

AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK

ACRIN 4701

RESCUE: Randomized Evaluation of Patients with Stable Angina Comparing Utilization of Diagnostic Examinations

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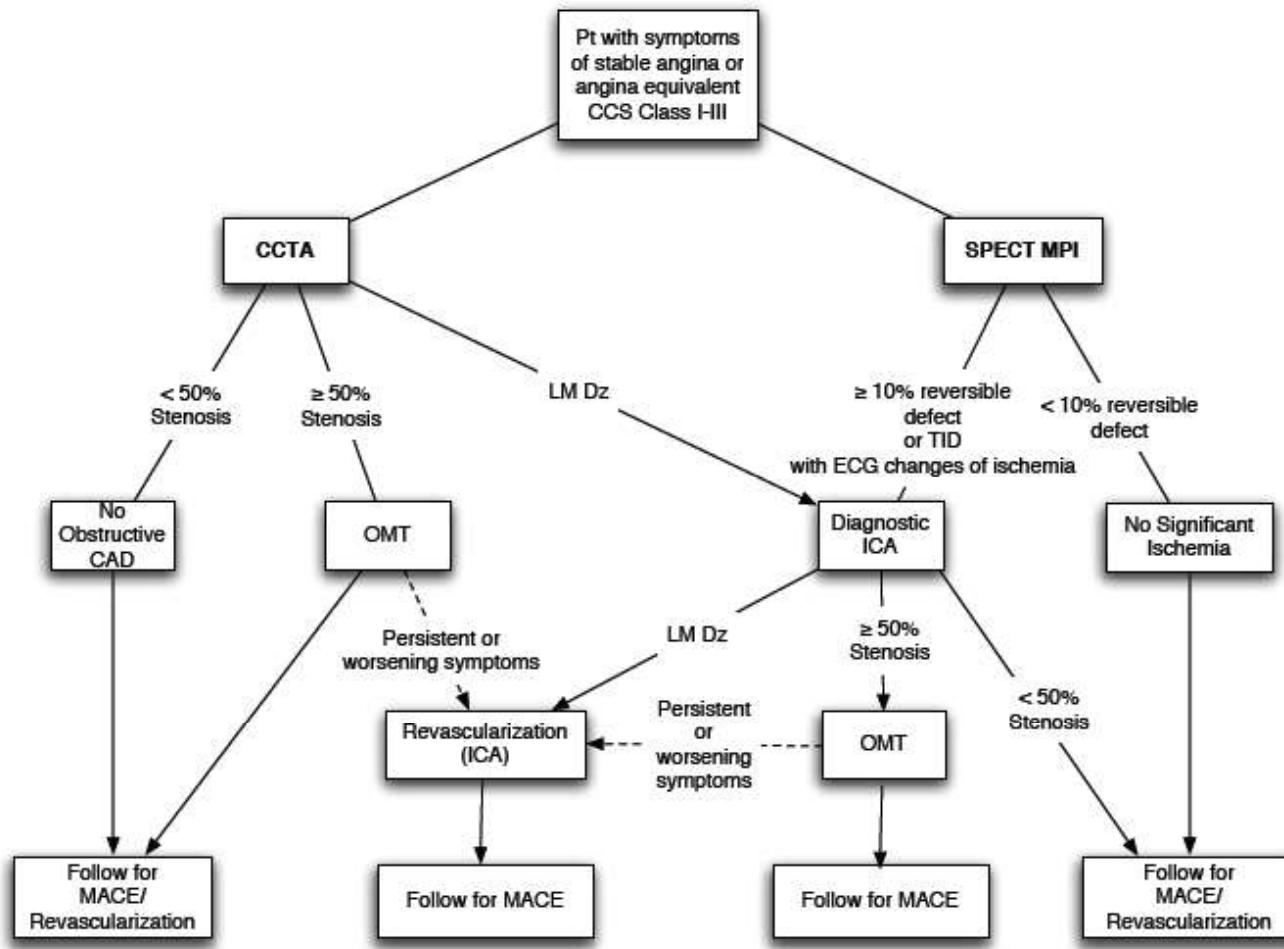
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AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK

ACRIN 4701

RESCUE: Randomized Evaluation of Patients with Stable Angina
 Comparing Utilization of Diagnostic Examinations
 (A Phase III, Multicenter, Randomized, Controlled, Comparative-Effectiveness Trial)

SCHEMA



Abbreviations: CCS, Canadian Cardiac Society; CCTA, coronary computed tomography angiography; SPECT, single photon emission tomography; MPI, myocardial perfusion imaging; TID, transient ischemic dilation; ECG, electrocardiogram; CAD, coronary artery disease; MACE, major adverse cardiac event; OMT, optimal medical therapy; ICA, invasive coronary angiography; LM Dz, left main disease ($\geq 50\%$ stenosis).

STUDY OBJECTIVES/SPECIFIC AIMS

This randomized, controlled, diagnostic, multicenter trial will follow participants at 6-month intervals for up to 24 months to determine the incidence of MACE, defined as myocardial infarction (MI) or cardiac-related death, and cross-over to revascularization. (Some participants will be followed only up to 12 months, dependent on when they join the trial and due to trial timeline completion limitations.)

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The primary endpoint of the study is a combined endpoint of occurrence of MACE and revascularization. We will calculate differences in the combined MACE/revascularization endpoint between the CCTA and SPECT MPI/ICA arms.

Primary Hypothesis: CCTA may be used to direct patients with symptoms of stable angina or angina equivalent to OMT. The use of CCTA as a diagnostic tool for angina symptoms will be associated with no increase in MACE or revascularization, decreased cost, reduced risks (e.g., less radiation exposure), additional insights into alternate explanations of chest pain, and increased cost-effectiveness in comparison with use of SPECT MPI/ICA.

ELIGIBILITY (see Section 5.0 for details)

Patients ages 40 or older presenting with symptoms of stable angina CCS Class I to III or angina equivalent, with or without known CAD, with planned non-invasive imaging for diagnosis.

