Duke Clinical Research Institute

PROTOCOL

Adenosine Contrast CorrELations in Evaluating RevAscularizaTION

The ACCELERATION Study

Date: March 23rd, 2022
Version: 5.0

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STATEMENT OF COMPLIANCE

This trial will be conducted in compliance with the protocol, International Conference on Harmonisation (ICH) guideline E6: Good Clinical Practice (GCP): Consolidated Guideline, and the applicable regulatory requirements from the United States Code of Federal Regulations (CFR), including 45 CFR 46 (human subjects protection, incorporating Subpart D Additional Protections for Children Involved as Subjects in Research), 21 CFR 312 (Investigational New Drug [IND]), 21 CFR 50 (Protection of Human Subjects, incorporating Subpart D Additional Safeguards for Children in Clinical Investigations), 21 CFR 11 (electronic records and signatures), 21 CFR 54 (financial disclosure), and 21 CFR 56 (institutional review board [IRB]).

All individuals responsible for the design and/or conduct of this study have completed human subjects' protection training and are qualified to be conducting this research.

SITE PRINCIPAL INVESTAGATOR STATEMENT

I have read the protocol, including all appendices and the investigator brochure or product label, and I agree that it contains all necessary details for my staff and me to conduct this study as described. I personally will oversee the conduct of this study as outlined herein and will make a reasonable effort to complete the study within the time designated. I agree to make all reasonable efforts to adhere to the attached protocol. I understand and am aware of my responsibilities as an investigator as described in the applicable GCP regulations.

I will provide all study personnel under my supervision with copies of the protocol and access to all information provided by the sponsor or its representative. I will discuss this material with them to ensure that they are fully informed about the efficacy and safety parameters and the conduct of the study in general. I am aware that, before beginning this study, the institutional review board responsible for such matters must approve this protocol in the clinical facility where it will be conducted.

I agree to provide all subjects with informed consent, as required by government regulations and the ICH guidelines. I further agree to report to the sponsor or its representative any adverse events in accordance with the terms of this protocol and the U.S. Code of Federal Regulations, Title 21, part 312.

_____

Principal Investigator name (print)

_____ _____

Signature Date

STUDY PRINCIPAL INVESTIGATOR SIGNATURE

Study Title: **Adenosine Contrast CorrELations in Evaluating RevAscularizaTION (The ACCELERATION Study)**

Version: 5.0

Date of Issue: March 23rd, 2022

I have read and approve this protocol and agree on its content.

Rajesh V. Swaminathan, MD, FACC, FSCAI Date

Sponsor:
Duke Clinical Research Institute

PROTOCOL VERSION AND AMENDMENT TRACKING

Version Number/Amendment	Approval Date
Protocol: Version 1.0	February 6, 2018
Protocol: Version 2.0	June 5, 2018
Protocol: Version 3.0	July 25, 2018
Protocol: Version 4.0	August 18, 2020
Protocol: Version 5.0	

PROTOCOL SYNOPSIS

Protocol Title	**Adenosine Contrast CorrELations in Evaluating RevAscularizaTION** (The ACCELERATION Study)
Main Criteria for Inclusion	Patients > 18 years old. All subjects who are clinically stable and undergoing non-emergent cardiac catheterization for appropriate indications. Diagnostic angiogram reveals at least one moderate (40-70%) stenosis by angiographic assessment.
Study Objectives	To evaluate the NAVVUS fractional flow reserve (FFR) device, as follows: • Determine the accuracy and correlation of contrast FFR (cFFR) using the ACIST CVi automated contrast injector to the current gold-standard adenosine FFR (aFFR) • Evaluate the association of post-percutaneous coronary intervention (PCI) FFR to long-term clinical outcomes (death, myocardial infarction [MI], target vessel revascularization [TVR]) with up to 1-year follow-up
Study Design	The ACCELERATION study is an investigator-initiated, multicenter, prospective, single-arm trial evaluating the method of delivery of contrast for FFR with use of the NAVVUS RXi microcatheter FFR system and the CVi automated contrast injector in patients with intermediate lesion coronary artery disease. Up to 200 subjects undergoing non-emergent PCI from approximately 5 centers will be enrolled. After NAVVUS FFR-guided PCI (with contrast and aFFR measurements), subjects will be contacted for follow-up at 30 days and 1 year by the enrolling site. Primary endpoint results will be reported after all subjects have completed the 30-day clinical follow-up.
Treatment Regimen	Patients with intermediate lesions meeting the clinical and angiographic inclusion/exclusion criteria will be enrolled. NAVVUS FFR will then be performed with contrast and aFFR. Contrast for cFFR will be injected via the ACIST CVi contrast injector with standardized settings, and adenosine for aFFR will be delivered systemically via intravenous infusion. If PCI is performed, a final post-PCI contrast and aFFR will be obtained.
Duration of Subject Study Participation	Sites will see patients for their standard-of-care follow-up visit approximately 30 days after their procedure. Patients will be contacted at 1 year to collect data for the secondary endpoint analysis.
Number of Patients	Up to 200 subjects
Number of Sites	Approximately 5 centers are planned in the US.

Objective/Endpoints for Evaluating the ACIST NAVVUS FFR microcatheter and ACIST contrast power injector.	*Primary Objective/Endpoint:* (1) Perform a methods comparison between cFFR and the reference standard aFFR, where cFFR is performed using an automated injector with a standardized volume and rate of delivery of contrast with known osmolality. *Secondary Objective/Endpoint:* (1) Evaluate the association between final post-PCI FFR and long-term clinical outcomes. The long-term clinical outcomes will include TVR and composite major adverse cardiac events (death, MI, and TVR) at index hospitalization (prior to discharge), 30 days and 1 year.
Statistical Analysis **Sample Size/ Power Considerations**	Up to 200 patients with intermediate lesions (see statistical analysis plan in protocol for details)

