The **REVEALPLAQUE** Study: A p**R**osp**E**cti**V**e, multic**E**nter study to **A**na**L**yze **PLAQUE** using CCTA

Study Objective

Current clinically available methods to quantify coronary artery plaque noninvasively from CCTA data are largely manual and as a result, have limited utility, reproducibility, accuracy, and precision. An automated deep learning based artificial intelligence method for segmenting the vessel wall and atherosclerotic plaque from CCTA data has been developed. This study will evaluate the level of agreement between this noninvasive CCTA-based quantification and characterization of coronary atherosclerosis and invasive IVUS.

Study Design

Patients who have a stenosis in at least one major epicardial vessel confirmed by CCTA and who are scheduled to undergo clinically indicated IVUS-guided invasive evaluation and/or treatment will be eligible for enrollment. Enrolling sites will have FFR_{CT} analysis incorporated when indicated into their standard evaluation of CCTA scans. Data collected will include CCTA and FFR_{CT} images, full angiographic images, IVUS images, and if obtained, any other imaging or physiologic data including OCT, FFR, any NHPR (e.g., dPR, RFR, iFR, etc.), and pre- and post-stent implantation invasive data. All non-invasive and invasive data collected will be obtained as clinical practice consistent with standard clinical care.

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Sponsor

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Protocol Signature Page

I have read and understood 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 or Ethics Committee. 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.

Site Name	Site Number
Site Co-Principal Investigator (print name)	
Site Co-Principal Investigator (signature)	Date
Site Co-Principal Investigator (print name)	
Site Co-Principal Investigator (signature)	Date

Protocol reviewed and approved by sponsor:

DocuSigned by:
Campbell Rogers
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Campbell Rogers, MD; HeartFlow, Inc., CMO	Date

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STANDARD ABBREVIATIONS

CAD	coronary artery disease
CCTA	coronary computed tomographic angiography
dPR	diastolic pressure ratio
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
IFR	instantaneous wave free ratio
IVUS	intravascular ultrasound
LoA	level of agreement
MACE	major adverse cardiovascular event
MI	myocardial infarction
NHPR	non-hyperemic flow reserve
NI	non-invasive
OCT	optical coherence tomography
PCI	percutaneous coronary intervention
RRF	resting full cycle ratio

STUDY SYNOPSIS

Protocol Title	A p**R**osp**E**cti**V**e, multic**E**nter study to **A**na**L**yze **PLAQUE** using CCTA
Subjects and Study Centers	Approximately 250 subjects across approximately 15 sites in the US and Japan.
Planned Study Duration	The duration of this study will be approximately 24 months: ● 3 - 9 months for study start-up (Site qualification, IRB approval, and site initiation) ● 12 months for enrollment ● 3 months for query resolution and database lock
Primary Study Objective	This study will evaluate the level of agreement between noninvasive CCTA-based quantification and characterization of coronary atherosclerosis and invasive IVUS .
Secondary Study Objectives	The secondary objectives of this study are to: 1) Compare total plaque volumes per-patient and per lesion as well as comparing different plaque type volumes to the IVUS reference standard and assess reproducibility of quantitative plaque measurements compared to the reference standard. 2) Perform exploratory analyses on plaque in previously stented vessels (protocol to allow up to 20% (50 patients) with one or two stented vessels vessels in this category. This can also include plaque proximal or distal to the stented vessel.
Hypotheses	The primary hypothesis of the study is that a deep-learning based automated method for segmenting coronary atherosclerotic plaques can quantify total plaque volume from CCTA with an acceptable level of agreement with IVUS measurements. The secondary hypothesis of the study is that CCTA-derived coronary models can accurately assess percent plaque burden as well as calcified, low attenuation, and fibrous plaque volumes with an acceptable level of agreement and repeatability compared to IVUS.
Population	Clinically stable patients with known CAD who have a CCTA showing stenosis in at least one major epicardial vessel of stentable/graftable diameter and in whom clinically-indicated IVUS is planned.
Study Design and Methods	This is a prospective, multi-center study. All patients who have a stenosis in at least one major epicardial vessel confirmed by CCTA, who have undergone FFR_{CT} analysis, and who are scheduled to undergo clinically indicated IVUS-guided invasive evaluation and/or treatment will be eligible for enrollment. Enrolling sites will have FFR_{CT} analysis incorporated when indicated into their standard evaluation of CCTA scans. Data collected will include CCTA and FFR_{CT}, full angiographic, and IVUS images, and if obtained, any other imaging or physiologic data including OCT, FFR, any NHPR (e.g., dPR, RFR, iFR, etc.), and pre-