Patients will be excluded if they have/are:

- Prior revascularization;
- Renal insufficiency or renal failure;
- History of allergy-like reaction to iodinated contrast;
- Atrial fibrillation or significant arrhythmia judged to potentially limit quality of CCTA;
- Acute ischemia;
- Acute myocardial infarction;
- Severe myocardial ischemia: known markedly positive exercise treadmill stress test (significant ST segment depressions or hypotensive response during stage I of the Bruce protocol);
- Unable to suspend respiration for 15 seconds or to follow instructions to do so;
- Unstable angina and symptoms refractory to maximal oral and intravenous medical therapy (persistent CCS Class IV);
- History of known left ventricular ejection fraction < 45%;
- Pulmonary edema or heart failure unresponsive to standard medical therapy;
- Pacemaker;
- Valvular heart disease likely to require surgery in the next 18 months;
- Congenital heart disease or cardiomyopathy likely to affect prognosis during follow up;
- Significant systemic hypertension (blood pressure > 200/100 mm Hg) unresponsive to medical therapy;
- Severe noncardiovascular comorbidity limiting survival (e.g., cancer or other life threatening illness for which the patient is expected to live less than 12 months);
- Prior imaging evaluation for this episode of symptoms (e.g., SPECT MPI or CCTA within the previous 72 hours);
- BMI > 40 kg/m²;
- Pregnant.

SAMPLE SIZE

A total of 4300 patients will be randomized to CCTA or SPECT MPI/ICA for diagnostic assessment of angina at up to 80 institutions internationally.

1.0 ABSTRACT

This protocol for human research study is conducted according to United States and international standards of Good Clinical Practice (International Conference on Harmonisation [ICH] Guidelines), applicable government regulations (e.g. Title 45, Part 46 Code of Federal Regulations) and the American College of Radiology Imaging Network (ACRIN) research policies and procedures.

Coronary computed tomography angiography (CCTA) represents a potentially disruptive technology in terms of its impact on the clinical evaluation and management of coronary artery disease (CAD). This was highlighted by its inclusion in the Consensus Report on Initial National Priorities for Comparative Effectiveness Research (CER) issued by the Institute of Medicine (IOM). Specifically, the report recommends: “Compare the effectiveness of [CCTA] and conventional angiography in assessing coronary stenosis in patients at moderate pretest risk of [CAD].” An additional IOM aim stated in the Consensus Report, most likely in response to the results of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, recommends research comparing the effectiveness of “aggressive medical management and percutaneous coronary interventions [PCIs] in treating stable coronary disease for patients of different ages and with different comorbidities.”

The results of the COURAGE trial suggest that patients with stable angina diagnosed with CAD and initially treated with pharmacologic therapy and lifestyle intervention, defined as optimal medical therapy (OMT), alone have no difference in outcomes in comparison to individuals treated with both OMT and PCI. CCTA, by explicitly identifying patients with potentially significant left main disease, can safely select patients for OMT without requiring diagnostic invasive coronary angiography (ICA). This is not the case for the more traditional single photon emission tomography myocardial perfusion imaging (SPECT MPI), where patients with a positive test for CAD will require diagnostic ICA to identify potential left main disease prior to the safe initiation of OMT. The proposed trial will compare these two diagnostic paradigms: CCTA versus SPECT MPI/ICA (SPECT MPI followed by diagnostic ICA) to determine extent of stenosis and subsequent therapeutic approach.

The **Randomized Evaluation of Patients with Stable Angina Comparing Utilization of Diagnostic Examinations (RESCUE)** is a multi-center randomized, controlled trial responding to the need for comparative analysis of these imaging technologies and the role of OMT in clinical care. This study builds on the results of the COURAGE trial by comparing CCTA and SPECT MPI/ICA integrated into a care paradigm featuring initial treatment with OMT for patients diagnosed with CAD without significant disease in the left main coronary artery. Participants will be followed for a composite endpoint of major adverse cardiac events (MACE) and cross-over to revascularization over a follow-up period up to two years (two to six time points depending on diagnostic results and time of enrollment into the trial). Participant outcomes will be assessed by age, gender, comorbidity, and angina classification class at presentation. Several comparative-effectiveness analyses will be performed. We hypothesize that the CCTA arm will be associated with no increase in MACE or revascularization, decreased cost, reduced risks (e.g., less radiation exposure), additional insights into or alternate explanations of chest pain, and increased cost-effectiveness in comparison with SPECT MPI/ICA. Findings are expected to result in validation of an evolving new standard of care for patients with stable angina that takes advantage of CCTA and OMT to more cost-effectively drive appropriate care while reducing the need for invasive diagnosis and increased radiation exposure with SPECT MPI/ICA.

2.0 BACKGROUND AND SIGNIFICANCE

In the United States, 9.8 million people have stable angina, with an annual incidence of 500,000.¹ Although millions of individuals present with symptoms of stable angina or angina equivalent annually, it is estimated that only about one-third of these patients will have abnormal results from exercise SPECT MPI.² Imaging plays a prominent role in establishing the diagnosis and, nationwide, represents a significant healthcare expense.

Treatment of stable angina has traditionally been a combination of medical therapy and revascularization. The COURAGE trial recently showed that “as an initial management strategy in patients with stable CAD, PCI did not reduce the risk of death, myocardial infarction [MI], or other major cardiovascular events when added to OMT.”³ This OMT-only paradigm as demonstrated in the COURAGE trial represents a substantial cost savings and is evolving into a new standard of care.

CCTA accurately detects coronary atherosclerotic plaque and stenosis. CCTA, alone, has the potential to be less expensive than SPECT MPI followed by diagnostic ICA when the SPECT MPI test is positive, and represents an attractive alternative diagnostic approach.

2.1 Standard Evaluation of Patients with Stable Chest Pain

Guidelines for the diagnosis and management of patients with chronic stable angina have been published.⁴ The probability of CAD is estimated on the basis of patient age, gender, cardiovascular risk factors, and pain characteristics. Patients with intermediate or high probability of CAD will undergo additional risk stratification through further testing. For patients with low probability of CAD, the decision to have additional testing is made on a case-by-case basis.

Exercise perfusion imaging, exercise echocardiography, or exercise ECG is recommended as the initial test for risk stratification in symptomatic patients who can exercise unless there are confounding factors on their ECG or the patients are taking digoxin. Pharmacologic stress imaging is recommended for the remainder of symptomatic patients. Patients with positive stress imaging demonstrating moderate to severe ischemia often undergo ICA to establish that the test was a true positive and to guide therapy including revascularization. Typically, on SPECT MPI, $\geq 10\%$ of a reversible perfusion defect is defined as moderate to severe ischemia.⁵ Evidence of transient ischemic dilation (TID) accompanied by electrocardiogram (ECG) changes of ischemia identified during SPECT MPI should lead to ICA.