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ABBREVIATIONS

ACT	activated clotting time
ADE	adverse device effect
AE	adverse event
aFFR	adenosine fractional flow reserves
AUC	area under the curve
CAD	coronary artery disease
cFFR	contrast fractional flow reserve
DCRI	Duke Clinical Research Institute
dPR	diastolic pressure ratio
eCRF	electronic case report form
EDC	electronic data capture
FDA	Food and Drug Administration (US)
FFR	fractional flow reserve
HR	hazard ratio
ICF	informed consent form
iFR	instantaneous wave free ratio
IFU	instructions for use
IRB	institutional review board
ITT	intent to treat
IV	Intravenous
LAR	legally authorized representative
MACE	major adverse cardiac events
MI	myocardial infarction
NCDR	National Cardiovascular Data Registry
OMT	optimal medical therapy
Pd/Pa	intracoronary distal pressure/aortic pressure
PCI	percutaneous coronary intervention

ROC	receiver operating characteristics
RR	relative risk
SAE	serious adverse event
SD	standard deviation
TVR	target vessel revascularization
UADE	unanticipated adverse device effect

1. INTRODUCTION AND BACKGROUND

Fractional flow reserve (FFR) has emerged as an effective invasive means of assessing the physiologic significance of an epicardial coronary stenosis. The test complements the visual assessment of a stenotic lesion based solely on anatomic features during angiography. The addition of FFR to the diagnostic armamentarium of interventional cardiologists has significantly impacted best practice recommendations for how and when to treat coronary lesions with percutaneous coronary intervention (PCI), selecting only ischemic lesions supplying viable myocardium. This disruptive technology received widespread utilization after multiple, large randomized controlled trials demonstrated superior patient outcomes with FFR-guided PCI compared with standard angiography-guided PCI.

The initial FAME trial was a randomized, prospective trial of 1,005 patients with stable, multivessel coronary artery disease (CAD) of >50% angiographic stenosis who were assigned to an angiography vs FFR-guided strategy in selecting lesions amenable to PCI. The primary endpoint of major adverse cardiac events (MACE) (including death, myocardial infarction (MI), repeat revascularization) occurred in 91 patients (18.3%) in the angiography group and in 67 patients (13.2%) in the FFR-guided group (relative risk [RR] 0.72, 95% CI 0.54-0.96, p=0.02). The utilization of FFR significantly reduced the total number of stents placed (2.7 vs 1.9), total length of stents (51.9 mm vs 37.9 mm), cost of materials ($6,007 vs $5,332), and hospital length of stay (3.7 days vs 3.4 days) (1).

FAME 2 built on the evidence from FAME and included an optimal medical therapy (OMT) arm. In this trial, 888 multivessel CAD patients with at least 1 FFR positive lesion were randomized to FFR-guided PCI with drug-eluting stents plus OMT or OMT alone. The primary endpoint was a composite of death, MI, hospitalization, or urgent revascularization. The study was prematurely halted after interim analysis revealed a statistically significant decrease in unplanned hospitalization leading to urgent revascularization in the FFR-PCI arm (1.6% vs 11.1%, hazard ratio [HR] 0.13, 95% CI 0.06-0.30, p<0.001). This drove a significant reduction in the primary endpoint for FFR-guided PCI plus OMT as compared to OMT alone (4.3% vs 12.7%, HR 0.32, 95% CI 0.19–0.53, p<.001] (2).

Based on FAME and other supporting data, FFR was incorporated into the 2011 American College of Cardiology/American Heart Association/Society for Cardiac Angiography and Interventions guidelines for PCI. The adjunctive device received a class IIa indication for assessment of angiographic intermediate coronary lesions to guide revascularization decisions in patients with stable ischemic heart disease (3). Fractional flow reserve is also an integral component of the multi-society–supported Appropriate Use Criteria for coronary revascularization (4-6).

As FFR utilization increases in clinical practice, various methods for inducing hyperemia have emerged. These methods are primarily designed to circumvent inherent risks associated with the use of adenosine, as well as decrease time and improve workflow in the catheterization laboratory, without compromising accuracy. Some challenges with traditional systemic intravenous (IV) adenosine administration for FFR measurement are: 1) heart block; 2) other undesirable patient side effects, including chest

pain, bronchospasm, and shortness of breath; 3) relative contraindications in patients with obstructive lung disease or recent caffeine use; 4) added time to prepare and infuse adenosine; and 5) associated costs. Intracoronary adenosine push is still associated with similar risks and limits the operator from assessing diffuse or tandem lesions given the shorter time frame of peak hyperemia. Alternative strategies include a measurement of resting physiologic gradients (distal pressure/aortic pressure [Pd/Pa], diastolic pressure ratio [dPR], and instantaneous wave free ratio (iFR). iFR assesses the gradient during a short period in diastole when resistance across the coronary vasculature is stable (the "wave free" period). During this time, coronary flow and pressure are proportional and the trans-lesion gradient approximates flow and lesion severity. iFR correlation to traditional hyperemia-induced FFR is moderate, yet strengthened by data that support conversion to FFR only in a pre-defined "yellow zone" (i.e., 0.86 to 0.93). Lesions with values in the "green zone" and "red zone" can be safely deferred or intervened, respectively, without the need for adenosine fractional flow reserves (aFFR). iFR with set protocols based on these zones received US Food and Drug Administration (FDA) clearance in 2014. Measurement of dPR is not proprietary and can be acquired during real-time resting gradient assessment or via post-procedure analysis of the resting gradient waveforms. dPR has been shown to be numerically equivalent to iFR regardless of the time period acquired within the diastolic period (7).

An emerging adenosine-free alternative is contrast-induced FFR (cFFR). Conventional non-ionic radiographic contrast medium has been shown to induce submaximal reactive hyperemia and Pd/Pa ratio measured post-contrast injection has been reported to approximate traditional FFR values (8). A prospective study with 80 patients and 104 intermediate lesions found a strong correlation between cFFR and aFFR ($r=0.94$, $p<0.001$). Receiver operating characteristics (ROC) curve analysis showed an excellent accuracy of a cFFR cut-off of ≤0.83 in predicting an FFR value ≤0.80 (area under the curve [AUC] 0.97, 95% CI 0.91-0.99, specificity 96.1, sensitivity 85.7). No cFFR value ≥0.88 corresponded to an FFR value ≤0.80. These data suggest that cFFR ≤0.83 is significant, ≥0.88 is non-significant, and borderline values in between should be further assessed with aFFR for inducement of maximal hyperemia (8).