	and post-stent implantation invasive data. All non-invasive and invasive data collected will be obtained as clinical practice consistent with standard clinical care. All details about cardiovascular testing and treatment (planned and actual) will be recorded at baseline. There will be no study required visits after the baseline invasive procedure.
Primary Endpoint	The primary endpoint is to assess the level of agreement between total plaque volume of a deep-learning based automated method for segmenting coronary atherosclerotic plaques, compared to IVUS, on a per-IVUS-pullback level.
Secondary Endpoints	Key secondary endpoints are: Per pullback: ● Total plaque volume ● Percent Plaque burden ● Calcified plaque volume ● Low attenuation plaque volume ● Fibrous plaque volume ● Segment involvement score (SIS) ● Adverse plaque characteristics (APC) Per lesion: ● Total plaque volume ● Percent plaque burden ● Calcified plaque volume ● Low attenuation plaque volume ● Fibrous plaque volume ● Minimum lumen area (MLA) ● Percentage area stenosis (%AS) ● Positive remodeling index Per lesion/pullback: ● Reproducibility of all metrics above when quantified from different CCTA series ● Reproducibility of all metrics above when processing the same series twice (analyst and process variation) ● Exploratory analysis of necrotic core volume
Inclusion Criteria	Inclusion criteria (all must be present): 1. Age ≥18 years 2. Clinically stable patient with known CAD 3. CCTA showing stenosis in at least one major epicardial vessel of stentable/graftable diameter, in whom clinically indicated IVUS is planned within 45 days of the CCTA and FFR_{CT} available

	4. FFR_{CT} successfully processed 5. Willing to comply with all aspects of the protocol 6. Agrees to be included in the study and able to provide written informed consent.
	Exclusion criteria (all must be absent): 1. CCTA showing no stenosis 2. Uninterpretable CCTA by HeartFlow assessment, in which image quality prevents FFR_{CT} from being processed. 3. Acute chest pain 4. CABG prior to CCTA acquisition 5. Prior history of PCI for 3 or more vessels 6. MI less than 30 days prior to CCTA or between CCTA and ICA. 7. Suspicion of acute coronary syndrome (acute myocardial infarction or unstable angina) 8. Known complex congenital heart disease 9. Tachycardia or significant arrhythmia 10. Subject requires an emergent procedure 11. Evidence of ongoing or active clinical instability, including acute chest pain (sudden onset), cardiogenic shock, unstable blood pressure with systolic blood pressure <90 mmHg, and severe congestive heart failure (NYHA III or IV) or acute pulmonary edema 12. Any active, serious, life-threatening disease with a life expectancy of less than 2 months 13. Currently enrolled in another study utilizing FFR_{CT} or in an investigational trial that involves a non-approved cardiac drug or device 14. Persons under the protection of justice, guardianship, or curatorship
Study Follow-Up	There will be no study required visits after the baseline cath.
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

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 rest and simulated maximal coronary hyperemic conditions (Taylor 2013). Results from four prospective trials suggest that FFR_{CT} accurately predicts the hemodynamic significance of coronary lesions when compared to invasively measured FFR (Koo 2011, Min 2012, Nørgaard 2014, Driessen 2018). 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).

One of the next key areas of interest in non-invasive disease identification is confirming whether a deep-learning based automated method for segmenting coronary atherosclerotic plaques can identify coronary atherosclerotic plaque location, quantity, and type. Recent studies have shown the importance of understanding plaque burden including non-calcified plaque and especially low attenuation plaque to better identify patients at risk of myocardial infarction (Thomsen 2016). A deep-learning based automated method for segmenting coronary atherosclerotic plaques which can quantify total plaque volume from CCTA has been designed and tested and now requires prospectively collected invasive imaging data to assess performance as compared to intravascular ultrasound imaging (IVUS), a gold standard in plaque quantification (Voros 2011, Fischer 2013).

