The Value of Fractional Flow Reserve Derived from Coronary CT Angiography and in the Triage of Low to Intermediate Risk Chest Pain Patients: Design: Single Center Prospective Clinical Trial; Target Disease: Coronary Artery Disease.

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List of Abbreviations

Fractional Flow Reserve: FFR
Coronary Computed Tomographic Angiography: CCTA
Computed Tomographic Fractional Flow Reserve: CT-FFR
Percutaneous Coronary Intervention: PCI
Cardiac Catheterization: Cardiac Cath
Coronary Artery Bypass Graft: CABG
Stress Myocardial Perfusion Imaging: Stress MPI
Invasive Coronary Angiography: ICA
Body Mass Index: BMI
Electrocardiogram: EKG
Estimated Glomerular Filtration Rate: eGFR
Portable document format: pdf

Study Summary

Title	*The Value of Fractional Flow Reserve Derived from Coronary CT Angiography and in the Triage of Low to Intermediate Risk Chest Pain Patients*
Short Title	*Value of FFR*
Protocol Number	*n/a*
Phase	*n/a – single phased study.*
Methodology	*Prospective clinical trail*
Study Duration	*15 months*
Study Center(s)	*Single center*
Objectives	*The purpose of this study is to evaluate the incremental benefit of Fractional Flow Reserve (FFR) derived from Coronary Computed Tomographic Angiography (CCTA) (CT-FFR) compared to CCTA with or without stress testing, using invasive FFR as the gold standard for patients with obstructive disease (> 30% stenosis). This study will also assess the capability of CT-FFR to enhance performance on both negative and positive predictive value for less experienced readers by providing feedback based on CT-FFR evaluation*
Number of Subjects	*Number of subjects projected for the entire study 572*
Diagnosis and Main Inclusion Criteria	*Chest Pain and stable angina patients with suspicion of coronary artery disease*
Study Product, Dose, Route, Regimen	*n/a. The study will assess the capability of measuring fractional flow reserve noninvasively utilizing computers and information provided by routine CCTA studies.*
Duration of administration	*n/a*
Reference therapy	*The standard reference will be invasive FFR.*
Statistical Methodology	*Defining an event as performance of ICA when no intervention is necessary, we expect to compare event rates for patients treated with CCTA and FFR-CT, using t-tests and a multivariate, risk adjusted 90 day hazard model with 95% confidence interval. Our null hypothesis is that outcomes will not vary regardless of which testing is used to assess obstructive disease. Our alternative hypothesis is that evaluation with FFR-CT as oppose to CTTA alone will reduce the event rate.* *We will assess the comparability of the CCTA readers' readings and compare them to the CT-FFR results and the noninvasive FFR results.*

1 Previous Study History

Has this study ever been reviewed and rejected/disapproved by another IRB prior to submission to this IRB?

X☐ No ☐ Yes – if yes, please explain:

2 Brief Summary of Research

Coronary Computed Tomography Angiogram (CCTA) is a non-invasive imaging modality that has high sensitivity and negative predictive value for the detection of coronary artery disease (CAD). The main limitations of CCTA are its poor specificity and positive predictive value, as well as its inherent lack of physiologically relevant data on hemodynamic significance of coronary stenosis, a data that is provided either by non-invasive stress tests such as myocardial perfusion imaging (MPI) or invasively by measurement of the Fractional Flow Reserve (FFR). Recent advances in computational fluid dynamic techniques applied to standard CCTA are now emerging as powerful tools for virtual measurement of FFR from CCTA imaging (CT-FFR). These techniques correlate well with invasively measured FFR [1-4]. The primary purpose of this study is to evaluate the incremental benefit CT-FFR as compared to CCTA in triaging chest pain patients in outpatient settings who are found to have obstructive CAD upon CCTA (> 30% stenosis). Invasive FFR and short term clinical outcomes (90 days) will be correlated with each diagnostic modality in order to evaluate positive and negative predictive value of each when used incrementally with CCTA.

Patients will undergo a CCTA, as part of routine care. If the patient consents to participate in the study and is found to have coronary stenosis of 30% to 100%, based on the cardiologist's reading, the CCTA study will be sent to HeartFlow, a vendor that will provide a computerized FFR reading, based on the CCTA study. If the noninvasive FFR diagnosis indicates obstructive disease, the patient will undergo cardiac catheterization with invasive FFR.

As CCTA utilization increases, the need to train additional imaging specialists will increase. This study will assess the capability of FFR-CT to enhance performance on both negative and positive predictive value for less experienced readers by providing feedback based on CT-FFR evaluation. CCTA readers will be grouped in two categories: those with more than 10 years reading experience and those with less than 10 years reading experience. Each CCTA will be read by a less experienced and a more experienced reader. Results from each reader will be correlated with each other and with the CT-FFR and invasive FFR results.

3 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312

and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

3.1 Background

Coronary Computed Tomography Angiogram (CCTA) is a non-invasive imaging modality that has high sensitivity and negative predictive value for the detection of coronary artery disease (CAD). The main limitations of CCTA are its poor specificity and positive predictive value, as well as its inherent lack of physiologically relevant data on hemodynamic significance of coronary stenosis, a data that is provided either by non-invasive stress tests such as myocardial perfusion imaging (MPI) or invasively by measurement of the Fractional Flow Reserve (FFR). Recent advances in computational fluid dynamic techniques applied to standard CCTA are now emerging as powerful tools for virtual measurement of FFR from CCTA imaging (FFR-CT). These techniques correlate well with invasively measured FFR [1-4]. The primary purpose of this study is to evaluate the incremental benefit FFR-CT as compared to CCTA in triaging chest pain patients in outpatient settings who are found to have obstructive CAD upon CCTA (> 30% stenosis). Invasive FFR and short term clinical outcomes (90 days) will be evaluated for each diagnostic modality in order to evaluate positive and negative predictive value of each when used incrementally with CCTA.