A recent international study of 763 patients sought to compare the diagnostic performance of aFFR with the spectrum of alternative FFR modalities, including Pd/Pa, iFR, and cFFR (9). Pd/Pa and iFR had equivalent performances against FFR ≤0.80 with ~80% accuracy. cFFR improved this accuracy to 86%. A significant limitation of this study was the lack of a standardized protocol for the type, volume, and rate of intracoronary contrast injection. These considerations were left to the operator's discretion, including the use of either manual (manifold) injection or an automated injector system, and the choice of contrast agents with different osmolalities. Standardizing these contrast and injection parameters could further improve the diagnostic accuracy of cFFR (9). This hypothesis forms the basis for the current proposed study.

While pre-PCI FFR is now an established modality, there remains limited data on whether immediate, post-PCI FFR might have an important long-term clinical impact. A recent systematic review and meta-analysis included 59 studies evaluating the relationship between post-PCI FFR and clinical outcomes up to 30 months. In general, higher post-PCI FFR values were associated with reduced rates of repeat interventions

and MACE. A post-PCI FFR ≥0.90 was associated with a 57% RR reduction of repeat PCI and a 30% RR reduction of MACE (10). In a multicenter registry of 750 patients, post-PCI FFR was the most significant independent predictor of clinical events (11). Death, MI, and target vessel revascularization (TVR) at 6 months were stratified by categories of immediate post-PCI FFR values and found to be 4.9% (post-FFR >0.95), 6.2% (post-FFR 0.90-0.95), and 20.3% (post-FFR <0.90). In the minority of patients with a post-FFR <0.80, the event rate was exceedingly high at 29.5%. The proposed study will add to the growing body of literature supporting use of post-PCI in routine clinical practice, particularly as the field moves towards adenosine-free FFR acquisition techniques.

2. OBJECTIVES

The ACCELERATION study will support a safer approach to FFR for patients by potentially reducing toxic drug exposure (adenosine) if cFFR with standardized injection settings is observed to have a strong correlation to traditional FFR. In addition, ACCELERATION will utilize the novel NAVVUS RXi microcatheter FFR technology in intermediate lesions, which will promote optimal vessel access with a workhorse wire of the operator's choosing during pre- and post-PCI FFR measurements. The 2 main objectives of the study are:

1. Perform a methods comparison between cFFR and the reference standard aFFR, where cFFR is performed using an automated injector with a standardized volume and rate of delivery of contrast with known osmolality.
2. Evaluate the association between final post-PCI FFR and long-term clinical outcomes. The long-term clinical outcomes will include TVR and composite MACE (death, MI, and TVR) at 30 days and 1 year.

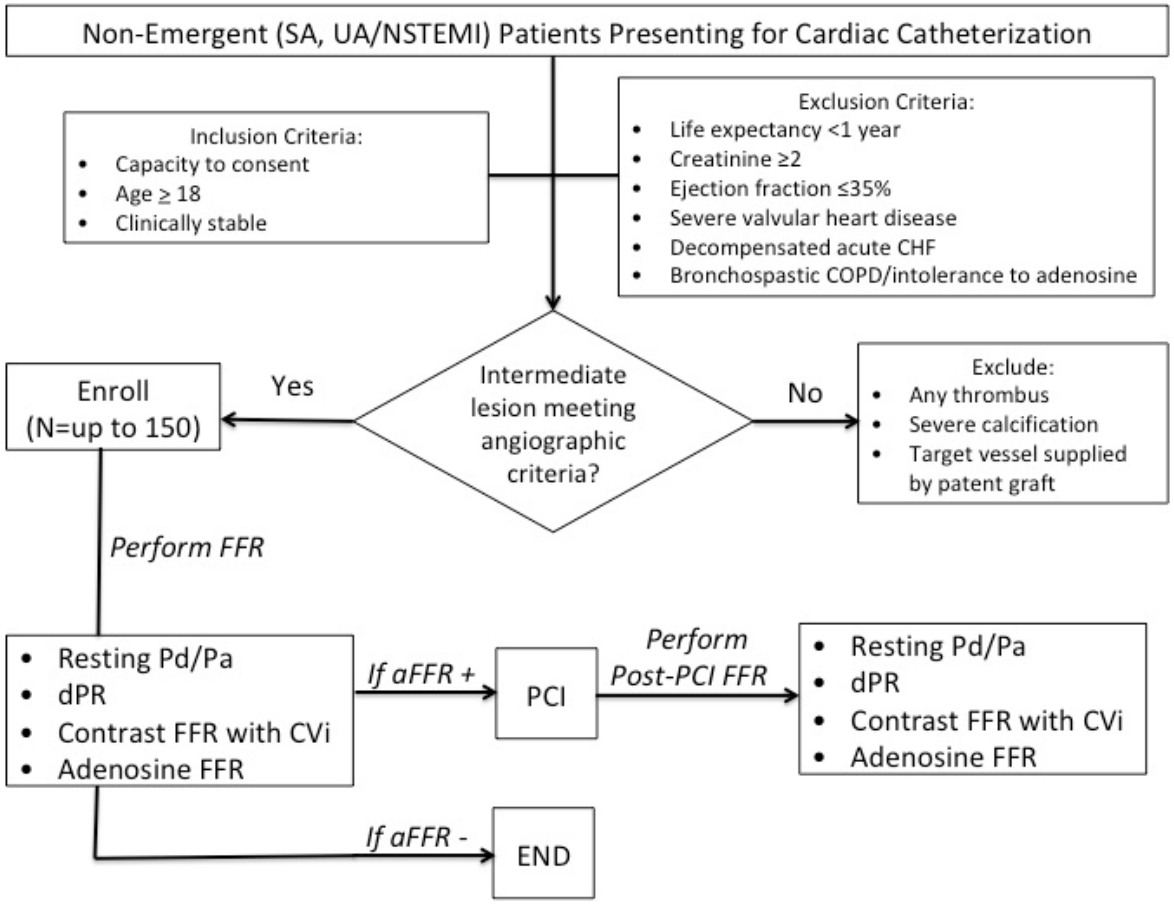
3. STUDY DESIGN

3.1 Overview of Study

The ACCELERATION study is an investigator-initiated, multicenter, prospective, single-arm trial evaluating optimal acquisition techniques of FFR using the NAVVUS RXi microcatheter FFR system in patients with intermediate lesion CAD. The study will determine the accuracy and correlation of cFFR (using the ACIST CVi automated contrast injector) to the current gold-standard aFFR, and evaluate the association of post-PCI FFR to long-term clinical outcomes including TVR and MACE with 1-year follow-up.

