.

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Site Name Site Number

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Co-Principal Investigator (print name)

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Co-Principal Investigator (signature) Date

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Co-Principal Investigator (print name)

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Co-Principal Investigator (signature) Date

Protocol reviewed and approved by trial leadership:

DocuSigned by:
Campbell Rogers
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12/21/2021 | 5:52 PM PST

Campbell Rogers, MD;
HeartFlow, Inc., CMO

Date

Standard Abbreviations

ACS	acute coronary syndrome
CAD	coronary artery disease
CCTA	coronary computed tomographic angiography
ED	emergency department
EDC	electronic data capture
eCRF	electronic case report form
FFR	fractional flow reserve
FFR_{CT}	non-invasive technique using CCTA to determine FFR
ICA	invasive coronary angiography
ICF	informed consent form
MACE	major adverse cardiovascular event
MI	myocardial infarction
MPI	myocardial perfusion imaging
NI	non-invasive
PCI	percutaneous coronary intervention

Study Synopsis

Protocol Title	ADVANCE-ED: Assessing Diagnostic VAlue of Non-invasive FFR_{CT} in Coronary carE in the Emergency Department
Subjects and Study Centers	Approximately 500 subjects will be enrolled at approximately 20 sites in the US. The sites will include approximately 10 who have incorporated CCTA with FFR_{CT} in the ED/observation unit pathway and approximately 10 control sites who use CCTA but do not use FFR_{CT} in the ED/observation unit.
Planned Study Duration	The duration of this study will be approximately 31 months: • 3 - 9 months for study start-up (Site qualification, IRB approval, and site initiation) • 18 months for enrollment • 1 month for follow up • 3 months for query resolution and database lock
Primary Study Objective	The primary objective of the ADVANCE-ED study is to compare decision plans prior to FFR_{CT} with the actual decision made after FFR_{CT}.
Secondary Study Objectives	The secondary objectives are to evaluate utility, length of stay, clinical outcomes, and resource utilization when CCTA and FFR_{CT} analysis are incorporated in the emergency department (ED) or observation unit for clinically stable, symptomatic patients with suspected CAD 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.
Hypothesis	The primary hypothesis of this study is that using HeartFlow's FFR_{CT} analysis as part of the treatment pathway for clinically stable, symptomatic patients with suspected CAD in the ED/observation unit can result in a more streamlined diagnostic pathway and therefore provide cost-effective clinical care for patients.
Population	The population for this study will be clinically stable, symptomatic patients who present to the ED or observation unit with suspected CAD and no history of coronary artery disease, and who while in the ED or observation unit have a CCTA performed which shows at least one ≥40% lesion and no lesions >90% in a major epicardial vessel, and a successfully processed FFR_{CT} (if applicable).

Study Design and Methods	This is a prospective multi-center study. All clinically stable, symptomatic patients who present to the ED or observation unit with suspected CAD and who have at least one ≥40% lesion and no lesions <90% lesion in a major vessel, confirmed by CCTA, are eligible for enrollment once their CCTA has been completed and FFR_{CT} (if applicable) has been ordered. All enrolling sites will have CCTA incorporated into their standard evaluation of chest pain in the ED/observation unit. Non-control sites will have CCTA and FFR_{CT} analysis incorporated into their standard evaluation of chest pain in the ED/observation unit. All sites will provide demographics, medical history, CCTA images, FFR_{CT} (for non-control sites), the decision plan post CCTA and pre FFR_{CT} (for non-control sites), length of stay for patients in the ED/observation unit/hospital, billing reports (UB-04 preferred), 30-day clinical outcomes, and any other hospital or office visits, imaging, and/or procedural data completed prior to the follow-up 30-day visit. Sites which do not have FFR_{CT} incorporated into the ED/observation unit will be control sites. If FFR_{CT} is implemented at a control site during the enrollment period, the site can request to switch over to the non-control arm once FFR_{CT} has been successfully implemented in the ED/observation unit at that site. This switch must be reviewed and approved by the HeartFlow Clinical Research team.
Primary Endpoint	The primary endpoint of ADVANCE-ED is the reclassification rate between the coronary management plan based on the review of the CCTA compared to the actual management.
Secondary Endpoints	The secondary endpoints include: • Cost utility analysis to include length of stay in ED/observation unit and overall, secondary CAD testing, and invasive procedures • Major Adverse Coronary Event (MACE) rates at day 30 • Rate of invasive catheterization without obstructive disease at day 30 • Time to diagnosis • Time to discharge