3.2 Investigational Agent

CCTA is increasingly becoming a preferred non-invasive imaging modality because of its high sensitivity and negative predictive value for the detection of CAD. It has been shown to be a robust imaging modality for evaluation of chest pain, and is associated with decreased unnecessary hospital admission, length of stay, major adverse cardiovascular event rates, recidivism rates, and downstream resource utilization compared to standard evaluation [5]. While findings so far are highly suggestive of CCTA's significance as a gatekeeper for ICA by ruling out obstructive CAD, fewer than half of obstructive stenosis identified by CCTA are ischemia-causing, signifying its poor positive predictive value and inherent lack of physiological information [6-8]. Consequently, utilization of CCTA has not entirely averted need for downstream testing for functional assessment of CCTA-detected obstructive lesions either by stress testing or ICA. Recently a major treatment modality, associated with the use of CCTA, has become available that offers promise for improving positive predictive value and physiological relevant hemodynamic data. Advances in computational fluid dynamic techniques applied to standard CCTA are now emerging as a powerful tool for virtual measurement of FFR from CCTA imaging (CT-FFR). This techniques correlate well with invasively measured FFR [1-4]. CT-FFR is not an investigational agent, having been approved by FDA in November, 2014. However, more work is necessary to delineate the patient population that could derive maximal benefit from this new technology.

3.3 Preclinical Data

While few publications regarding the use of CT-FFR specifically address the cost of diagnostic work-up for obstructive disease, it is clear that the cost structure resulting from changes in diagnostic testing will also change. Deferral or avoidance of cardiac catheterization and nuclear stress testing will likely yield significant reductions in the cost of the diagnostic testing.

3.4 Clinical Data to Date

From 1/1/2009 to 3/31/2015 our team introduced and operated a CCTA Chest Pain triage program for low to intermediate risk patients at Stony Brook University Hospital ED and non-emergency outpatient services, the only tertiary care hospital in Suffolk County. Concurrently, we established a registry to monitor patient outcomes for all patients receiving CCTA at Stony Brook Medicine. Our registry contained nearly 15,000 patient CCTA procedures. Our major registry study established the effectiveness of CCTA as an imaging modality for evaluating ED chest pain in a cost efficient manner with a false negative rate less than 1% [5]. However, our registry reflects the poorer positive predictive values documented by other industry studies [6-8].

False positive workup results in the necessity of performing cardiac catheterization on patients at risk for obstructive disease based on assessment with current standard of care (combined screening with CCTA and stress MPI). Reduction in the rate of false positive testing would lead to reduction in risk from invasive procedures and radiation exposure to patients and reduced cost to the health care system.

Several medical institutions currently use HeartFlow CT-FFR as standard of care for evaluating obstructive disease. Generally, the standard of care at these institutions is to refer patients who are 30 to 100 percent obstructed by CCTA and who have reduction of flow <= to 0.8 that is deemed to be medical significant by the attending cardiologist to Invasive FFR. HeartFlow has reported to us confidentially that this routine use of CT-FFR has resulted in a 54% reduction in false positive rate as compare to use of CCTA alone.

3.5 Dose Rationale and Risk/Benefits

n/a This is not a pharmaceutical study.

4 Study Objectives

The purpose of this study is to evaluate the incremental benefit of Fractional Flow Reserve derived from CCTA (FFR-CT) compared invasive FFR as the gold standard for patients with obstructive disease (> 30% stenosis). This study will also assess the capability of CT-FFR to

enhance performance on both negative and positive predictive value for less experienced readers by providing feedback based on CT-FFR evaluation.

5 Resources Available to Conduct the Human Research

The primary data collection for the study will be generated from stable chest pain and angina patients receiving routine CCTA as part of their workup. Patients will be offered the opportunity to participate in clinical trial. Lenox Hill hospital routinely provides more than 1,000 CCTA scans annually to this patient population. Therefore, out target of 572 cases should be achievable. Our noninvasive cardiology imaging team, including 6 attending cardiologists, and 2 cardiology fellows, and a cardiac imaging fellow will participate in the study. In addition, we will employ a study coordinator, an IT specialist who works in cardiology, our lead CCTA technician, and a PhD with training in statistics and economics. All team members attend weekly research group meetings to plan and monitor the study, including duties of team members and study process and flow.

6 Study Design

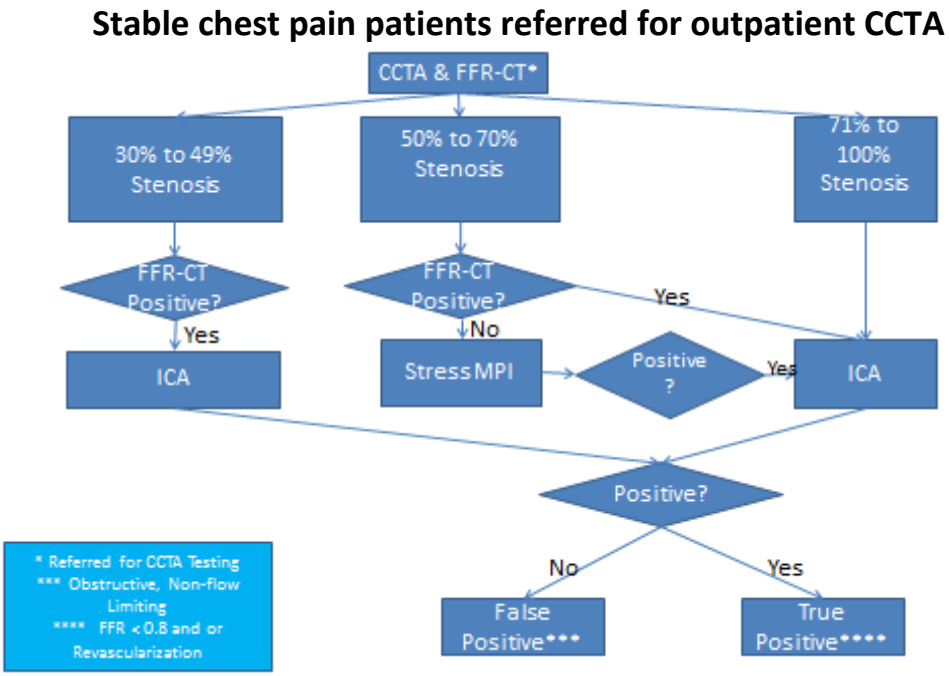
6.1 General Design

This will be a prospective clinical trial designed to evaluate the incremental benefit of virtual FFR measured from CCTA, compared to invasive FFR and CCTA for the detection of flow-limiting coronary stenosis, as defined by invasive FFR <=0.8 and vessel diameter of >=2mm.