2.2 Definition of Angina Class

The severity of symptoms of stable angina is generally graded by an angina class such as defined by the Canadian Cardiovascular Society (CCS).⁶ This is clinically based on the patient’s symptoms at various levels of activity (Table 1).

Table 1. Canadian Cardiovascular Society Classification for Stable Angina⁶

Class I	Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation.
Class II	Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.
Class III	Marked limitation of ordinary physical activity. Walking one to two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace.
Class IV	Inability to carry on any physical activity without discomfort—anginal syndrome may be present at rest.

2.3 Management of Patients with Stable Angina

The landmark COURAGE trial recently showed that, “as an initial management strategy in patients with stable CAD, PCI did not reduce the risk of death, MI, or other major cardiovascular events when added to OMT”.³ All of the participants in the study had a $\geq 70\%$ stenosis in at least one epicardial coronary artery and documented objective evidence for myocardial ischemia. Another recent randomized trial studied participants with type 2 diabetes and stable CAD comparing treatments of OMT to OMT + revascularization.⁷ As in COURAGE, no significant difference in outcomes was found. Nevertheless, who will derive benefit from revascularization based on extent of patient ischemia remains unclear. A small nuclear medicine substudy of participants in the COURAGE trial showed a greater reduction of ischemia treated by PCI + OMT over OMT alone for participants with larger reversible perfusion defects.⁵ While this substudy was not powered sufficiently to detect differences in outcomes, it suggests that patients with severe ischemia may benefit from PCI. Hachmanovitch et al showed in a non-randomized single-center study that revascularization improved survival for participants with moderate-severe ischemia, whereas participants with no or mild ischemia had better outcomes with OMT.⁸ Certainly, the prognosis of patients with more ischemia is known to be worse.^{8,9}

A single center trial of participants in Brazil with stable 3-vessel disease and normal ventricular function (MASS II) randomized 611 patients into OMT alone or in combination with PCI or CABG.^{10,11} There was no significant difference in overall mortality in the three groups at either 5 or 10 years. Nevertheless, there was a higher incidence of acute MI, cardiac-related death, and subsequent revascularization due to refractory angina in the OMT alone group. While suggestive that OMT alone may be inferior to PCI and CABG for patients with 3-vessel disease, the study is limited by the single center design and relatively small number of participants in each arm. This result was not seen in COURAGE, but there were fewer patients with 3-vessel disease in COURAGE than MASS II. Participants with significant stenosis of their left main coronary artery did benefit from revascularization compared with medical therapy in the Veterans Administration Cooperative Study of Surgery for Coronary Arterial Occlusive Disease.¹² This may be a particularly risky anatomy but the numbers of

participants in this study were relatively small (N=91), and there have been significant advances in medical therapy since this study was performed.

2.4 Differences in Stable Angina Management: Patient Age, Gender, and Comorbidity

2.4.1 Age

A substudy of the COURAGE trial examined participants with stable CAD stratified by age and randomized to PCI + OMT or OMT alone. A total of 1381 participants younger than 65 years and 904 participants 65 years and older were followed. The addition of PCI to OMT did not improve or worsen clinical outcomes in participants 65 years and older during a median 4.6-year follow-up.¹³ In the TIME study (Trial of Invasive versus Medical therapy in Elderly), although early evaluation favored invasive therapy, 1-year follow-up of elderly participants ages 75 or older with CCS Class II or higher angina showed no significant difference in participants treated with OMT versus invasive therapy with regard to symptoms, quality of life (QoL), and death or non-fatal infarction.¹⁴ To our knowledge, no literature specifically addresses outcomes differences stratified by age in patients with stable angina treated by OMT as directed by the initial non-invasive imaging procedure of CCTA and imaging using SPECT MPI followed by diagnostic ICA.

2.4.2 Gender

A substudy of the Euro Heart Survey of Stable Angina sought to determine gender differences in participant outcomes.¹⁵ A total of 3779 participants were included in the survey; 42% were female. In a multivariable model adjusted for age, abnormal left ventricular function, the presence of diabetes, and the severity of CAD defined as one-, two-, or three-vessel disease, female gender remained significantly predictive of death or MI, with women twice as more likely than men to die or have an MI during one-year follow up. Many other studies also have suggested gender differences in treatments and outcomes in patients with CAD.^{7,16,17} In RESCUE, we will also stratify outcomes by participant gender to identify any differences.

2.4.3 Comorbidity

A study by Sachdev et al assessed a cohort of 1471 participants with CAD who underwent cardiac catheterization and were followed for 10 to 15 years through the Duke Databank for Cardiovascular Diseases.¹⁸ The Charlson index,¹⁹ a widely used index of patient comorbidity, and a newly-created CAD-specific index¹⁸ were highly associated with long-term survival, almost equivalent to left ventricular ejection fraction. Components of the Charlson index with the greatest prognostic significance among patients with CAD were diabetes, renal insufficiency, chronic obstructive pulmonary disease, and peripheral vascular disease. As comorbid disease is strongly associated with long-term survival in patients with CAD, RESCUE will assess co-existing illnesses using these two indices to determine any impact of comorbidity upon differences in participant outcomes.

2.5 Scores to Identify Myocardium at Risk

Several myocardial jeopardy scores have been proposed to identify myocardium at risk. These generally take into consideration the location and extent of CAD. Three common scoring tools (Duke Prognostic Index),²⁰ Myocardial Jeopardy Index described in the Bypass Angioplasty Revascularization

Investigation (BARI),²¹ Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH)²² have been compared.²³ All were found to be predictive of mortality and have been suggested as tools for cardiovascular outcome studies. The Duke index has the advantage of being the easiest to apply and most widely used. It also has been adapted for use with CCTA¹ (Table 2) and for estimating the size of ischemic myocardium from ICA.²⁴

Table 2. Duke Prognostic Index Modified for CCTA (patients are assigned to the highest disease category)¹	
Subgroup	Severity of CAD
1	< 50% Stenosis
2	> 2 Mild Stenoses With Proximal CAD in 1 Artery or 1 Moderate Stenosis
3	2 Moderate Stenoses or 1 Severe Stenosis
4	3 Moderate Stenoses, 2 Severe Stenoses, or Severe Stenosis in Proximal LAD
5	3 Severe Stenoses or 2 Severe Stenoses in Proximal LAD
6	> 50% Left Main Stenosis
CCTA, coronary computed tomography angiography; CAD, coronary artery disease; LAD, left anterior descending coronary artery	