In the REVEALPLAQUE study, all patients who have a stenosis confirmed by CCTA, have had FFR_{CT} completed, and are scheduled to undergo IVUS will be eligible for enrollment. Enrolling sites will have FFR_{CT} analysis incorporated when indicated into their standard evaluation of CCTA scans. All sites will provide demographic and medical history of enrolled subjects, CCTA and FFR images, full angiographic images, IVUS images, and if obtained, any other imaging or physiologic data including OCT, FFR_{CT}, any NHPR (e.g., dPR, RFR, iFR, etc.), and pre- and post-stent implantation invasive data. All non-invasive and invasive data collected will be obtained as clinical practice consistent with standard clinical care.

Data may be used to train deep learning artificial intelligence algorithms for image segmentation and physiological modeling, to improve current and future products.

II. STUDY OBJECTIVE

Primary Objective:

Current clinically available software packages to quantify coronary artery plaque noninvasively from CCTA data are largely manual and as a result, have limited reproducibility, accuracy, and precision. An automated deep-learning based artificial intelligence method for segmenting the vessel wall and atherosclerotic plaque from CCTA data has been developed. This study will evaluate the level of agreement between noninvasive CCTA-based quantification and characterization of coronary atherosclerosis and invasive IVUS.

Secondary Objectives:

The secondary objectives of this study are to:

1. Compare total plaque volumes per-patient and per lesion as well as comparing different plaque type volumes to the IVUS reference standard and assess reproducibility of quantitative plaque measurements compared to the reference standard.

2. Perform exploratory analyses on plaque in previously stented vessels (protocol to allow up to 20% (50 patients) with one or two stented vessels in this category). This can also include

plaque proximal or distal to the stented vessel.

III. STUDY ENDPOINTS

III. A. Primary Endpoint

The primary endpoint is to assess the level of agreement between total plaque volume of a deep-learning based automated method for segmenting coronary atherosclerotic plaques, compared to IVUS, on a per-IVUS-pullback level.

III. B. Secondary Endpoints

Key secondary endpoints are:

Per pullback:

- Total plaque volume
- Percent plaque burden
- Calcified plaque volume
- Low attenuation plaque volume
- Fibrous plaque volume
- Segment involvement score (SIS)
- Adverse plaque characteristics (APC)

Per lesion:

- Total plaque volume
- Percent Plaque burden
- Calcified plaque volume
- Low attenuation plaque volume
- Fibrous plaque volume
- Minimum lumen area (MLA)
- Percentage area stenosis (%AS)
- Positive remodeling index

Per lesion/pullback:

- Reproducibility of all metrics above when quantified from different CCTA series
- Reproducibility of all metrics above when processing the same series twice (analyst and process variation)
- Exploratory analysis of necrotic core volume

IV. STUDY DESIGN

The REVEALPLAQUE study is a prospective, multi-center study designed to evaluate a deep-learning based automated method for segmenting coronary atherosclerotic plaques. All patients who have a stenosis confirmed by CCTA and FFR_{CT} available and who are scheduled to undergo IVUS will be eligible for enrollment. Enrolling sites will have FFR_{CT} analysis incorporated when indicated into their standard evaluation of CCTA scans. All sites will provide CCTA and FFR_{CT} images, full angiographic images, IVUS images, and if obtained, any other imaging or physiologic data including OCT, FFR, any NHPR (e.g., dPR, RFR, iFR, etc.), and pre- and post-stent implantation invasive data. All non-invasive and invasive data collected will be obtained as clinical practice consistent with 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 250 subjects will be enrolled from approximately 15 experienced clinical research sites in the US and Japan.

IV. B. Patient Population

Clinically stable patients with known CAD who have a CCTA showing stenosis in at least one major epicardial vessel of stentable/graftable diameter and FFR_{CT} available, and in whom clinically indicated IVUS is planned within 45 days of CCTA will be prospectively enrolled.