572 consecutive patients who present to Lenox Hill Hospital Outpatient Clinics for CCTA due to chest pain or stable angina over a ten month period and meeting the study inclusion criteria are eligible for the study (Figure 1). Our team will employ CCTA-appropriateness criteria to ensure proper selection of patients, derived from the Appropriate Use Criteria for Cardiac Computed Tomography published in 2010 and jointly authored by multiple societies including ACCF, SCCT, and ACR [10]. FFR-CT measurements will be performed by a core laboratory in a blinded fashion. All eligible patients will undergo 64-slice or greater multi detector CCTA and CT-FFR measurements. The severity of the stenosis will be determined on site by level III CCTA readers. Patients with obstructive lesions of (30% to 100% stenosis) will receive Stress-MPI, per SOC protocol, and CT-FFR. Patients with positive Stress-MPI and CCTA (50% - 70%) or positive CCTA (71% to 100%) will undergo ICA with invasive FFR measurement in accordance to accepted guidelines and established practice standard. Those patients with invasively measured FFR<=0.8 and with vessel diameter of >= 2mm, or those who require revascularizations based on invasively estimated stenosis severity will be considered to have flow-limiting obstructive CAD, while the rest will be considered to have non-flow limiting obstructive CAD (if also >50% stenosis on ICA). If stenosis severity turns out to be < 50% after ICA (the gold standard), we will conclude that these patients have non-obstructive CAD. (Figure 1). Patients with 30% to 49% obstructive disease, according to CCTA, will be referred to optimal follow up care only. Any in this group who have positive CT-FFR will return for

ICA with invasive FFR measurement, and follow the protocol for those with 50% to 100% obstruction.

Figure 1:



In order to assess the primary endpoint of comparison of event rates for patients treated with CCTA and FFR-CT, we will perform a retrospective chart review of Invasive Coronary Angiograms performed at Lenox Hill Hospital from 2014 to 2018. We will specifically review Cardiac Catheterization reports to screen patients and record data for cases where the indication for Catheterization was (1) Positive stress test and/or (2) Positive CCTA.
Based on the catheterization report we will determine whether the patient had obstructive coronary artery disease with/without flow limitation, in the same manner and following the same definitions as those used to categorize level of obstruction in subjects enrolled in the prospective cohort of the study.
This data will be used as comparison/control group to assess trends and rates of invasive coronary catheterization when no intervention is necessary, in cases where CCTA and/or stress test without CT-FFR was used to determine the need for cardiac catheterization. Only the minimum amount of data required for a robust comparison of event rates will be collected.

6.2 Primary Study Endpoints

Defining an event as performance of ICA when no intervention is necessary, we expect to compare event rates for patients treated with CCTA and FFR-CT, using t-tests and a multivariate, risk adjusted 90 day hazard model with 95% confidence interval. Our null hypothesis is that outcomes will not vary regardless of which testing is used to assess

obstructive disease. Our alternative hypothesis is that evaluation with FFR-CT as oppose to CTTA will change the event rate. We will also correlate noninvasive and invasive FFR studies.

6.3 Secondary Study Endpoints

We will assess inter-observer reliability of the two reader cohorts' (> 10 years experience and less than 10 years experience) readings for CCTA and CT-FFR.. We will also assess the nondiagnostic rate for CT-FFR exams as compared to independent quality ratings of CCTA scans by the scan reader. Scans will be rated as excellent, good, adequate, or non-diagnostic. Non-diagnostic exams will not be sent to CT-FFR. For those sent to CT-FFR we will compare the percentage of non-diagnostic exams to the percentage of non-diagnostic for CT-FFR, and we will also correlate exam results by level of obstruction.

6.4 Primary Safety Endpoints

The study design evaluates the potential to substitute non-invasive for invasive FFR. Safety endpoints of the study include: 1. Evaluating the diagnostic accuracy of non-invasive FFR. If the end result demonstrates that the procedure is less accurate than invasive FFR, patients receiving this procedure, as an alternative to the current standard will be at greater risk. 2. Patients who undergo invasive procedures experience increased risk of infection or other comorbidities or complications, as compared to those who do not undergo invasive procedures. Therefore, if the noninvasive protocol results are not significantly different than the invasive results, patient safety might potentially be increased by using the noninvasive technology. 3. Noninvasive technology has the potential to reduce radiation exposure by reducing the number of invasive angiography and Stress MPI procedures necessary to complete patient evaluation. This increases patient safety relative to the adverse effects of radiation exposure.

7 Subject Selection and Withdrawal

7.1 Inclusion Criteria

1. *Patients must be capable of giving informed consent.*
2. *Patients must be able to cooperate with technician performing the procedure.*
3. *Patients must have BMI <= 50.*
4. *Patients must have non-STEMI EKG without acute changes*

5. *Patients must present to Lenox Hill Ambulatory CCTA Clinic with medically necessary appointment for CCTA for the purpose of evaluation coronary stenosis for the provisional diagnoses of chest pain or angina or angina equivalent.*
6. *Patient must be able to take nitroglycerin and beta blockers.*

7.2 Exclusion Criteria

Create a numbered list of criteria that would exclude a subject from study enrollment. If appropriate, should generally include that subjects cannot be homeless persons, or have active drug/alcohol dependence or abuse history. If exposure to certain medications or treatments at screening is prohibited, that must be noted in the exclusion criteria—if these are also prohibited concomitant medications during the study period that should be noted here as well.