2.6 Patient Reported Outcomes

The importance of patient self-reported outcomes is widely recognized in the literature and by the US Food and Drug Administration.^{25,26} Global measures of health, such as the 36-Item Short Form Survey Instrument, version 2 (SF-36 v2), are useful to compare participant health status across studies of different health conditions²⁷⁻³⁰ as well as to derive health utilities for use in cost-effectiveness analyses.³¹ Disease-specific measures of participant health status, such as the Seattle Angina Questionnaire (SAQ), are useful to collect detailed information regarding the specific disease outcome of interest.³² Both the SF-36 and the SAQ have been used to assess health-related QoL in patients with angina and have been demonstrated to be internally consistent with good test-retest reliability.^{27-30,32} Selected subscales from both tools have been correlated with patient angina severity measured using the CCS Classification (Table 1),³² and both of these tools have been used to measure participant health status in a prior large clinical trial of PCI and OMT interventions for patients with angina.³³

2.7 Significance of the Proposed Research

CCTA has been shown in recent multicenter studies to have high negative predictive value for obstructive CAD.^{34,35} Another multicenter study showed only moderate negative predictive value, but considered un-evaluable coronary artery segments to have no significant disease, which is contrary to common practice, and included these data in the trial analysis.³⁶ All of these multicenter studies showed limited positive predictive value for obstructive CAD on a per-segment basis. Nevertheless, CCTA can be used effectively for prognosis, as was shown recently by Min et al.¹ This study showed that the location and extent of CAD as assessed with a modified Duke coronary artery prognostic index (Table

2)³⁷ may be used for predicting all-cause mortality. Larger scores represent poorer prognosis and were representative of greater myocardium ischemic risk.

Given the linkage of the modified Duke coronary artery prognostic index to ischemic burden, it is reasonable to hypothesize that CCTA may be used as a primary tool to guide the clinical decision to prescribe OMT versus revascularization for patients with symptoms of stable angina. We note that the myocardial jeopardy score and angina variables were found to be the strongest predictors of revascularization in the Coronary Artery Surgery Study (CASS) registry.³⁸

A CCTA approach could provide considerable savings over the current common practice of SPECT MPI followed by diagnostic ICA when the SPECT MPI test is positive. The high negative predictive value of CCTA would exclude patients without CAD as a cause of their symptoms. The positive predictive value of CCTA for obstructive CAD on a per-patient basis is higher than that found for per-segment analyses and is more appropriate for guiding the patient to OMT. Moreover, the positive predictive value for the presence of plaque is high, as has been demonstrated in studies comparing CCTA to intravascular ultrasound. The major limitation of using CCTA to guide treatment is that some patients without obstructive CAD may be treated with OMT or may possibly be misdirected to coronary angiography to evaluate for revascularization because of suspected left main disease ($\geq 50\%$ stenosis). However, it is anticipated that this cost should be more than offset by eliminating the current practice of SPECT MPI followed by diagnostic ICA in those patients who demonstrate myocardial ischemia. Even if plaque seen by CCTA is non-obstructive, the presence of plaque may indicate that microvascular disease is the cause of the symptoms, so OMT would be appropriate.

The incidence of stable angina pectoris in the US is estimated to be 500,000 patients per year with a prevalence of 9.8 million.³⁹ The diagnostic costs in evaluating these patients are substantial. Far more patients are evaluated for the presence of possible stable CAD as the cause of their symptoms. A recent study showed only about one-third of participants with symptoms of stable angina or anginal equivalent evaluated by SPECT MPI demonstrate evidence of ischemia.² The high negative predictive value of CCTA can be expected to provide an effective filter to reduce the need for further evaluation for CAD. It has recently been suggested from an analysis of Medicare Category III transaction codes that substantial savings may be found using CCTA to establish the diagnosis.⁴⁰

3.0 STUDY OBJECTIVES/SPECIFIC AIMS

The primary endpoint of the study is a combined endpoint of occurrence of MACE, comprising cardiac-related death or acute MI, and revascularization (see Appendix IV for definitions). We will calculate differences in the combined MACE/revascularization endpoint between the CCTA and SPECT MPI/ICA arms.

3.1 Primary Aim

3.1.1 To compare outcomes of participants with symptoms of stable angina or angina equivalent evaluated with an anatomic imaging strategy using CCTA as initial method of CAD diagnosis (Group A) to a combined functional and anatomic imaging strategy of SPECT MPI/ICA (Group B) as a guide to OMT.

3.2 Secondary Aims

- 3.2.1** To evaluate the ability of available prognostic indices to predict revascularization or MACE using CCTA information and to develop new indices using the RESCUE trial data.
- 3.2.2** To determine the cost, effectiveness, and incremental cost-effectiveness of CCTA versus SPECT MPI/ICA in the evaluation of participants with symptoms of stable angina.
- 3.2.3** To compare angina symptoms and self-reported health status of participants with symptoms of stable angina undergoing CCTA as initial method of CAD diagnosis to SPECT MPI/ICA as a guide to OMT.

4.0 STUDY OVERVIEW

The RESCUE study is designed as a phase III, randomized, controlled, diagnostic, multicenter trial. We will enroll 4300 participants at a maximum of 80 sites during an 18-month period. Patients with stable angina or anginal equivalent (nausea, dyspnea, syncope, etc) who consent and are enrolled in the trial will be randomized to CCTA (Group A) or SPECT MPI/ICA (Group B) as initial method of CAD-symptom diagnosis. All participants diagnosed with CAD by either strategy will be treated initially by OMT unless there is evidence of significant left main CAD ($\geq 50\%$ stenosis) or markedly abnormal stress test, in which case they will undergo ICA and possibly revascularization as is standard practice.

Participants with CCTA or SPECT MPI/ICA findings of stenosis $\geq 50\%$ in diameter will be treated with OMT unless the stenosis is in the left main coronary artery. Participants with moderate-severe ischemia by SPECT MPI ($\geq 10\%$ reversible perfusion defect or evidence of TID accompanied by ECG changes of ischemia) will undergo diagnostic ICA to confirm no significant left main CAD ($< 50\%$ stenosis) and that the diagnosis is not a false positive. Participants with a stenosis $\geq 50\%$ in diameter on diagnostic ICA will be directed to OMT. Un-evaluable proximal and mid segments will be regarded as being positive for CAD for the purposes of the study and the participant directed to OMT. Participants with left main CAD found on CCTA will undergo diagnostic ICA. Participants with CCTA findings of stenosis $< 50\%$ in diameter; SPECT MPI findings of reversible ischemia $< 10\%$ of the myocardium; or SPECT MPI findings of $\geq 10\%$ reversible perfusion defect or evidence of TID accompanied by ECG changes of ischemia followed by ICA findings of $< 50\%$ stenosis will be treated per institutional standard of care or discharged and followed per protocol for MACE and revascularization.