IV. C. General Inclusion and Exclusion Criteria

Inclusion Criteria (all must be present):

1. Age ≥18 years
2. Clinically stable patient with known CAD
3. CCTA showing stenosis in at least one major epicardial vessel of stentable/graftable diameter, in whom clinically indicated IVUS is planned within 45 days of the CCTA
4. CCTA meets eligibility criteria for FFR_{CT} as defined in the IFU
5. Willing to comply with all aspects of the protocol, including adherence to follow up visits
6. Agrees to be included in the study and able to provide written informed consent

Exclusion Criteria (all must be absent):

1. CCTA showing no stenosis
2. Uninterpretable CCTA by HeartFlow assessment, in which image quality prevents FFR_{CT} from being processed.
3. Acute chest pain
4. CABG prior to CCTA acquisition
5. Prior history of PCI for 3 or more vessels
6. MI less than 30 days prior to CCTA or between CCTA and ICA.
7. Suspicion of acute coronary syndrome (acute myocardial infarction or unstable angina)
8. Known complex congenital heart disease
9. Tachycardia or significant arrhythmia
10. Subject requires an emergent procedure
11. Evidence of ongoing or active clinical instability, including acute chest pain (sudden onset), cardiogenic shock, unstable blood pressure with systolic blood pressure <90 mmHg, and severe congestive heart failure (NYHA III or IV) or acute pulmonary edema
12. Any active, serious, life-threatening disease with a life expectancy of less than 2 months
13. Currently enrolled in another study utilizing FFR_{CT} or in an investigational trial that involves a non-approved cardiac drug or device
14. Persons under the protection of justice, guardianship, or curatorship

V. STUDY WORKFLOW

The workflow for the REVEALPLAQUE study is described in the following sections.

V. A. Study/Site Selection

HeartFlow will identify and qualify the clinical research sites for the REVEALPLAQUE study. Participating sites will be screened for:

- CCTA acquisition practices conforming to SCCT guidelines
- Invasive Coronary Angiography (ICA) and other invasive data collection following best practices
- High quality IVUS data collection experience and ability to use automatic pullback for IVUS

- Adequate resources and past clinical research experience

V. B. Subject Selection

Institutional Review Board (IRB) approval will be obtained at all participating sites prior to screening subjects. All subjects who meet all inclusion criteria and do not meet any exclusion criteria, and are able and willing to participate, are candidates for the REVEALPLAQUE study. All subjects providing written informed consent and meeting all selection criteria will be enrolled into the REVEALPLAQUE 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 and FFR_{CT} results
    d. Results and images from non-invasive/invasive tests performed during 90 days prior to enrollment

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.

Subjects included in the study will have anatomic and physiological data obtained as standard clinical care during ICA recorded. A guide advising how to obtain IVUS measurements will be provided to sites during site protocol training; in summary the below mentioned data will be collected. A maximum of 20% of enrolled subjects may have at least one vessel with prior stent implantation.

ICA procedure:

1. The subject's vital signs (blood pressure and heart rate) will be recorded prior to ICA procedure.
2. Medications (adenosine and nitrates) taken within 24 hours of ICA will be recorded.
3. Angiography is advised to be performed according to the study guides provided during site protocol training.
4. The data from IVUS (mandatory), FFR measurements (as deemed necessary), and OCT (as deemed necessary) by the physician will be collected.
5. All angiographic images will be collected.
6. IVUS data for non-targeted lesions that are standard clinical care will be collected.
7. Radiation exposure will be documented.
8. Total procedural volume of iodinated contrast will be recorded
9. Fluoroscopy duration will be documented.
10. Diagnostic and therapeutic procedures and equipment used, including catheters, balloons, wires, and stents, and vessels treated will be documented.

11. Procedural complications will be documented (e.g., dissection from catheter or wire, reaction to medication, side branch occlusion, slow/no flow)

V. E. Follow up

No follow up with the subjects will be done as a part of this study.