7. *Patient must not have a history of coronary stenting or coronary artery bypass graft.*
8. *Patients must not have severe or end stage renal disease as diagnosed as eGFR < 50.*
9. *Patients must not have a BMI > 50.*
10. *Patients must not have active asthma requiring bronchodilator therapy.*
11. *Must not have any allergies to contrast.*

7.3 Vulnerable Populations

Indicate whether you will target any of these vulnerable populations.

- ☐ *Children or viable neonate*
- ☐ *Cognitively impaired*
- ☐ *Pregnant Women, Fetuses or neonates of uncertain viability or nonviable*
- ☐ *Prisoners*
- ☐ *NSLIJ Employees, residents, fellows, etc*
- ☐ *poor/uninsured*
- ☐ *Students*
- ☐ *Minorities*
- ☐ *Elderly*
- ☐ *Healthy Controls*

If any of these populations are included in the study, describe additional safeguards that will be used to protect their rights and welfare.

None of these vulnerable populations are targets of this study.

7.4 Subject Recruitment and Screening

Patients scheduled to present or presenting to the Lenox Hill Ambulatory Care CCTA Clinic for evaluation of coronary stenosis with the provisional diagnosis of chest pain of angina will be offered the opportunity to participate in this clinical trial. If possible, patients will be contacted in advance of the visit by the study coordinator and educated on the study. All eligible patients will receive education about the study and offered the opportunity to participate upon arrival to the clinic.

The study coordinator, cardiology fellow, or cardiologist will take the patient's medical history as it relates coronary stenting, CABG and other cardiac risk factors (including smoking, family history of heart disease, hyperlipidemia, diabetes, hypertension.) Routine preparation for CCTA with be conducted by clinic staff. As part of this activity patient height and weight will be obtained, and a blood draw for Serum Creatinine to calculate patient eGFR will be taken.

In order to assess the primary endpoint of comparison of event rates for patients treated with CCTA and FFR-CT, we will perform a retrospective chart review of Invasive Coronary Angiograms performed at Lenox Hill Hospital from 2014 to 2018. We will specifically review Cardiac Catheterization reports to screen patients and record data for cases where the indication for Catheterization was (1) Positive stress test and/or (2) Positive CCTA. Based on the catheterization report we will determine whether the patient had obstructive coronary artery disease with/without flow limitation, in the same manner and following the same definitions as those used to categorize level of obstruction in subjects enrolled in the prospective cohort of the study.

7.5 Consent Process

The study cardiology fellow or cardiologist will obtain the informed consent from the patient in the Lenox Hill Ambulatory CCTA Clinic. An attempt at outreach will be made for scheduled patients to apprise them of the fact that a study is being conducted. Consent will be obtained on the days of the study. Before consent is obtained, the cardiologist or cardiology fellow will review the major activities of the study with the patient, provide an opportunity for the patient to ask questions, and ask the patient to sign the consent. The patient will receive a copy of the informed consent form (attached), explaining the procedure. Signed informed consent forms will be maintained by the Study Coordinator.

We would like to request a waiver of consent and HIPAA Authorization for the retrospective chart review portion of the study. There will be no intervention, testing, or contact with subjects included in this portion. Only the minimum amount of data required for a robust comparison of event rates will be collected. The retrospective portion of the study meets the criteria for a complete waiver of consent 1) The research involved no more than minimal risk as it simply involves the collection and analysis of previously collected health information of patients who underwent CCTA and invasive cardiac catheterization. 2) The wavier will not adversely affect the rights or welfare of participants because, given that the research would

not impact the participant's current or future care; 3) the study could not be practicably conducted without the waiver given the large sample size and the fact that the participants were never or are no longer patients of the PI. It is also possible that the subjects are now deceased or no longer part of the Northwell system. 4) The outcome of the chart review will not impact the future care of participants so no additional information will be provided to them. The study will protect the identifiers by storing information in REDCap.

PHI (date of procedure and participant name) is required for the conduct of the retrospective portion of the study as the researchers will need to access the charts of individuals who meet study criteria in order to collect the test results of interest.

No study participants under the age of 18 will be recruited.

Cognitively impaired subjects will not be recruited, due to the need for the subjects to be capable of following the technologist's instructions during the CCTA exam.

If the study will enroll non-English speaking subjects:

The study does not target non English speaking populations. However, we will utilize Northwell approved short forms combine with HIPAA authorization forms translated in the appropriate language as necessary to ensure that the subject can provide appropriate consent.

7.6 Early Withdrawal of Subjects

7.6.1 When and How to Withdraw Subjects

Subjects may withdraw from the study for any reason at their request. Subjects who cannot or will not cooperate with the CCTA technologists instructions will be withdrawn from the study, because we will not be able to perform a CCTA. For some subjects, FFR results may not be available due to poor quality of CCTA scan. In this case, the subject will remain in the study, following standard of care, but no FFR reading will be available. If at any time a patient experiences an adverse reaction to medical care, the procedure will be ended and the patient will be withdrawn from the procedural part of the study. Wherever possible, when patients withdraw from the procedure part of the study (the CCTA) we will make every effort to conduct study follow-up.

7.6.2 Data Collection and Follow-up for Withdrawn Subjects

We will make every effort to conduct study follow up for all subjects, regardless of their ability to receive CCTA and CT-FFR. The study coordinator will make a minimum of 5 attempts to follow up with the subjects by telephone. If this does not work, he will try to contact the patients 3 times by email, if patient contact information is available, and once by U.S. postal service certified mail. The team will also check records for follow up at Lenox Hill Hospital and will review death registries to ascertain whether the patient is still alive.

8 Study Drug/Device

8.1 Description

The agent in this study is the computer program that provides the CT-FFR interpretation of flow. This is not an investigational agent, having been approved by the IRB in November 2014. The results will allow the physician to visualize flow through the coronary arteries and measure the level of obstructive disease. The physician will dictate a report based on his/her interpretation of the images. The report and a portable document format (pdf) file of a major view of the coronaries will be maintained as part of the patient's medical record.

8.2 Treatment Regimen

The CCTA data will be collected as part of the standard of care delivered for patients undergoing CCTA with contrast.

8.3 Method for Assigning Subjects to Treatment Groups

This is not a randomized study. Treatment assignments will follow the clinical protocol.