Inclusion Criteria	Inclusion criteria (all must be present): 1. Age ≥18 years 2. Clinically stable, symptomatic patients who present to ED/observation unit with suspected CAD 3. CCTA shows at least one ≥40% lesion and no lesions >90% in at least one major epicardial vessel 4. FFR_{CT} processed successfully (if applicable) 5. EKG with no acute ischemic changes 6. Willing to comply with all aspects of the protocol, including adherence to follow up visit 7. Agrees to be included in the study 8. Able to provide written informed consent
Exclusion Criteria	Exclusion criteria (all must be absent): 1. CCTA showing no ≥40% lesion in a major epicardial vessel 2. CCTA showing a lesion >90% in a major epicardial vessel 3. CCTA showing other incidental, non-cardiac findings requiring admission, e.g., pneumonia, pulmonary embolism, or aortic dissection 4. Uninterpretable CCTA which is not of diagnostic quality 5. CABG or PCI prior to CCTA acquisition 6. Left main lesion >50% 7. Confirmed acute coronary syndrome (acute myocardial infarction or unstable angina) 8. Known complex congenital heart disease or any history of coronary artery disease 9. Patients with tachycardia or significant arrhythmia which cannot be adequately controlled with medications to allow CTA 10. Any active, serious, life-threatening disease with a life expectancy of less than 2 months 11. Inability to comply with follow-up requirements 12. Currently enrolled in another study utilizing FFR_{CT} or in an investigational trial that involves a non-approved cardiac drug or device 13. Persons under the protection of justice, guardianship, or curatorship
Study Follow-Up	There will be a 30-day follow-up phone visit following the baseline visit.
Clinical Research Organization	Peachtree BioResearch Solutions 4985 Lower Roswell Road Marietta, GA 30068

Sponsor	HeartFlow, Inc. 1400 B Seaport Blvd Redwood City, CA 94063

I. BACKGROUND AND RATIONALE

Acute chest-pain syndromes are the second most common reason for emergency department (ED) visits with more than 6.5 million such visits occurring annually in the United States. Although acute coronary syndrome (ACS) is ultimately diagnosed in only 5.1% of patients who present with chest pain, many of these patients are admitted to hospitals, at an estimated cost of over $3 billion annually (1,2). In addition, patients with chest pain return for additional care within one week at a rate of up to 10% (3). This places additional strain on EDs and hospitals.

Recent updates to the guidelines for acute chest pain management in the emergency department setting place CCTA as a 1A “for intermediate-risk patients with acute chest pain and no known CAD”. Further, FFR_{CT} was given 2aB-NR as an add-on diagnostic test “for intermediate-risk patients with acute chest pain and no known CAD, with a coronary artery stenosis of 40% to 90% in a proximal or middle coronary artery on CCTA. FFR_{CT} can be useful for the diagnosis of vessel-specific ischemia and to guide decision-making regarding the use of coronary revascularization” (1).

In the ED, coronary computed tomography angiography (CCTA) is a beneficial noninvasive technique for use in patients with acute chest pain, due to its high accuracy for detection of coronary artery disease (CAD); however, an increase in CCTA can often be followed by an increase in invasive coronary angiography (ICA) (4). With increasing health care expenditures, there is ever-expanding focus on appropriate resource utilization. To that end, the historically high rates of nonobstructive disease at the time of ICA are being increasingly scrutinized.

HeartFlow, Inc. (‘HeartFlow’) provides a non-invasive method to determine the hemodynamic significance of CAD (FFR_{CT}) from subject-specific CCTA data using computational fluid dynamics under simulated maximal coronary hyperemic conditions (5). Results from two prospective trials suggest that FFR_{CT} accurately predicts the hemodynamic significance of coronary lesions when compared to invasively measured FFR (6,7). FFR_{CT} is available in Japan, in many European countries (CE mark 2011), in Canada, and in the U.S. (De Novo 510K clearance 2014).