Both CCTA and SPECT MPI will be read locally at participating sites. Local-read results will be used to guide participants into additional diagnostic procedures (such as ICA in the SPECT MPI arm) and the various post-diagnostic arms of the study (Figure 1). All CCTA and SPECT MPI scans will be sent to the ACRIN core lab for archiving. The first two (2) scans from each site and a random subset of 10% of CCTA and SPECT MPI scans from each participating site will be reviewed centrally at the CCTA and SPECT MPI core labs for quality assurance. A modified Duke Prognostic Index will be calculated from the completed local-read CRF. The myocardial perfusion defect size will be determined for each SPECT MPI case locally both for determining participant direction to revascularization vs. OMT and for later prognostic analysis. Imaging recommendations have been suggested by ACRIN and the respective core labs and are available online at www.acrin.org/RESCUE_imagingmaterials.aspx.

OMT includes antiplatelet therapy, aggressive lipid lowering targets,⁴¹ treatment for hypertension,

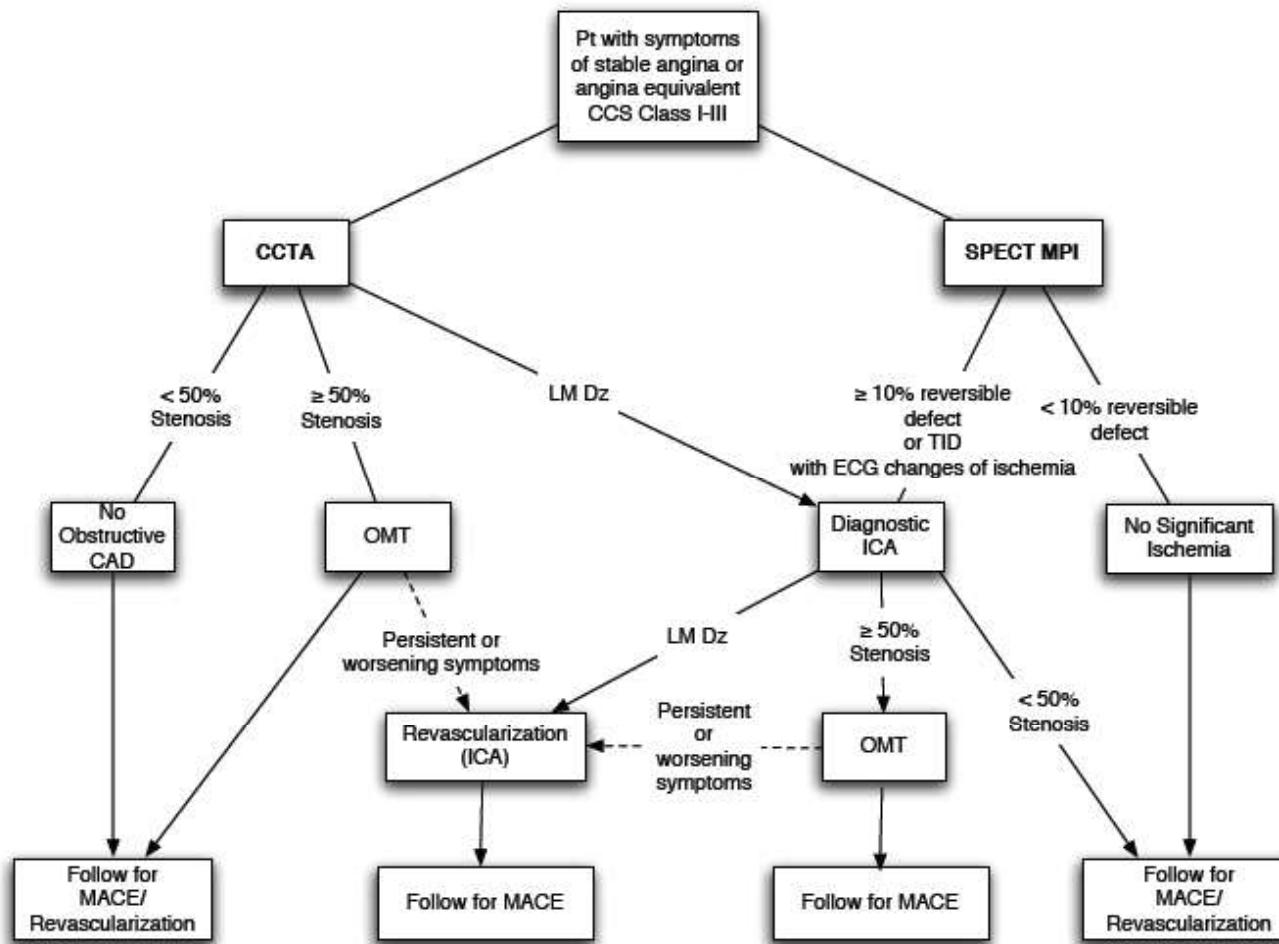
treatment for angina, diabetes control, smoking cessation, exercise, and nutritional/dietary and other lifestyle changes as was done in COURAGE.³ Changes to OMT by participants or by physician prescription will be tracked throughout trial follow up. (See Section 8.1.5.2 for OMT specifics.) Participants with persistent or worsening symptoms will be evaluated for revised therapeutic approaches and possible revascularization (see Section 8.1.5.3).

Angina class (CCS Class I to III, Canadian Cardiovascular Society)⁶ will be assessed on entry into the study and at 6-month intervals for up to 24 months. Risk factors for CAD (including Diamond-Forrester),⁴² Charlson Comorbidity Index,¹⁹ and CAD-specific Morbidity Index¹⁸ will be acquired at baseline only. The SAQ⁴³ and SF-36 for QoL (quality-of-life) assessment will be administered by the site RA to all participants in the United States at baseline. A subset of US participants will complete the QoL questionnaires at 12 months; if necessary, telephone follow up will be used to encourage completion by mail or to conduct an interview to complete. Lifestyle questions will be administered by the site RA at baseline and be included during telephone follow up at 12-months only.