Figure 1 depicts the study flow diagram with clinical and angiographic screening criteria. The enrollment cap is controlled at 200 subjects between 5 centers.

Figure 1. Study Design and Treatment Schema



aFFR, adenosine fractional flow reserve; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVi, ACIST automated contrast injector; dPR, diastolic pressure ratio; FFR, fractional flow reserve; NSTEMI, non–ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; SA, stable angina; UA, unstable angina

3.2 Procedural Steps

3.2.1 Angiographic Confirmation Eligibility

Patients will be enrolled in the study following angiographic confirmation of a target vessel with an intermediate coronary lesion(s) that meet the inclusion and exclusion criteria. Serial stenosis or diffuse disease can be included if the operator would normally assess these lesions with FFR and plan for PCI if positive. 1 vessel per patient can be enrolled in the study.

3.2.2 Procedural Planning

Operators should use FFR per their usual practice and follow standard of care per clinical guidelines and appropriate use criteria. The protocol calls for a recording of resting Pd/Pa, dPR (in real-time or post-procedure waveform analysis), contrast FFR, and adenosine FFR every time a physiologic assessment is made. The protocol also requires the same measurements immediately post-PCI. Below are specific procedural details to ensure uniformity across sites. Any deviations should be recorded.

1. Access site, guide catheter (minimum 6F), 0.014" coronary workhorse wire, and antiplatelet/anticoagulant strategy will be at the discretion of the operator.
2. Systemic anticoagulation confirmation will be achieved by activated clotting time (ACT) measurement prior to coronary wire exiting the guide catheter.
3. After wiring the lesion, administer 1-200 micrograms of intracoronary nitroglycerin and chase with saline to clear the guide catheter. Await return of baseline blood pressure prior to hemodynamic measurement
4. Resting Pd/Pa, dPR, contrast FFR, and adenosine FFR will be obtained for each physiologic assessment based on the following procedural steps:
    a. Equalization
        i. NAVVUS RXi FFR microcatheter will be advanced until guide exit and equalized.
        ii. Equalization step will be performed each time the NAVVUS FFR catheter is used during the protocol and should equal 1.0.
    b. Resting Pd/Pa and dPR
        i. The Rxi FFR microcatheter will be advanced 1-2cm just distal to the lesion of interest. Position microcatheter based on reference still images from diagnostic angiogram. Ensure the guide is cleared with saline if contrast is needed to position the catheter.
        ii. An initial period of 20 seconds to provide stable assessment of resting physiology will be performed
        iii. Resting gradient will be documented. dPR can be documented at same time (if available) or can be documented post-procedure after waveform analysis.

c. Contrast Injection FFR (cFFR)

i. Injector-based intracoronary bolus of contrast with the ACIST automated injector will deliver contrast medium: Iopamidol (ISOVUE®-370), a low-osmolality contrast medium at 796 mOsmol/kg water

ii. Settings:

- Rate of 4 mL/sec, volume of 10 cc (left coronary system)
- Rate of 3 mL/sec, volume of 6 cc (right coronary system).

iii. Any deviation from these settings due to operator judgment will be documented.

iv. Inject contrast to fill guide catheter and wait for return of baseline hemodynamics.

v. Press record on ACIST FFR console and then inject contrast at standard settings above for cFFR. Within the first minute of contrast injection, the nadir cFFR value will be logged.

vi. The recorded tracings will be captured and saved for an independent FFR core lab review.

d. Adenosine FFR (aFFR)

i. Return of baseline hemodynamics

ii. Intravenous adenosine administered at a rate of 140 μg/kg of body weight per minute x 2 minutes will then be performed and the aFFR value logged.

iii. If the aFFR is >0.80, then no PCI is performed and this final FFR value will be logged for correlation to long-term outcomes.

iv. If the aFFR is ≤0.80, then PCI according to standard techniques will be performed. Post-PCI, the NAVVUS FFR microcatheter will be used to measure resting Pd/Pa, dPR, contrast FFR, and adenosine FFR in the same manner as above with values recorded.

v. The recorded tracings will be captured and saved for an independent FFR core lab review.

5. Drift

a. Drift check will be performed at least once during each procedure and ideally after each use/measurement of the NAVVUS FFR microcatheter

b. Clinically significant drift will be defined as > ±0.03 (12).

c. The presence of any significant drift (yes/no) will be recorded. If there is clinically significant drift, the FFR measurements will be repeated after repositioning of the guide catheter and re-equalization.

3.2.3 Documentation

Data including baseline clinical and procedural characteristics with all FFR values (pre- and post-PCI resting, dPR, contrast, and adenosine) will be entered into the electronic case report form (eCRF) and used to analyze the primary and secondary study endpoints. These data will be stored in the IBM Clinical Data platform mirroring the NCDR dataset.

The post-PCI (final) aFFR will be used for correlation to 1-year clinical outcomes of death, MI, and TVR. These clinical endpoints will be recorded during the index hospitalization (prior to discharge), 30-day visit (at the routine follow-up appointment or telephone call if this appointment is missed), and at 1 year by telephone. See post-procedure follow-up section for details on data acquisition and definitions.

3.3 Endpoints

3.3.1 Primary Endpoint

The primary endpoint of the study is the accuracy and correlation of cFFR in comparison to aFFR, where cFFR is performed using the ACIST CVi automated contrast injector with a standardized volume and rate of delivery of contrast with known osmolality.