The ROMICAT II trial showed that CCTA in the ED reduces cost and length of stay when compared to standard of care (8). Additional studies such as the PLATFORM (Prospective Longitudinal Trial of FFR_{CT}: Outcome and Resource Impacts Study) and CONSERVE (Coronary Computed Tomographic Angiography for Selective Cardiac Catheterization) trials have highlighted the potential for CCTA and FFR_{CT} to help inform ICA referral in an effective and safe fashion. Work by Chinnaiyan, et al done in the ED, went on to show that FFR_{CT} leads to cost savings with no increase in MACE, and a negative FFR_{CT} (suggestive of a non-hemodynamically significant lesion) is particularly useful in patients with >50% stenosis showing significantly lower revascularizations and costs (9).

The ADVANCE-ED study is a prospective multi-center study in which clinically stable, symptomatic patients who present to the ED or observation unit with suspected CAD will have at least one >40% lesion and no lesions >90% in a major vessel, confirmed by CCTA. All enrolling sites will have CCTA incorporated into their standard evaluation of chest pain in the ED. Non-control sites have CCTA and FFR_{CT} analysis incorporated into their standard evaluation of chest pain in the ED/observation unit. For non-control sites, the treating healthcare provider will be asked to provide a management plan prior to the results of the FFR_{CT} being available. Subjects will be followed up at 30 days, and data will be collected for

any additional testing, office visits, hospital admissions, procedures, and outcomes.

II. STUDY OBJECTIVE

Primary Objective

The primary objective of the ADVANCE-ED study is to compare decision plans prior to FFR_{CT} with the actual decision made after FFR_{CT}.

Secondary Objectives

The secondary objectives are to evaluate utility, clinical outcomes, and resource utilization when FFR_{CT} analysis is incorporated in the emergency department (ED) or observation unit for clinically stable, symptomatic patients with suspected CAD to further inform patients, health care providers, and other stakeholders about which technologies are most effective and efficient in the diagnosis and management of ACS and CAD.

III. STUDY ENDPOINTS

A. Primary Endpoint

The primary endpoint of ADVANCE-ED is the reclassification rate between the coronary management plan based on the review of the CCTA compared to the actual management.

B. Secondary Endpoints

The secondary endpoints include:

- Cost utility analysis to include length of stay, secondary coronary testing, and invasive coronary procedures
- Major Adverse Coronary Event (MACE) rates at day 30
- Rate of invasive catheterization without obstructive disease at day 30
- Time to diagnosis
- Time to discharge

IV. STUDY DESIGN

All non-invasive and invasive data collected will be obtained from clinical practices that are standard clinical care. All details about cardiovascular testing and treatment (planned and actual) will be recorded at baseline.

IV. A. Location and Number of Subjects

Approximately 500 subjects will be enrolled from approximately 20 experienced clinical research sites across the US.

All enrolling sites will have CCTA incorporated into their standard evaluation of chest pain in the ED/observation unit. Approximately half of the sites will be FFR_{CT} sites who will have CCTA and FFR_{CT} analysis incorporated into their standard evaluation of chest pain in the ER/observation unit. Sites who have CCTA but not FFR_{CT} incorporated into the ED/observation unit will be control sites.

If FFR_{CT} is implemented at a control site during the enrollment period, site can request to switch over to the non-control arm once FFR_{CT} has been successfully implemented. This switch must be reviewed and approved by the HeartFlow Clinical Research team.

No site may enroll more than 75 (15%) subjects in the trial.

IV. B. Patient Population

The population for this study will be clinically stable, symptomatic patients who present to the ED or observation unit with suspected CAD and while in the ED or observation unit, have a CCTA performed which shows at least one >40% lesion and no lesions >90% in a major epicardial vessel, a successfully processed FFR_{CT} (if applicable), and no history of coronary artery disease.

IV. C. General Inclusion and Exclusion Criteria

Inclusion Criteria (all must be present):

1. Age ≥18 years
2. Clinically stable, symptomatic patients who present to ED/observation unit with suspected CAD
3. CCTA shows at least one >40% lesion and no lesions >90% in at least one major epicardial vessel
4. FFR_{CT} processed successfully (if applicable)
5. EKG with no acute ischemic changes
6. Willing to comply with all aspects of the protocol, including adherence to follow up visit
7. Agrees to be included in the study
8. Able to provide written informed consent

Exclusion criteria (all must be absent):