Follow up at the site level will comprise telephone participant/proxy contact at 2 weeks and 2 months after enrollment **only** for participants who have positive cardiac findings on diagnostic CCTA or SPECT MPI. **All** participants (or their proxies) will be contacted by telephone for additional medical information at 6-month intervals after enrollment for up to 24 months. Number of time points and duration of follow up depend on diagnostic results and timing of enrollment, respectively. See Section 8.2.1 for additional details.

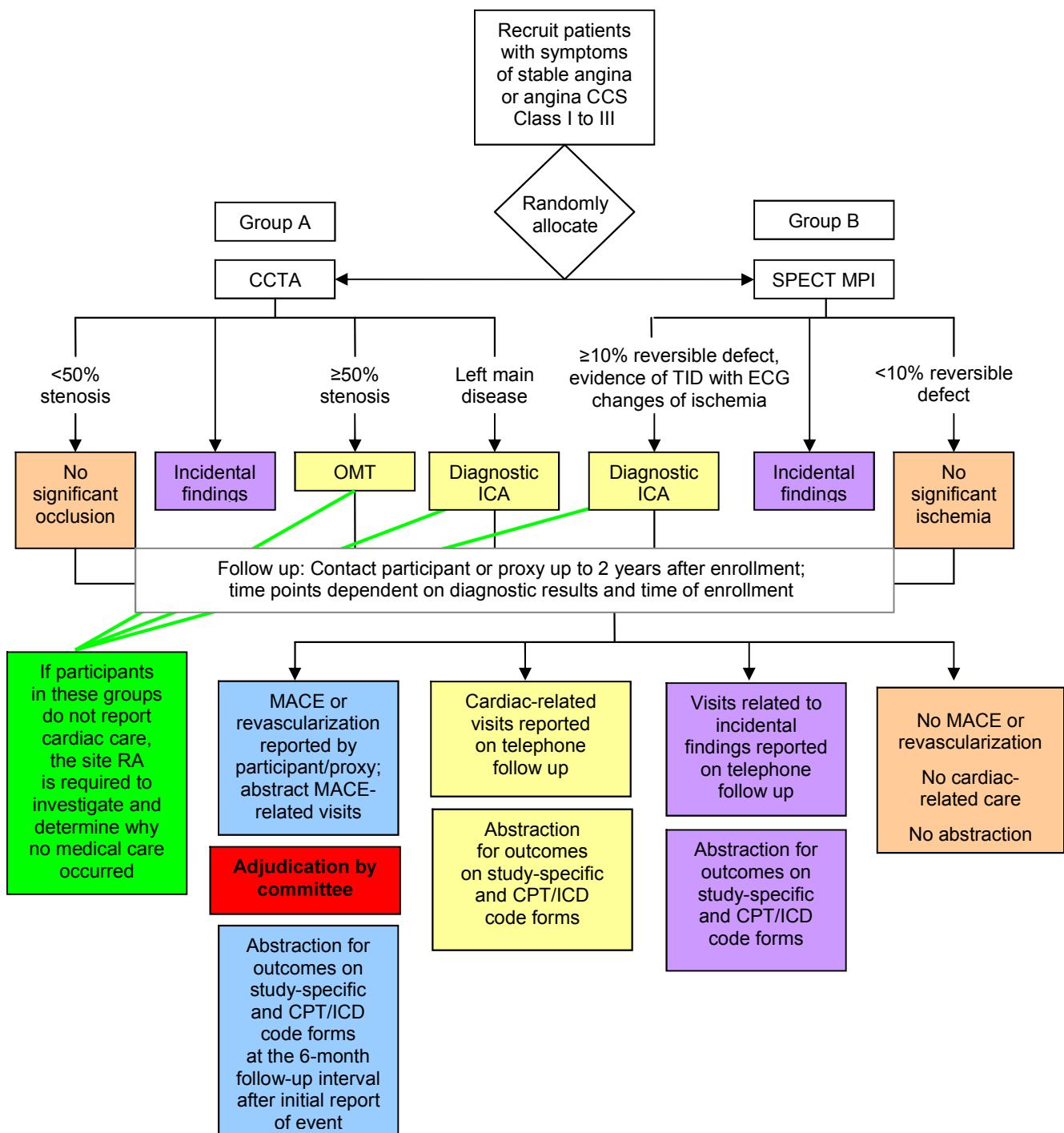
Medical records collection will be conducted for the subset of participants who self-report MACE, stroke, revascularization, cardiac-related visits, or visits related to incidental findings associated with the diagnostic tests. Procedures for medical record collection are dependent on site location and local standard practice in releasing participant protected health information (PHI). The schema of the trial is shown in Figure 1 below. Figure 2 below shows the selection process for medical record collection.

Figure 1. RESCUE Schema



Abbreviations: CCS, Canadian Cardiac Society; CCTA, coronary computed tomography angiography; SPECT, single photon emission tomography; MPI, myocardial perfusion imaging; TID, transient ischemic dilation; ECG, electrocardiogram; CAD, coronary artery disease; MACE, major adverse cardiac event; OMT, optimal medical therapy; ICA, invasive coronary angiography; LM Dz, left main disease (≥ 50% stenosis).

Figure 2. RESCUE Medical Chart Abstraction Flow Chart



Abbreviations: CCS, Canadian Cardiac Society; CCTA, coronary computed tomography angiography; SPECT, single photon emission tomography; MPI, myocardial perfusion imaging; TID, transient ischemic dilation; ECG, electrocardiogram; MACE, major adverse cardiac event; OMT, optimal medical therapy; ICA, invasive coronary angiography; CPT, Current Procedural Terminology; ICD, International Classification of Diseases.

Definition: MACE is defined as myocardial infarction or cardiac-related death.

5.0 PARTICIPANT SELECTION/ELIGIBILITY CRITERIA

Patients ages 40 or older presenting with symptoms of stable angina CCS Class I to III or angina equivalent, with or without known CAD, with planned non-invasive imaging for diagnosis may enroll in the study.

5.1 Inclusion Criteria

- 5.1.1** Willing and able to provide a written informed consent;
- 5.1.2** 40 years or older;
- 5.1.3** Presentation with symptoms of stable angina (CCS Class I to III) or angina equivalent with or without known CAD;
- 5.1.4** Planned non-invasive imaging for CAD diagnosis;
- 5.1.5** Able to tolerate CCTA or SPECT MPI per randomization as required by protocol, to be performed at an ACRIN-qualified facility with a RESCUE-qualified scanner.