3.3.2 Secondary Endpoints

The secondary endpoint is the association between the final post-PCI aFFR and long-term clinical outcomes. The long-term clinical outcomes will include TVR and composite MACE (death, MI, and TVR) during the index hospitalization, 30 days, and 1 year.

4. SELECTION AND WITHDRAW OF PATIENTS

Up to 200 patients ≥ 18 years of age who are eligible for non-emergent PCI will be enrolled.

4.1 Clinical Inclusion Criteria

To be eligible for enrollment, subjects must meet all the following criteria:

1. Have the capacity to understand and sign an informed consent or have a legally authorized representative (LAR) that can understand and sign an informed consent prior to initial arteriotomy access
2. Age ≥ 18 years of age at the time of signing the informed consent
3. Clinically stable and undergoing non-emergent cardiac catheterization for appropriate indications
4. Willing to be contacted by telephone at 30 days (if no standard of care visit) and at 1 year with chart review for events.

4.2 Clinical Exclusion Criteria

If a subject meets any of the following criteria, he or she will not be consented:

1. Any condition associated with a life expectancy of less than 1 year
2. Participation in another clinical study using an investigational agent or device within the past 3 months
3. Ejection fraction ≤ 35%
4. Creatinine ≥ 2
5. Severe valvular heart disease
6. Decompensated acute diastolic or systolic heart failure
7. Bronchospastic chronic obstructive pulmonary disease or other intolerance to adenosine

4.3 Angiographic Inclusion/Exclusion Criteria

After the diagnostic angiography, patients having an intermediate lesion(s) meeting the following angiographic criteria will be enrolled:

Inclusion:

Target vessel with an intermediate lesion of 40-70% stenosis by angiographic assessment (a visual estimation by the operator). Serial lesions, diffuse disease, or ostial lesions (“all-comer” lesions) are acceptable if the operator would normally perform FFR and proceed with PCI (or other revascularization) if positive.

Exclusion:

1. ST-segment elevation myocardial infarction culprit lesion or lesions with any thrombus burden

2. Lesions with severe calcification
3. Lesions in a target vessel supplied by a patent graft

4.4 Withdrawal of Patients

Patients may voluntarily withdraw for any reason without penalty or loss of benefits to which they are entitled.

If a patient withdraws from the study at any time either at his or her request or at the investigator's discretion, the reasons for withdrawal must be recorded on the relevant page of the patient's eCRF. Patients who withdraw from the study prematurely should undergo all end-of-study assessments, if possible. Study site personnel should make every effort to prevent losing patients to follow-up.

5. KNOWN AND POTENTIAL RISKS

The risks of FFR assessment in stable CAD are well described in large-scale randomized controlled trials (1, 2). These risks are generally considered to be low and acceptable, even in the setting of multivessel disease (1, 2), acute coronary syndromes (13, 14), and serial lesions (15). Based on low risk, high value in characterizing lesion significance, and improving clinical outcomes, FFR has been incorporated into multi-society supported Guidelines and Appropriate Use Criteria for coronary revascularization (3-6).

The goal of this study is to compare two different methods of acquiring FFR – contrast FFR to the gold-standard adenosine FFR. Contrast FFR is potentially a safer approach to FFR. Contrast FFR has been previously studied and compared with aFFR; however, there has been variability in the type, volume, and rate of contrast injected to induce vessel hyperemia with a manual (manifold) injection setup. Standardizing the injection with the ACIST CVi automated contrast injector may mitigate the variability for induction of hyperemia and provide a more robust comparator to systemic adenosine. The risk of contrast-induced nephropathy in contrast FFR is expected to be neutral compared with aFFR, since approximately the same amount of contrast would be injected during cFFR for hyperemia induction as would be delivered during the wiring and verification of wire position steps for traditional pressure wire FFR with adenosine. To mitigate risk, only patients without renal insufficiency will be enrolled. Furthermore, use of the ACIST automated injector is known to be associated with a significant reduction in the total volume of contrast media used and in the net amount of contrast delivered to patients when compared with traditional methods of manual (manifold) contrast injection (16). This pattern held true across varying types of procedures—97.4%, 53.8%, and 57.3% more contrast media was used during manual injection compared with the ACIST automated contrast injector for diagnostic, diagnostic with PCI, and PCI alone procedures, respectively (16).

This protocol will use the FDA-cleared NAVVUS RXi microcatheter for FFR assessment, which comes with several advantages that would render the assessment and management of all-comer intermediate lesions safer and with greater success, even in tortuous vessels. For example, the operator can choose any standard workhorse coronary guidewire for initial wiring. In addition, the unique design of the fiber-optic pressure sensor near the tip of a monorail microcatheter allows for ease of traversing forward and backwards over the standard 0.014” coronary guidewire without losing wire position. In the CONTRACT study evaluating over 200 patients randomized to either NAVVUS (n=87) or pressure wire (n=141), the NAVVUS catheter had a high lesion crossing success rate (96.9%) and was safe (17). There were no differences between the 2 groups with respect to contrast or radiation dose.

In the current study, there is the possibility of requiring multiple FFR recordings per vessel. Each run will include a repeat dose of systemic adenosine (risk of known patient side effects from adenosine), contrast (risk of contrast-induced nephropathy), time on anticoagulation (risk of bleeding), and radiation exposure (risk of skin injury). We will mitigate these risks by including patients with no contraindications to adenosine, normal baseline renal function, careful monitoring of ACT while on procedural anticoagulation, and safe radiation practices, such as using radiation filters and changing camera

angulation. We do not anticipate any additional safety concerns, as multiple FFR acquisitions per patient has already been shown to be safe in the setting of multivessel disease. In fact, in the initial FAME trial of multivessel disease, the number of indicated lesions undergoing FFR assessment with systemic IV adenosine was 2.8, yet this arm was found to have improved clinical outcomes compared with the angiography-guided PCI arm (1). Multiple studies have also demonstrated the value of measuring post-PCI FFR in clinical practice, as there is strong correlation to long-term outcomes (10, 11).