1. CCTA showing no >40% lesion in a major epicardial vessel
2. CCTA showing a lesion >90% in a major epicardial vessel
3. CCTA showing other incidental, non-cardiac findings requiring admission, i.e., pneumonia or pulmonary embolism
4. Uninterpretable CCTA which is not of diagnostic quality
5. CABG or PCI prior to CCTA acquisition
6. Left main lesion >50%
7. Confirmed of acute coronary syndrome (acute myocardial infarction or unstable angina)
8. Known complex congenital heart disease or any history of coronary artery disease
9. Patients with tachycardia or significant arrhythmia which cannot be adequately controlled with medications to allow CTA
10. Any active, serious, life-threatening disease with a life expectancy of less than 2 months
11. Inability to comply with follow-up requirements
12. Currently enrolled in another study utilizing FFR_{CT} or in an investigational trial that involves a non-approved cardiac drug or device
13. Persons under the protection of justice, guardianship, or curatorship

V. STUDY WORKFLOW

The workflow for ADVANCE-ED is described in the following sections.

V. A. Study/Site Selection

HeartFlow will identify and qualify the clinical research sites for ADVANCE-ED. Participating sites will be screened for:

- CCTA acquisition practices conforming to SCCT guidelines
- Adequate resources and past clinical research experience
- HeartFlow's ED Connect in active use and an ED/observation unit pathway including CCTA and FFR_{CT} in place for non-control sites
- An ED/observation unit pathway including CCTA for control sites

V. B. Subject Selection

Institutional review board approval will be obtained at all participating sites prior to screening patients. All patients who meet all inclusion criteria and do not meet any exclusion criteria, and are able and willing to participate, are candidates for ADVANCE-ED. All patients providing written informed consent and meeting all selection criteria will be enrolled into the study.

V. C. Screening Period

1. All subjects must fulfill all study inclusion criteria and no study exclusion criteria.
2. Each subject will undergo the following assessments to be documented in the appropriate electronic case report form (eCRF) upon enrollment:
    a. Collection of demographic information
    b. A summary of the subject's relevant medical history and cardiovascular risk factors
    c. Information about the subject's CCTA results
    d. Information about the subject's FFR_{CT} results (non-control sites)
    e. Decision plan prior to FFR_{CT} results (non-control sites)

V. D. Enrollment

All subjects must provide written informed consent prior to enrollment. A notation will be made in the subject's medical chart, if required by the institution, and in the study records that he/she is participating in the study, has had his/her questions answered, has read, signed, and dated the Informed Consent Form (ICF), and been given a copy of the ICF.

All subjects who meet eligibility requirements will be asked to participate. Subjects will be considered enrolled in the study after the following criteria have been met:

1. Informed consent form has been signed and subject has been provided a copy.
2. All inclusion criteria and no exclusion criteria have been met.

V. E. Follow up

A 30 day (±7 days) follow up phone call with the subject following baseline visit will be done as a part of this study. Data collected will include:

- Current cardiac health status
- Any additional hospital admissions

- Any additional ED/observation unit visits
- Any cardiac procedures/tests
- MACE

Sites will also be asked to provide billing information (UB-04 preferred) from baseline to day 30. Reports and images for CCTA, FFR_{CT} (if applicable), ICA, and other cardiac tests will be uploaded to the eCRF.

VI. STUDY DURATION

The anticipated enrollment duration of ADVANCE-ED will be approximately 18 months. A 30 day follow up phone call is planned for this study.

VI.A. Rules for Subject Withdrawal

Each subject is free to withdraw from the study at any time. No additional data will be collected after a subject informs the Investigator that they want to withdraw.

VI. B. Rules for Terminating the Study

There are no formal termination criteria for this study. The sponsor reserves the right to terminate ADVANCE-ED at any time. Investigators have the responsibility to comply with all applicable regulatory guidelines and regulations. Specific reasons which may cause the sponsor, the Institutional Review Board, or local regulatory authorities to terminate a center include, but are not limited to:

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 study.

VI. C. Rules for switching from Control arm

Sites who do not have FFR_{CT} incorporated into the ED/observation unit will be control sites. If FFR_{CT} is implemented at a control site during the enrollment period, site can request to switch over to the non-control arm once FFR_{CT} has been successfully implemented. This switch must be reviewed and approved by the HeartFlow Clinical Research team.

VI.D. SAFETY ASSESSMENT

Patients will undergo a clinically indicated CCTA and any other invasive physiological measurements, which do not require additional radiation, extra contrast, or additional procedure time for this study/protocol. All procedures performed will be per standard clinical care, and data obtained will be documented as per standard of clinical care. Therefore, there will be no additional clinical risks for subjects who participate. MACE will be collected at day 30. 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.