Once the CCTA results are interpreted by the physician, the physician will order CT-FFR exams for patients whose level of stenosis by CCTA standards is 30% to 100%.

If CT-FFR is positive patients will be referred for Cardiac Catheterization and invasive FFR.

If CT-FFR is negative, and level of obstruction is 30 to 49% by CCTA standards, patients will be referred to optimal medical care.

If CT-FFR is negative and level of obstruction is 50% to 70% by CCTA standards, patient will be referred for stress MPI. If stress MPI is positive patients will be referred for Cardiac Cath and invasive FFR. If stress MPI is negative, patients will be referred to optimal medical care.

If the patient has had a stress MPI within one year of the CCTA exam and the CCTA exam result is 50% to 70% obstructive, the physician will rely on the prior stress testing result, rather than repeating the stress test. If the stress testing results was negative, the patient will be referred to optimal medical care. If, in the investigator's opinion, the results indicate that the patient is at increased risk of obstructive disease, when considered with the CCTA findings, the patient will be referred to Cardiac Cath and Invasive FFR.

If CT-FFR is negative and level of obstruction is 70% to 100% by CCTA standard, patient will be referred to Cardiac Cath and Invasive FFR.

8.4 Preparation and Administration of Study Drug/Implantation of Study Device

The device in this study is the computer program that provides the CT-FFR interpretation of flow. The results will allow the physician to visualize flow through the coronary arteries and measure the level of obstructive disease. The physician will dictate a report based on his/her interpretation of the images. The report and a pdf of a major view of the coronaries will be maintained as part of the patient's medical record.

The use of the devise requires no variance from the routine standard of care for CCTA. The CCTA results will be sent to HeartFlow for CT-FFR analysis if the physician finds that the patient has 30% to 100% obstructive disease based on CCTA standards.

8.5 Subject Compliance Monitoring

Study treatment regimen requires that the patient follow physicians' recommendations concerning follow-up care as described above. The study coordinator will monitor the patients to determine whether the patient follows the recommended treatment plan. If not, a study cardiologist will contact the patient and encourage compliance with the treatment plan.

8.6 Prior and Concomitant Therapy

Prior and concomitant medical therapy will be collected and documented at the time of patient referral to Lenox Hill Hospital Ambulatory Care CCTA Clinic as part of the medical history. The coordinator will also contact the patient 90 to 120 days after the CCTA exam and interview the patient on follow up care, including any additional medical interventions. Specifically, the coordinator will maintain a record of patients' documented cardiac risk history and track cardiac interventions for obstructive disease, including PCI and CABG during the study.

8.7 Packaging

n/a

8.8 Blinding of Study Drug/Device

This is not a blinded study, in terms of patient randomization into study cohorts. However, when patients are referred for CT-FFR, no information regarding the CCTA results will be provided to HeartFlow (the provider of CT-FFR services.) When Cardiologists interpret CCTA and Stress-MPI results, no information regarding CT-FFR results will be available to them for review.

8.9 Receiving, Storage, Dispensing and Return

8.9.1 Receipt of Drug Supplies/Device

The device will not be obtained. The CCTA imaging results will be sent to the HeartFlow computer for interpretation. Cardiologists participating in the study will have access to FFR images and results, and make their final recommendations based on these images.

8.9.2 Storage

n/a

8.9.3 Dispensing of Study Drug/Device

n/a

8.9.4 Return or Destruction of Study Drug/Device

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At the completion of the study, there will be a final reconciliation of subjects who received FFR and those who did not, and related follow up testing and interventions. This reconciliation will be logged on a reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented.

9 Study Procedures

Figure 1 and Appendix 1 describe this information.

Patients scheduled for an outpatient CCTA to evaluate stable chest pain or angina and meet the study criteria will be asked to participate in the study. All study patients will receive a CCTA as part of standard of care.

A physician Cardiologist will interpret the CCTA as per current operating protocol. If the Cardiologist diagnoses stenosis in the range of 30% to 100%, the CCTA scan will be uploaded to Heart Flow for noninvasive FFR, via HIPAA compliant cloud-based technology reviewed and approved by the Northwell security team.

The Noninvasive CT-FFR is considered to be a research procedure at Northwell (though FDA approved) and is not part of the standard of care currently offered at Northwell. However, some institutions do use noninvasive CT-FFR as part of their standard of care. According to HeartFlow representatives, these include William Beaumont Hospital (Detroit), Sanger Heart and Vascular (Charlotte), Weill Cornell Medical College (New York), St Pauls Hospital (Vancouver) Cedars Saini (Los Angeles), Baylor Plano (Dallas), Sutter PAMF (SF Bay Area), Baylor St Lukes (Houston), Loyola Medical College (Chicago), Duke University (Durham), University Hospitals (Cleveland), and Minneapolis Heart Institute (Minneapolis). Considering this, and the preliminary results of which we are aware, we believe that CT-FFR should be considered a minimal risk procedure.

Once the data has been analyzed by HeartFlow, the physician will receive a notification from HeartFlow that will allow for the physician to sign on to the HeartFlow server and analyze the flow of all vessels on an interactive program. The physician will interpret the HeartFlow results and the study coordinator will download the best quality phase on a PDF to be stored with the study report on RIS System. The physician will dictate an addendum to the CCTA scan discussing the CT-FFR findings.

*Patients who have borderline obstructive disease (50% to 70% stenosis) who have negative CT-FFR will be referred for Stress MPI to confirm, unless the patient has had stress testing within a year of the CCTA. This is an accepted practice as part of the standard of care at Lenox Hill Hospital. If the stress test is negative, the patient will be referred to his/her physician for follow-up. If the stress test is positive, the patient will be referred to Invasive Coronary Angiography for Invasive FFR and diagnostic cardiac catheterization. If the patient has had a history of negative stress testing within a year of the CCTA, then the patient will be referred to his/her physician for follow-up. It the patient's prior stress test had findings that, in the investigator's opinion, increase the patient's risk of obstructive disease when viewed with the CCTA findings, the patient will be referred to Invasive Coronary Angiography for diagnostic cardiac catheterization and Invasive FFR. This is an accepted practice as part of the standard of care at Lenox Hill Hospital.**

Patients who have borderline obstructive disease (50% to 70% stenosis) who have positive FFR will be referred for Invasive Coronary Angiography for Invasive FFR and diagnostic

*cardiac catheterization. This is an accepted practice as part of the standard of care at Lenox Hill Hospital. **

Patients with 71% or greater stenosis will be referred for Invasive Coronary Angiography for Invasive FFR and diagnostic cardiac catheterization. This is an accepted practice as part of the standard of care at Lenox Hill Hospital.