5.2 Exclusion Criteria

- 5.2.1** Prior revascularization;
- 5.2.2** Not suitable to undergo CT with an iodinated contrast agent:
 - 5.2.2.1** Known allergy-like reaction to contrast media as defined by the American College of Radiology (ACR) (see www.acr.org/SecondaryMainMenuCategories/quality_safety/contrast_manual.aspx for reaction definition) or moderate to severe allergic reactions to more than one allergen;
 - 5.2.2.2** Renal failure, as determined by glomerular filtration rate (GFR) < 30 mL/min/1.73 m² based on a serum creatinine level obtained within 28 days prior to registration;
 - 5.2.2.3** Renal insufficiency at the time of enrollment, as determined by GFR 30 to 60 mL/min/1.73 m² based on a serum creatinine level obtained within 28 days prior to registration, unless permitted by the institution's policy and/or ACR guidance for risk reduction strategies (see www.acr.org/SecondaryMainMenuCategories/quality_safety/contrast_manual.aspx for guidance on contrast selection and pre-treatment strategies);
- 5.2.3** Atrial fibrillation or significant arrhythmia judged to potentially limit quality of CCTA;
- 5.2.4** Acute ischemia;
- 5.2.5** Acute myocardial infarction;
- 5.2.6** Severe myocardial ischemia: known markedly positive exercise treadmill stress test (significant ST segment depressions or hypotensive response during stage I of the Bruce protocol);
- 5.2.7** Unable to suspend respiration for 15 seconds or to follow instructions to do so;
- 5.2.8** Unstable angina and symptoms refractory to maximal oral and intravenous medical therapy (persistent CCS Class IV);
- 5.2.9** History of known left ventricular ejection fraction < 45%;
- 5.2.10** Pulmonary edema or heart failure unresponsive to standard medical therapy;

- 5.2.11** Pacemaker;
- 5.2.12** Valvular heart disease likely to require surgery in the next 18 months;
- 5.2.13** Congenital heart disease or cardiomyopathy likely to affect prognosis during follow up;
- 5.2.14** Significant systemic hypertension (blood pressure $> 200/100$ mm Hg) unresponsive to medical therapy;
- 5.2.15** Severe noncardiovascular comorbidity limiting survival (e.g., cancer or other life threatening illness for which the patient is expected to live less than 12 months);
- 5.2.16** Prior imaging evaluation for this episode of symptoms (e.g., SPECT MPI or CCTA within the previous 72 hours);
- 5.2.17** $\text{BMI} > 40 \text{ kg/m}^2$;
- 5.2.18** Pregnancy or intent to become pregnant (if a female is of childbearing potential—defined as a premenopausal female capable of becoming pregnant—a pregnancy test should be done prior to enrollment).

5.3 Recruitment and Screening

Patients will be recruited from office-based clinical practices and from referrals to radiology departments and outpatient imaging centers where CCTA and SPECT MPI/ICA are performed. Patients presenting to the emergency department may be eligible for the trial as long as acute coronary syndrome is ruled out and all other eligibility criteria are met for trial participation. Informed consent will be obtained as soon as the potential participant is identified. Consent will be completed by an appropriate investigator-designated research staff.

Referring physicians will need to be in agreement with the principles of the trial, *especially in agreement to adhere to OMT (non-revascularization) after imaging unless the participant has left main disease or has persistent or worsening symptoms while on OMT (in which case the participant may go to revascularization or other treatment)*. A sheet describing possible OMT and a description of the trial will be sent to referring physicians.

ACRIN will develop materials to aid participant recruitment. All materials used for participant recruitment will be reviewed and approved by each institution's Institutional Review Board (IRB).

5.4 Inclusion of Women and Minorities

Subjects will not be excluded from entry based on sex or ethnicity. Training specific to inclusion of women and minorities will be provided at our Investigators Meeting. The sex and racial makeup of RESCUE will reflect the overall US population undergoing cardiovascular disease diagnosis. RESCUE will be conducted in compliance with the National Institutes of Health (NIH) Policy of Inclusion of Women and Minorities in Clinical Research, and with Federal Law PL 103-43 (NIH Revitalization Act of 1993). Minority groups are categorized according to the Revisions to the Standards for the Classification of Federal Data on Race and Ethnicity.

As consecutive patients in need of receiving CCTA or SPECT MPI will be approached for participation in this trial, we anticipate that we will have commensurate representation from women and minorities in the study population. The trial results should therefore have broad generalizability and be in compliance

with NIH policy. In addition, as part of the secondary analyses, we will assess the effects of sex as well as race and ethnicity on the primary and secondary study outcomes.

Both men and women and members of all ethnic groups are eligible for this trial. In conformance with the NIH Revitalization Act of 1993, with regard to inclusion of women and minorities in clinical research, the projected gender and minority accrals are shown below:

Table 3. Gender and Minority Accrual Estimates

Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	279	409	688
Not Hispanic or Latino	1462	2150	3612
Ethnic Category: Total of all subjects	1741	2559	4300
Racial Category			
American Indian or Alaskan Native	35	51	86
Asian	181	266	447
Black or African American	592	870	1462
Native Hawaiian or other Pacific Islander	10	25	26
White	923	1356	2279
Racial Category: Total of all subjects	1741	2559	4300

6.0 SITE SELECTION

6.1 Institution Requirements

All sites must submit a Protocol Specific Application (PSA) (available online at www.acrin.org/RESCUE_protocol.aspx), which documents that the site has the necessary personnel, equipment, and referral base to carry out the requirements specific to the ACRIN 4701 RESCUE protocol. It will be reviewed and approved by the ACRIN Institutional Participant Committee.

The potential sites for this study are cardiology or radiology institutions, including US Department of Veterans Affairs (VA) medical facilities, that meet qualifications for participating in this study (see below). See Section 9.0 for additional information regarding imaging qualification for this trial.

6.1.1 CCTA

The ACRIN core lab will work with the CCTA core lab, the Cardiovascular Imaging Core (CVIC) Laboratory at the Massachusetts General Hospital, to identify and implement criteria to qualify clinical and testing referral sites for RESCUE.

Criteria for qualification of sites interested in participating will include:

- 1) \geq 64-slice multidetector CT technology for cardiac CT;
- 2) Technologist expertise as defined by relevant certifying bodies for each test;
- 3) At least minimum reader expertise defined as self attestation of:

- a) Completed American College of Cardiology (ACC) Core Cardiology Training (COCATS) level II; **or**
- b) ACR CCTA minimum proficiency as defined by the [ACR CCTA Practice Guidelines](#) (50 cases interpreted in previous 36 months);
- 4) Intersocietal Commission for the Accreditation of Computed Tomography Laboratories (ICACTL) or ACR laboratory accreditation; and
- 5) Adequate IT capabilities defined as compatibility of storage and transfer in DICOM format.