VI.E. RATIONALE AND ETHICAL CONSIDERATIONS

This prospective, multi-center study is being conducted to provide real world evidence potentially in support of including FFR_{CT} in an ED pathway.

The potential risks to subjects participating in this study include potential breach of confidentiality. Data transmitted to HeartFlow will not contain any PHI identifiers and will be coded with a unique identifier for each subject. All applicable study data will be transferred to HeartFlow and core laboratories in a secure manner and in accordance with all applicable regulations.

Anticipated benefits

There are no specific benefits to subjects participating in the study. There may be some benefit to other patients who undergo FFR_{CT}-guided management in the future.

Anticipated risks

ADVANCE-ED is a prospective study which collects data from clinically-indicated CCTA imaging and other procedures. These procedures will have been planned as part of routine clinical practice; therefore, no additional clinical risks are related to participating in the study.

IX. STATISTICAL CONSIDERATIONS

IX. A. General Considerations

Descriptive statistical methods will be used to summarize the data from this study, with confidence intervals and hypothesis testing performed for the primary and other selected efficacy endpoints. Unless stated otherwise, the term “descriptive statistics” refers to number of events (n), mean, median, standard deviation (SD), standard error, (SE) minimum, maximum, and coefficient of variation (CV) for continuous data and frequencies and percentages for categorical data.

All data collected during the study will be included in data listings.

Unless specified otherwise, all statistical testing will be two-sided and will be performed using an overall significance (alpha) level of 0.05.

All statistical analyses will be conducted with the SAS® System, version 9.4 or higher.

A statistical analysis plan (SAP) will describe the methods of data collection, validation, analysis, and reporting. The sections below provide a brief overview of statistical consideration for the study.

IX. B. Subject Characteristics

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

IX. C. Endpoint Analysis

The null hypothesis for the primary endpoint is that the reclassification rate between the coronary management plan based on the review of the CCTA compared to the actual

management after FFR_{CT} is obtained is zero. A one-sample exact binomial test will be used to analyze the primary endpoint. In addition, the proportion with reclassification along with the 95% exact confidence interval will be produced.

IX. D. Sample Size

FFR_{CT} arm: Approximately 250 subjects may be enrolled into this study. A sample size of 208 produces a two-sided 95% exact confidence interval with a width equal to 0.14 when the proportion with reclassification is 0.5.

Control arm: The control arm will contribute only to secondary endpoints and is therefore not included in the powering of the primary endpoint but will be the same size as the FFR_{CT} arm and will include approximately 250 subjects.

IX. E. Analysis Populations

All subjects who meet the study criteria, and who sign the written informed consent, are enrolled in the study.

X. DATA HANDLING AND QUALITY ASSURANCE

X. A. Completing and Signing Case Report Forms

This study will utilize eCRFs for the collection of all data. 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.

X. 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, Case Report Form Guidelines will be created to assist with eCRF completion. All site staff including investigators and research coordinators will undergo site initiation training to become thoroughly familiar with the protocol, case report forms, and with methods of data verification.

X. C. Archiving of Data

All study 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 5 years following completion of the study.

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. All data that is transferred to HeartFlow will be anonymized.

XI. SPECIAL REQUIREMENTS AND PROCEDURES

XI. A. Institutional Review

Before starting this study, 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 IRB. The study will not start before the 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 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 IRB without delay.

XI. B. Guidelines for Obtaining Subject Informed Consent

Written informed consent approved by HeartFlow and the IRB will be obtained from each subject, or their legal guardian as required according to section V.B. Subject Selection.

XI. C. Site Initiation/Training

Prior to sites enrolling subjects, the sponsor or its designee will contact the investigator and research coordinator for the site initiation visit. This visit will include the protocol review the data requirements for the study, including eCRF completion instructions, PI responsibilities and ensure all other applicable regulatory documents and trainings are completed.

XI. D. Study Monitoring and Audit

Edit checks will be included in the study database to ensure that out of range values are checked prior to inclusion in the dataset. If unusual outliers are found in any of the individual study populations, an audit plan may be developed at that time.

XI. E. Clinical Events Committee

There will not be a Clinical Events Committee for this study.

XII. FINAL REPORT

Following conclusion of the study, a final report from HeartFlow or its designee and may distributed to all investigators. This final report will include all enrolled, eligible subjects.

XIII. REFERENCES

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