> **In current standard of care practice at Lenox Hill Hospital, for borderline obstructive coronary disease, the decisions as to whether to proceed with stress testing or refer to invasive coronary angiography is left to the medical discretion of the attending cardiologist.*

Invasive Coronary Angiography and Invasive FFR are considered to be the gold standard procedures for evaluation of obstructive coronary artery disease. Patients deemed to be at high risk for obstructive disease based on CCTA or Stress testing are referred for invasive testing to determine whether cardiac intervention consisting of Percutaneous Coronary Intervention or Coronary Artery Bypass Graft is necessary.

In order to assess the primary endpoint of comparison of event rates for patients treated with CCTA and FFR-CT, we will perform a retrospective chart review of Invasive Coronary Angiograms performed at Lenox Hill Hospital from 2014 to 2018. We will specifically review Cardiac Catheterization reports to screen patients and record data for cases where the indication for Catheterization was (1) Positive stress test and/or (2) Positive CCTA.
Based on the catheterization report we will determine whether the patient had obstructive coronary artery disease with/without flow limitation, in the same manner and following the same definitions as those used to categorize level of obstruction in subjects enrolled in the prospective cohort of the study.
This data will be used as comparison/control group to assess trends and rates of invasive coronary catheterization when no intervention is necessary, in cases where CCTA and/or stress test without CT-FFR was used to determine the need for cardiac catheterization. Only the minimum amount of data required for a robust comparison of event rates including the following identifiers -name, date of procedure and age will be collected.

9.1 Visit 1

1. Visit 1 is an ambulatory visit to Lenox Hill Outpatient CCTA Clinic. Consent for study participation will be collected and routine CCTA will be administered.

9.2 Visit 2

If CCTA shows < 30% obstruction, visit 2 will be a referral for optimal follow-up cardiac care.
If CCTA shows 30 to 49% obstructive disease and CT-FFR is negative, visit 2 will be a referral for optimal follow-up care.

If CCTA shows 50% to 70% obstructive disease and CT-FFR is negative, visit 2 will be a referral for Stress MPI testing.
If stress testing has been performed in the past year, then the results of those test will be considered, and new stress testing will not be performed.
If prior stress test was negative, visit 2 will be a referral for optima follow-up cardiac care.
If the investigator assessed that the prior stress test results increase the risk of acute obstructive cardiac disease for the patient, Visit 2 will be a referral to cardiac catheterization and invasive FFR.
If CCTA shows >= 70% obstructive disease visit 2 will be referral to cardiac catheterization and invasive FFR.
If CT-FFR is positive, visit 2 will be a referral to cardiac catheterization and invasive FFR.

9.3 etc.

Visit 3:
If patient receives a stress MPI, and it is negative, visit 3 will be referral to optimal follow-up care.
If patient receives a stress MPI, and it is positive, visit 3 will be to cardiac cath and invasive FFR.

If patient undergoes a cardiac cath and invasive FFR at visit 2, visit 3 will be a referral to optimal follow-up care.

Visit 4: If patient receives a cardiac cath with invasive FFR at visit 3, visit 4 will be to optimal follow-up care.

10 Risks to Subjects

The risks to subjects in this study are minimal, compared to the risks faced by the population of patients receiving standard of care for potential coronary artery disease and stable chest pain or angina at Lenox Hill Hospital. Most patients will receive the standard of care currently in place, but will have an additional test run (CT-FFR). This test does not require any additional activity of the patient beyond completion of the CCTA with contrast (Standard of Care). This test will be used to assess whether improvements in the standard of care can be made for future patients.
A small percentage of patients, those who have positive CT-FFR, but 30 to 49% obstructive disease by CCTA standard will undergo an additional invasive exam. This exam may identify obstructive disease. If so, the patient will benefit. If not, the patient will undergo an invasive procedure unnecessarily. We believe that very few patients, if any, will fall into this category.

Patients who undergo Invasive FFR and Diagnostic Cardiac Catheterization will face increased risk, as compared to standard of care. According to the NIH National Heart Lung and Blood Institute, this procedure is very common, and rarely causes serious problems. [22] However, complications can include bleeding, infection and pain at the catheter insertion site. On rare occasions the catheter can scrape or poke a hole in a blood vessel during insertion

causing damage to the blood vessel. Patients may also experience an allergic reaction to the dye that is used during the procedure. Less common reactions include arrhythmias, or irregular heart beats; kidney damage caused by the dye that is used during the procedure; blood clots that can trigger stroke or heart attack or other serious problems; low blood pressure; or a buildup of fluid in the sac that surrounds the heart. This may cause the heart not to beat properly. [22]

The anticipated benefit of this study is to identify a more accurate means of diagnosing coronary artery disease without invasive procedures and with less exposure to radiation. The use of CT-FFR should address the weakness of CCTA – its lack of specificity. CT-FFR is expected to increase the test's positive predictive value. We believe that the use of this technology can make significant reductions in the use of diagnostic cardiac catheterization without intervention and in the use of stress MPI to validate uncertain findings when CCTA is used as a first test.

11 Potential Benefit to Subjects

A small percentage of patients, those who have positive CT-FFR, but 30 to 49% obstructive disease by CCTA standards will undergo an additional invasive exam. This exam may identify obstructive disease. If so, the patient will benefit from treatment of obstructive disease. If not, the patient will undergo an invasive procedure unnecessarily. We believe that very few patients, if any, will fall into this category.