Our study sites will only include centers that currently use the ACIST contrast injector and NAVVUS FFR microcatheter in routine clinical practice. Familiarity with these devices will assist in mitigating risk. Furthermore, most operators in our study perform diagnostic and coronary interventions via radial access, a method known to reduce bleeding risk, which will mitigate the risks of procedural anticoagulation.

As with any clinical investigation, study records that identify subjects will be kept confidential as required by law. Information systems used to maintain study records will comply with federal privacy regulations and safeguards for privacy, security, and authorized access. Informed consent will be obtained. Subjects will be assigned a unique code number to identify their records for other study-related activities.

As part of the study, sites will report the results of study-related tests and images to the DCRI. These would include cardiac catheterization reports and FFR tracings for review by an independent FFR core lab. Risks will be further minimized by appropriate review by the individual site IRBs.

6. STUDY PROCEDURES

Medical questions regarding subject eligibility, procedures, or patient care should be directed to the study principal investigator, who can be reached as follows:

Dr. Rajesh V. Swaminathan at 919-684-1284 during US Eastern Time business hours, or 919-684-8111 after US Eastern Time business hours.

6.1 Screening Procedures

Potentially eligible subjects will be screened upon confirmation of non-emergent PCI. Study personnel will assess each subject against study inclusion and exclusion criteria, and the investigator will determine the subject's eligibility for participation.

6.2 Informed Consent

Each site will submit the study protocol, informed consent form (ICF), and other study documents to their ethics committee IRB for approval. A copy of the signed and dated IRB approval for each enrolling center will be stored at the Data Coordinating Center (DCRI). Any amendments to the protocol, other than minor administrative changes, must be approved by the site's IRB before the changes are implemented at the site.

The informed consent process will be documented in the subject's medical record or comparable source document.

Consent will be obtained from the subject or their LAR prior to arterial access and, if the subject is consenting, prior to the administration of any medications that might affect patient cognition.

6.3 Enrollment

Once a subject has met all clinical inclusion/exclusion criteria and provided informed consent, the subject will be eligible for study enrollment. Study staff is encouraged to appropriately identify candidates consistent with study objectives.

After the diagnostic angiogram, subjects who meet angiographic criteria of any intermediate lesion(s) as defined by the protocol will be enrolled.

6.4 Screen Failures

All subjects who are consented but not enrolled due to angiographic inclusion and exclusion criteria will be logged in the eCRF as a screen failure.

6.5 Post-procedure Follow-up

Subjects will be seen for their standard post-procedure visit (approximately 30 days post-procedure). Additional follow-up will be completed at 1 year via telephone call. Subjects will be asked to report indications for any hospitalizations, cardiac catheterization procedures, and/or coronary interventions since the index enrollment procedure. Subjects will be asked specifically about clinical events including MI and revascularization with further stents. Source documents will be collected and reviewed to verify clinical endpoints.

6.6 Schedule of Events

The schedule of study assessments and procedures is provided in Table 1:

Table 1 Schedule of Assessments

	Screening and Pre-enrollment	Enrollment /Procedure	Post-procedure	30 (± 7) Days	1 Year (± 30 Days)
Inclusion/exclusion criteria - enrollment	X				
Informed consent and patient contact form details	X				
Medical history	X			X	X
Physical assessment, vital signs (standard of care)	X[a,]			X	
Concomitant medications	X[a]			X	X
Diagnostic angiogram	X				
Coagulation labs		X[b]			
Perform resting, dPR, contrast, and adenosine FFR		X			
Perform post-PCI FFR if applicable		X			
Collection of specified CV endpoints (death, MI, TVR)			X[c]	X[c]	X[c]

FFR, fractional flow reserves; dPR, diastolic Pressure Ratio; PCI, percutaneous coronary intervention; MI, myocardial infarction; TVR, target vessel revascularization

[a] Within 7 days or immediately before enrollment .

[b] confirm anticoagulation prior to coronary wire exiting the guide catheter

[c] All serious adverse events related to the NAVVUS Rxi FFR microcatheter system. Specified cardiovascular endpoint events data collection will be reported on the eCRF endpoint pages only

7. DATA CAPUTURE

An electronic data capture (EDC) system will be used for this study (IBM Clinical Data/eCOS). All users will be trained on the technical features of the EDC as well as the content of the eCRF by qualified personnel prior to gaining access to the EDC. A user ID/password will be granted after training. This ID is not to be shared amongst the study staff. All users must have a unique account to enter or review data. The eCRF should be filled out by the site 3 days after each visit. It is not expected that the eCRF will serve as source for any data collected in this study. If there is a reason for a site to do so, it must be approved by and documented in the site files.

Prior to the database being locked, the investigator or designee will review, approve, and sign/date each completed eCRF. This signature serves as attestation of the investigator's responsibility for ensuring that all data entered into the eCRF are complete, accurate, and authentic.

8. SUBJECT SAFETY AND ADVERSE EVENTS

Subject safety from pre-procedure evaluation through discharge is the responsibility of the treating physician. The procedural aspects should follow published guidelines for appropriate use criteria. Post-discharge follow-up visits are part of routine standard of care.

All devices used in this study are FDA-cleared and will be used according to current instructions for use (IFU). A device has failed or malfunctioned if it is used in accordance with the IFU but does not perform according to the IFU. Because all devices used in this study are marketed and being used from hospital supply, any device failures or malfunctions will be reported to the device manufacturer per local policy.

In addition, the inability to position the NAVVUS Rxi microcatheter at the desired location (~1-2 cm beyond the target lesion) will be considered an event of interest. This device failure rate will be recorded in the eCRF but will not be mandated for reporting to the device manufacturer, as it is not considered a serious adverse event.

8.1 Device Failures, Device Malfunctions, and User Error

In the case of a device failure or malfunction related to the investigation that does not constitute a UADE, the manufacturer should be notified and the device returned to the manufacturing company, if possible. Since these are approved devices, device failures, malfunctions, and user errors will be reported to the appropriate company and FDA per local site policy.

Contact ACIST Medical Customer Service to arrange for a return of the involved hardware and to report the device failure or malfunction.