VI. STUDY DURATION

The anticipated enrollment duration of the REVEALPLAQUE study will be approximately 12 months. No subject follow up 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. Withdrawn subjects will be considered screen failures if the collected data does not allow for adequate selection criteria assessment.

VI. B. Screen Failures

Subjects who sign consent will be deemed a screen failure if:

- Automatic pullback for IVUS catheter was not used during the procedure
- Prior to IVUS, the vessel was predilated (medications OK)

No data beyond reason for screen failure will be collected.

VI. C. Rules for Terminating the Study

There are no formal termination criteria for this study. The sponsor reserves the right to terminate the REVEALPLAQUE study at any time. Investigators have the responsibility to comply with all applicable regulatory guidelines and regulations. Specific reasons which may cause the sponsor, IRB, 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.

VII. SAFETY ASSESSMENT

Subjects will undergo a clinically indicated ICA and 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 with adherence to revascularization guidelines and data obtained will be documented. Therefore, there will be no additional clinical risks for subjects who participate. Procedural complications will be documented (i.e., dissection from catheter or wire, reaction to medication).

VIII. RATIONALE AND ETHICAL CONSIDERATIONS

This prospective, multi-center study is being conducted to expand existing datasets to improve the performance of FFR_{CT} and support development of future products.

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 management in the future based on deep-learning based automated methods for segmenting coronary atherosclerotic plaques.

Anticipated risks

The REVEALPLAQUE study is a prospective study which collects data from clinically indicated CCTA imaging and ICA 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. Procedural complications will be documented that are related to IVUS or FFR (e.g.,. dissection from catheter or wire, reaction to medication).

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, 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 9.1.3 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 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 primary endpoint is to assess the level of agreement between total plaque volume of a deep-learning based automated method for segmenting coronary atherosclerotic plaques, compared to IVUS, on a per-IVUS-pullback level.

Bland Altman plots will be constructed. If the deep-learning based automated method CCTA measurements fall with the limits of agreement (LoA) estimated from the IVUS measurements, the

measures will be assumed to agree. Additionally, Pearson's correlation and paired t-test will be constructed to further describe the relationship between IVUS measurements and deep-learning based automated method for segmenting coronary atherosclerotic plaques from CCTA.

All secondary endpoints which are continuous (e.g., per lesion total plaque volume, per lesion calcium volume, per lesion low attenuation volume, per lesion non-calcified plaque volume, segment involvement score) will be similarly compared using a Bland Altman plot, Pearson's correlation and paired t-tests. Reproducibility will be estimated with Intra Class correlation (ICC).

IX. D. Sample Size

Approximately 250 subjects may be enrolled into this study.

From published data (Conte 2019), the maximum allowable difference between the measurements is 36 $mm^{3.}$ Assuming a standard deviation of 12 mm^3, a sample size of 223 patients achieves 90% power to detect agreement when the mean is 8, confidence level of the (LoA) is 0.950 and the confidence level of the confidence intervals about the LoA is 0.950.

IX. E. Analysis Populations

All subjects who meet the study criteria, sign the written informed consent, and are enrolled in the study, and provide paired assessments of CCTA and IVUS measurements will be included in the analysis set.

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. 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. 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 to 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.

XI. F. IVUS Core Lab

There will be an IVUS core lab responsible for annotating the angio images, IVUS images, and HeartFlow provided Paraview models according to predefined study workflows. These workflows will be the joint responsibility of HeartFlow and the core lab and will be approved by both parties prior to implementing any study case reviews. All imaging data and annotations will be housed in a centralized EDC database.

XI. G. HeartFlow Technology / Data Team

The HeartFlow technology / data team will be responsible for exporting the coronary models for all enrolled subjects via Paraview and uploading them into the EDC system for the core lab.

Following the core lab analysis and blinded to the core lab results, the technology/data team will have access to the x,y,z coordinates from the annotated Paraview models and will use those to determine the plaque volume from the deep-learning based automated method for segmenting coronary atherosclerotic plaques from CCTA. Further details will be included in the study manuals separate from the main protocol.

XII. FINAL REPORT

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

XIII. REFERENCES

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