The anticipated benefit of this study is to identify a more accurate means of diagnosing coronary artery disease without invasive procedures and with less exposure to radiation in the future. The use of CT-FFR should address the weakness of CCTA – its lack of specificity. CT-FFR is expected to increase the test's positive predictive value. We believe that the use of this technology can make significant reductions in the use of diagnostic cardiac cath without intervention and in the use of stress MPI to validate uncertain findings when CCTA is used as a first test.

12 Research Related Harm/Injury

The only possible research related injury we can identify would be an adverse reaction to a cardiac cath procedure that a patient might not have otherwise undergone, if not participating in the study. We expect few if any of these procedures. Standard treatments for adverse reaction to cardiac cath would apply if such an event occurs. Patients will be informed of this risk at the time of obtaining informed consent. The consent states that the patient would be financially liable if such an event were to occur.

13 Provisions to Protect Privacy Interests of Subjects

We have described above the method of recruitment. Because the recruitment will be added to the process of care for patients already scheduled for a diagnostic workup, we do not believe there is a risk for invasion of privacy. When contacting patients by telephone, we will not disclose the purpose of our call, except to the patient, and leave the message specifically for the subject who we need to contact. All email or certified mail communications will be addressed explicitly to the subject. We will obtain permission to contact the subject as part of the informed consent process.

14 Statistical Plan

14.1 Sample Size Determination

Based on data from Stony Brook and confidential data HeartFlow reported from providers who have been using CT-FFR in a similar manner as we propose for this study, we estimated that about 60% of stable chest pain patients who had CCTA were diagnosed with coronary stenosis of 30% to 90% and received CT-FFR. Of these patients, about 35% had an ICA test, and 14% of those had a negative ICA test result (i.e. the false-positive rate of CTTA+CT-FFR was 14%). A sample of 121 patients who received ICA will yield 80% statistical power of detecting a 60% reduction in the false-positive rate (from 14% to 6%), based on a two-sided one sample Chi-square test with 0.05 significance level. Assuming a similar prevalence of flow-limiting obstructive CAD and assuming that similar proportions of stable chest pain patients who had CCTA will receive CCT-FFR and then ICA, 576 stable chest pain patients who had CCTA need to be complete the clinical trial. In order to target 576 subjects completing the trial, we estimate that number of patients, it will be necessary to 594, because 18 patients who enrolled were screen failures.

14.2 Statistical Methods

Statistical Aims

1. To determine the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the CCTA test (with or without stress MPI, as specified in Figure 1) + CT-FFR evaluation to identify chest pain patients with flow-limiting obstructive CAD. The ICA test will be used as gold standard.

2. To determine inter-observer reliability of CCTA and CCTA+CT-FFR test readings between an experienced and a non-experienced reader, and compare the results between CCTA and CCTA+CT-FFR; to determine the intra-observer reliability of CCTA and CCTA-FFR reading, for both the experienced and non-experienced reader, and for each reader compare the results between CCTA and CCTA+CT-FFR.

3. To identify factors of return visit within 90 days in patients who had no ICA test or a negative ICA test result.

Outcome Variables

- *CCTA+CT-FFR test status (Positive/Negative). The test is deemed positive if ICA is required and negative if ICA is not required (see Figure 1).*
- *ICA (gold standard) test status (Positive / Negative). ICA is deemed positive if FFR<0.8 and vessel diameter >=2mm or if the patient requires revascularizations based on invasively estimated stenosis severity. It is deemed negative otherwise.*
- *Return visit within 90 days (Y/N). Return visit is defined as patients who return for unplanned cardiac care, including emergency room visits, emergency hospital admissions, urgent percutaneous coronary intervention, coronary artery bypass graft, or acute myocardial infarction. Descriptive statistics (n, mean, median, standard deviation, IQR, frequencies and percentages) will be used to describe the demographic and clinical characteristics of the whole sample.*

For Aim 1, sensitivity, specificity, PPV, and NPV will be computed using the ICA result as the 'true' flow-limiting obstructive CAD status and the CTTA+CT-FFR test result as the 'test' status. Exact binomial 95% confidence intervals will be computed.

For Aim 2, inter- and intra-observer reliability for the CTTA and CTTA+CT-FFR tests will be assessed using Cohen's Kappa coefficient. Dependent Kappa coefficients will be compared using a method developed by Donner et al .

For Aim 3, a survival analysis regression model will be carried out to determine which risk factors are associated with "time-to-return visit". Proposed factors will include age, sex, race, diabetes, hyperlipidemia, hypertension, active smoking and smoking history, family history of premature heart disease, obesity, and the number of cardiac risk factors present. In addition we will consider adding whether the admission was surgical or medical, and the MS or AP DRG case weight as a measure of severity.

Statistical Methods

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history of premature heart disease, obesity, and the number of cardiac risk factors present. In addition we will consider adding whether the admission was surgical or medical, and the MS or AP DRG case weight as a measure of severity.

14.3 Subject Population(s) for Analysis

This is not a randomized trial. Data for all subjects who enroll in the study will be subject to analysis, with appropriate adjustments for those who were unable to finish any part of the study.

15 Safety and Adverse Events

15.1 Definitions

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study, as a result of study activities. Intercurrent illnesses or injuries will be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious will be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period

The study period during which adverse events must be reported will be defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 90 days following the last administration of study treatment.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. Preexisting conditions will be recorded as an adverse event if the errors in diagnosis cause less than optimal treatment decisions.

General Physical Examination Findings

At screening, any clinically significant abnormality will be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that were not diagnosed through the study protocol will meet the definition of an adverse event and will also be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization will be documented and reported as a serious adverse event. Any condition responsible for surgery will be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery will be reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery will ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is the result of inaccurate diagnostic information provided in the study.

15.2 Recording of Adverse Events

At the follow-up contact with the subject, the study coordinator will seek information on adverse events by specific questioning and, as appropriate, by referral to a study coordinator for examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period will be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious

adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

15.3 Reporting of Serious Adverse Events

15.3.1 Study Sponsor Notification by Investigator

This is an investigator initiated trail funded by a charitable contribution from a grateful patient. There is no study sponsor outside of Northwell Health.