ACIST Customer Support

Phone: 888-670-7701

FAX: 952-256-4524

Email: customer.support@acistmedical.com

9. STATISTICAL ANALYSIS AND DETERMINATION OF SAMPLE SIZE

9.1 Intent-to-Treat Population

The intent-to-treat (ITT) population is consented patients that meet the clinical inclusion/exclusion criteria will be screened in the catheterization laboratory to determine whether they meet the angiographic inclusion/exclusion criteria. Those that meet the angiographic inclusion/exclusion criteria will be officially enrolled in the study and considered part of the intent-to-treat population.

9.2 Per-Protocol Evaluable Population

The per-protocol population is patients in the ITT population that have successfully completed both FFR methods on at least 1 target lesion.

9.3 Primary Endpoint Analysis

9.3.1 Quantitative Method Comparison Between Contrast Fractional Flow Reserves and Adenosine Fractional Flow Reserves

Contrast FFR and aFFR will be quantitatively compared using the procedure described in *CLSI EP09-A3 Measurement Procedure Comparison And Bias Estimate Using Patient Samples* Approved Guideline (18). A summary of this comparison is described below.

The measurements from the 2 methods will be plotted against each other. The aFFR will be plotted on the x-axis, and the cFFR will be plotted on the y-axis. The plot will be examined for highly influential points and heterogeneity of variance along the range of measurement values. In addition, several types of difference plots similar to the Bland-Altman plot will be used to examine whether:

- the size of the variance changes with changing measurement value
- the bias changes with changing measurement value
- the coefficient of variation changes with changing measurement value

Based on the above information, the appropriate model will be applied to describe the relationship of aFFR measured values to their corresponding cFFR values. Assuming:

- sample size of 208 pairs (see the next section) of FFR measurements
- linear model will be applied in quantitative method comparison
- width of the 2-sided 95% CI for the slope is expected to be $\pm$ 0.06
- width of the 2-sided 95% CI for the bias is expected to be within $\pm$ 0.06

9.3.2 Qualitative Method Comparison Between Contrast Fractional Flow Reserves and Adenosine Fractional Flow Reserves

The qualitative method comparison consists assessing the agreement as to which lesion is flow limiting. If a lesion has an adenosine FFR measurement $\leq$ the cutoff value of 0.8, then the lesion is considered flow limiting. Using the model developed above, the contrast FFR measurement that corresponds to adenosine FFR measurement value of 0.8 will be used as the cutoff value for determining whether a lesion is flow limiting for contrast FFR. The expected cutoff value for the contrast FFR is 0.83.

The 2 methods will be compared qualitatively using the AUC under the ROC curve. The analysis will incorporate the following:

1. The contrast FFR will be the new diagnostic compared to the adenosine FFR as the reference standard.

2. The hypotheses will be designed to demonstrate that that AUC for these two methods is greater than 0.8.

The null and alternative hypotheses are as follows:

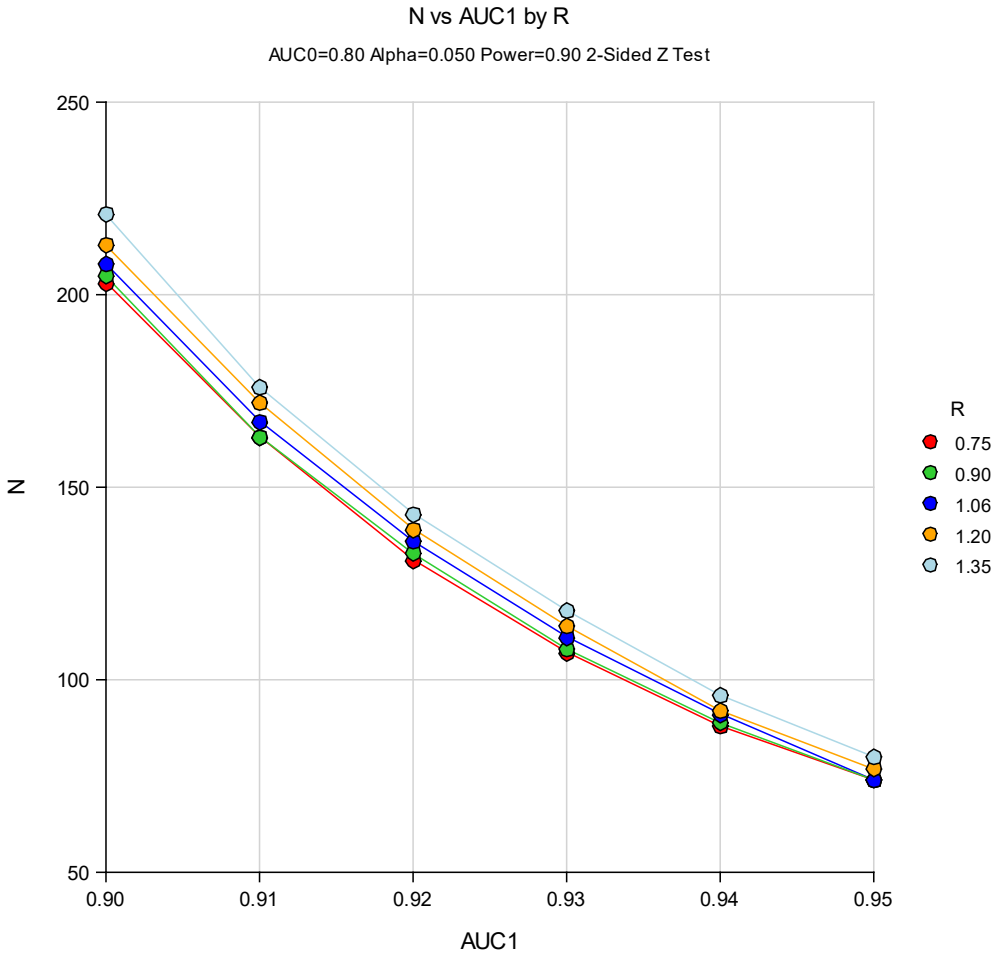
H_0: ROC AUC $\leq$ 0.8

H_A: ROC AUC > 0.8

Two hundred and eight pairs of measurements are needed assuming an AUC of 0.9, the ratio of negatives to positives is 1.06, the ratio of the standard deviation of the negatives to the SD of the positives is 1, a 2-sided alpha of 0.05 and a power of 0.9. Figure 2 shows how the sample size changes with varying assumptions of AUC and ratio of negatives to positives.