15.3.2 EC/IRB Notification by Investigator

Reports of all serious adverse events (including follow-up information) will be submitted to the EC/IRB according to their policies. Copies of each report and documentation of EC/IRB notification and receipt will be kept in the Clinical Investigator's binder.

15.4 Unblinding Procedures

This is not a blinded clinical trial. Blinding in this study will not affect patient outcome, and, therefore, no unblinding is necessary. Cardiologists will interpret CCTA scans without access to FFR results. This is standard of care, and the interpretation will be necessary to determine which cases should be sent for FFR. The FFR is a computerized procedure. At the time the procedure is run, the computer operator will not know the exact level of obstruction documented by the cardiologist. This information is irrelevant to the operations of the computerized procedure and will not change the outcome of the CT-FFR test or the follow up patient care.

15.5 Stopping Rules

This study is low risk to patients, because essentially, it requires the use of protocols that are currently in place and represent standard of care. There may be a few instances in which a Cardiac Catheterization might be recommended for a patient who would not have received one if not a study participant. If the patient's cardiologist documents concern regarding patient safety if a Cardiac Catheterization were to be performed, the procedure will be discontinued.

15.6 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring

plan (see section 17 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

15.7 Data and Safety Monitoring

Only one of the following three sections needs to be included in the protocol.

15.7.1 Data and Safety Monitoring Plan

Michael Kim, M.D. will conduct data safety monitoring for the study.

His role as Director of the Cardiac Catheterization program at lenox Hill Hospital makes him the most appropriate person to review the study safety, because he will have the most complete information on the cardiovascular condition of the patient, and the patients response to invasive ICA, the primary study activity that has potential to influence patient safety.

The expected types of events that will be monitored include major adverse cardiac events resulting from any Cardiac Catheterization, Percutaneous Coronary Intervention, or Coronary Artery Bypass Graft in a patient who, if not enrolled in the study, would not have received Cardiac Cath or invasive treatments. In addition, the monitor will review any medical complications for these subjects. The study coordinator will refer all patients who received Cardiac Cath, who would not have otherwise have received it if not part of the study. The monitor will review whether adverse events were the result of the study activity or related to procedures provided as part of standard of care, and whether safety policies and procedures were followed within one week of the all referrals. The monitor will present any recommendations for changes to the study resulting from the review to the study PI.

The monitor will conduct reviews as near as possible to the time the event was identified and always within a month of the identification of the event.

We do not expect to need to alter or interrupt the study design, because of the very low risk nature of the study. However, any unexpected safety events related to the study design will be carefully reviewed by the Safety Monitor and the study PI and reported to the IRB and Hospital quality assurance. If improvement in patient safety can be made by changing the design, immediate consideration will be given to the prospective change.

There are no issues with toxicity in this study.

If the study should be temporarily suspended, we will report this to the IRB, Clinical trials.gov, and to HeartFlow.

16 Data Handling and Record Keeping

16.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

16.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in the clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts, CCTA and FFR results, notes, memoranda, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

16.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, the study coordinator will indicate this by writing "N/D". If the item is not applicable to the individual case, the study coordinator will indicate this by writing write "N/A". All entries will be maintained on RedCap, this includes the retrospective study as well.

16.4 Records Retention

The investigator will be responsible to retain study essential documents for at least 2 years after the last publication of initial findings.

17 Study Monitoring, Auditing, and Inspecting

17.1 Study Monitoring Plan

This is a private study. No external monitor has been assigned.

Auditing and Inspecting:
The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

18 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment _2__ for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

19 Study Finances

19.1 Funding Source

This study will be financed through a charitable contribution supporting the research of Michael Poon, M.D. on the use of CT-FFR.

19.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the

conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All North Shore-LIJ Health System investigators will follow the University conflict of interest policy.

20 Publication Plan

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Neither the complete nor any part of the results of the study carried out under this protocol, will be published or passed on to any third party without the consent of the Principal Investigator.

References Cited

1. Koo, B.K., et al., Diagnosis of ischemia-causing coronary stenosis by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. Results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenosis Obtained via Noninvasive Fractional Flow Reserve) study. J Am Coll Cardiol, 2011. 58(19): p. 1989-97.
2. Min, J.K., et al., Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. JAMA, 2012. 308(12): p. 1237-45.
3. Norgaard, B.L., et al., Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). J Am Coll Cardiol, 2014. 63(12): p. 1145-55.
4. Ko, B.S., et al., Computed tomography stress myocardial perfusion imaging in patients considered for revascularization: a comparison with fractional flow reserve. Eur Heart J, 2012. 33(1): p. 67-77.
5. Niska, R., F. Bhuiya, and J. Xu, National Hospital Ambulatory Medical Care Survey: 2007 emergency department summary. Natl Health Stat Report, 2010(26): p. 1-31.
6. Poon, M., et al., Associations between routine coronary computed tomographic angiography and reduced unnecessary hospital admissions, length of stay, recidivism rates, and invasive coronary angiography in the emergency department triage of chest pain. J Am Coll Cardiol, 2013. 62(6): p. 543-52.
7. Budoff, M.J., et al., Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. J Am Coll Cardiol, 2008. 52(21): p. 1724-32.
8. Meijboom, W.B., et al., Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study. J Am Coll Cardiol, 2008. 52(25): p. 2135-44.
9. Miller, J.M., et al., Diagnostic performance of coronary angiography by 64-row CT. N Engl J Med, 2008. 359(22): p. 2324-36.

10. Taylor, A.J., et al., ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography. A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. J Am Coll Cardiol, 2010. 56(22): p. 1864-94.
11. NIH National heart, Lung and Blood Institute, What are the risks of cardiac catheterization. https://www.nhlbi.nih.gov/health/health-topics/topics/cath/risks, accessed on 11/8/2016.

21 Attachments

This section should contain all pertinent documents associated with the management of the study. The following list examples of potential attachments:

- *Attachment 1: Study Flow Chart*
- *Attachment 2: Sample Consent Form*
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