Figure 2: Sample Size by AUC by various ratio of negative to positive

Contrast FFR compared to Adenosine FFR



The number of pairs of FFR measurements will be tracked and enrollment will be stopped once the requisite number of pairs of FFR measurements have been reached.

9.4 Secondary Endpoint Analysis

9.4.1 Assessment of the Relationship Between Post-Percutaneous Coronary Intervention Fractional Flow Reserves and Long-Term Clinical Outcomes

A logistic model will be developed that assesses whether there is a relationship between final PCI FFR (resting, dPR, cFFR, aFFR) and long-term outcomes (death, MI, TVR). The model will include the known covariates for predicting revascularization outcomes: stent length, vessel diameter, diabetes, history of cardiovascular disease, and multi-vessel disease.

9.4.2 Additional Endpoints

Descriptive statistics will be provided for any additional endpoints. For binary measures, the rate and Clopper-Pearson 95% CI will be provided. For continuous endpoints, the mean, median, SD, and the interquartile range will be provided. For time to event measures, the Kaplan-Meier product limit estimate and 95% CI will be provided for each year of follow-up.

9.4.3 Missing Data

If the missing data for the per-protocol population are less than 10%, no attempt will be made to impute the missing data. However, a tipping analysis will be performed as a sensitivity analysis. If the missing data are greater than 10%, based on the type of missing data (missing at random, not missing at random, missing completely at random, etc.), the appropriate multiple imputation method will be employed as a sensitivity analysis to assess the impact of the missing data on the primary endpoint.

9.5 Estimated Duration of the Study

The estimated enrollment duration is approximately 1 year. It is estimated that the study involvement for all sites will extend approximately 1 year after the last entered subject's procedure.

10. STUDY ETHICAL CONSIDERATIONS

10.1 Confidentiality of Patients

Patient confidentiality will be maintained throughout the clinical study in a way that ensures the information can always be tracked back to the source data. For this purpose, a unique patient identification code will be used that allows identification of all data reported for each study patient.

Patient information collected in this study will comply with the standards for protection of privacy of individually identifiable health information as promulgated in the Health Insurance Portability and Accountability Act of 1996 (HIPAA). All records will be kept confidential, and the patient's name will not be released at any time. Patient records will not be released to anyone other than sponsor or its designees, and responsible regulatory authorities, when requested.

11. ADMINISTRATIVE PROCEDURES

11.1 Duke Clinical Research Institute Coordinating Center Responsibilities

11.1.1 Investigator Training

All Investigators and their study personnel will receive training regarding the study procedures. This training will take place prior to enrollment of the first patient at each study center. Any new personnel joining the study after initiation will receive the same training prior to participation.

Questions around eCRF completion or study procedures should be directed to the site's clinical research associate.

11.2 Investigator's Responsibilities

11.2.1 Reporting and Recording of Study Data

It is the investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported on the patient's eCRF. Source documentation supporting the eCRF data should indicate the patient's participation in the study and should document the dates and details of study procedures and patient's clinical status from informed consent though the 1 year contact.

11.2.2 Source Documentation

The investigator must maintain adequate and accurate source documents upon which case reports for each patient are based. They are to be separate and distinct from eCRFs.

These records should include detailed notes on:

- The medical history prior to participation in the study
- The basic identifying information, such as demographics, that link the patient's source documents with the eCRF
- The results of all diagnostic tests performed, diagnoses made, therapy provided, and any other data on the condition of the patient
- The patient's exposure to study treatment
- The patient's exposure to any concomitant therapy (including date and quantity dispensed)
- All relevant observations and data on the condition of the patient throughout the study

- The oral and written communication with the patient regarding the study treatment (including the risks and benefits of the study)

- The date of informed consent recorded in the source documentation

11.2.3 Records Retention

The investigator must inform, and receive approval from, the Sponsor prior to the destruction of any documents, if documents are to be transferred to a different facility or transferred to a different owner.

The investigator shall maintain the records required for this investigation for a period of 6 years after the date on which the investigation is terminated or completed.

12. STEERING COMMITTEE, DATA AND SAFETY MONITORING COMMITTEE, AND ADJUDICATION COMMITTEE

12.1 Steering Committee

The Steering Committee for this study will supervise the conduct, administration, and course of the clinical trial. They will provide scientific and clinical oversight and will meet periodically to monitor subject enrollment and overall study progress. This committee will also be responsible for reviewing the final results, determining the methods of presentation and publication, and selection of secondary projects and publications. The steering committee for this study will include the study chair, principal investigator, up to 2 additional clinicians experienced in FFR clinical trials, a DCRI statistician, and a member from the ACIST team.

12.2 Fractional Flow Reserve Core Lab

This purpose of the core lab will be to review the quality and validity of each FFR tracing obtained from all subjects enrolled in the study as well as derive the dPR via waveform analysis. The core lab will consist of 1 physician knowledgeable in FFR physiology and the catheter techniques employed for proper FFR acquisition and 1 engineer from the ACIST team with specific knowledge about FFR acquisition and data analysis from the NAVVUS Rxi FFR system. These 2 members will perform an independent, blinded review of all FFR tracings and will make a recommendation for exclusion if any of the following criteria are noted: ventricularization of aortic waveform, change in dampening/distortion of aortic waveform, or significant signal drift. Discrepancies in recommendations will be resolved by joint review of the 2 members of the tracing in question.

13. POLICY FOR PUBLICATION AND PRESENTATION OF DATA

The sponsor will encourage the scientific publication of data from clinical research trials. However, investigators may not present or publish partial or complete study results individually. The principal investigators and the partners may propose appropriate scientific manuscripts or abstracts from the study data. Any manuscript or abstract proposed by the investigators must be reviewed and approved in writing by the Steering Committee before submission for publication.

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