6.1.2 SPECT MPI

The ACRIN core lab will work with the SPECT MPI core lab at Tufts Medical Center, to identify and implement criteria to qualify clinical and testing referral sites for RESCUE. SPECT myocardial perfusion studies will be performed in accordance with best practice standards as delineated in the imaging guidelines of the American Society of Nuclear Cardiology (ASNC) by appropriately credentialed physicians.

The following minimal criteria will be used as guidelines for selecting sites:

- 1) Use of standard equipment for exercise and pharmacologic testing and SPECT MPI as defined in current ASNC practice guidelines;⁴⁴⁻⁴⁶
- 2) Technician expertise as defined by relevant certifying bodies for each test;
- 3) Reader expertise defined as:
 - a) Completed at least ACC COCATS II level training; **or**
 - b) Certification by the Certification Board of Nuclear Cardiology (CBNC); **or**
 - c) Board certification in Nuclear Medicine or Radiology;⁴⁷
- 4) Intersocietal Commission for the Accreditation of Nuclear Medicine Laboratories (ICANL), ACR, or Joint Commission laboratory accreditation; and
- 5) Availability of standard commercial analytic software to calculate reversible and fixed defect size in order to determine % ischemia.

6.1.3 Test Scan Submission

One (1) test image in each modality (that is, one for CCTA and one for SPECT MPI) will be sent from the sites to ACRIN core lab to ensure that: the recommended protocols are followed; image quality is adequate; and that all technical issues related to image transmission and receipt are resolved. The CCTA test case will be assessed for adequate test protocol adherence, radiation exposure, image quality, data/image reconstruction, and transfer capability for final certification. Technical performance for CCTA and SPECT MPI will be judged by ACRIN technologists according to the criteria for each test listed in Table 4 below. Images that are technically challenging or where quality is considered borderline may be delivered electronically to the respective core labs for consultation with experts in each modality. For sites with inadequate studies, the ACRIN core lab will review the test protocol with the site in detail and request an additional study for the modality until the site fulfills all requirements.

Table 4. Criteria for Technical Site Qualification and Quality Assessment	
CCTA	<ol style="list-style-type: none"> 1) Complete data set without major motion artifacts and sufficient contrast enhancement, additional data sets if motion artifacts are present (retrospective ECG gating), and protocol description with radiation dose details; 2) Use of heart-rate lowering drug and retrospective ECG gating for heart rate > 65 bpm, unless a dual-source CCTA scanner is available.
SPECT MPI	<ol style="list-style-type: none"> 1) High quality non attenuated-corrected AND attenuated-corrected (if attenuation-correction is used) raw rest and stress projection images with attention to minimal motion and acceptably low levels of hepatic and bowel uptake. 2) Reconstructed files (short axis, vertical long axis, and horizontal short axis). 3) Screen capture of quantitative analysis results page displaying “% of LV ischemia or “% LV reversibility” from a commercial quantitative software program (i.e., Emory Cardiac Toolbox, 4D-MSPECT, QPS [Cedars Sinai], etc.). 4) High quality gated SPECT MPI with Beat Length Histogram (if available).

For site qualification questions or technical assistance on CCTA during the study from the ACRIN core lab, contact Cynthia Price, RT(R)(MR)(ARRT), via email or phone.

Email: cprice@acr.org

Phone: 215-940-8863

For site qualification questions or technical assistance on SPECT MPI during the study from the ACRIN core lab, contact Rebecca Scaven, CNMT, via email or phone.

Email: rscaven@acr.org

Phone: 215-574-3175

For CCTA questions related to image acquisition or interpretation, sites may contact the CCTA core lab at Massachusetts General Hospital via email or phone.

Email: rescuehelp@partners.org

Phone: 408-6RESCUE (408-673-7283)

For SPECT MPI questions related to image acquisition or interpretation, sites may contact the SPECT MPI at Tufts Medical Center core lab via email, phone, or pager, to the attention of Deb Kinan, RTN.

Email: dkinan@tuftsmedicalcenter.org

Phone: 617-636-2357

SPECT Core Lab Hot Line: 617-604-4848 (pager)

Images per protocol specifications must be reviewed and approved prior to participant enrollment. All scanner and image qualification materials are available at

www.acrin.org/RESCUE_protocol.aspx, and Section 9.0 provides additional information regarding the CCTA with iodinated contrast and SPECT MPI imaging recommendations.

6.2 Regulatory Requirements

All regulatory documentation must be submitted to ACRIN Headquarters (via fax: 215-717-0936, ATTN: ACRIN Protocol Development and Regulatory Compliance Department). All institutions must have study-specific, initial full-board Institutional Review Board (IRB) approval for the protocol and informed consent form (ICF). An ICF Template is included in this protocol as Appendix I and may be adjusted for local IRB submission. Appendix II contains an Authorization to Release/Disclose Medical Records Template, which is designed for use by a site that will allow ACRIN to coordinate medical record collection for the trial. This document should be adjusted for local IRB submission, will be signed by the patient at time of consent, as it will be included in requests to outside healthcare providers that treat the participant during the trial follow-up timeline. Sites coordinating their own medical record collection, such as VA facilities, will not need to provide a local IRB-approved version of this document to ACRIN and will follow institutional protocols for medical record procurement and de-identification.

The investigator and the investigator-designated research staff must follow OHRP-approved consent procedures (Title 45, Part 46 Code of Federal Regulations), as well as those set by the local IRB overseeing the study for the site. A copy of the IRB approval letter, a copy of the IRB-approved, site-specific ICF and authorization document (as appropriate), ACRIN Statement of Investigator, Federalwide Assurance documentation, and evidence of completion of the Protecting Human Research Participants training from the NIH Office of Extramural Research (or institution-specific equivalent) must be delivered to the trial monitor to review the approved forms and keep on file at ACRIN Headquarters prior to activation of the study at the local site.

6.3 Accrual Goals and Monitoring

6.3.1 ACRIN BDMC

The ACRIN Biostatistics and Data Management Center (BDMC) will monitor participant accrual. Total target accrual for this study is 4300 participants. During the first year, accrual will be reviewed monthly with the intention of discovering and resolving any recruitment barriers.

6.3.2 ACRIN Steering Committee and RESCUE DSMC

The ACRIN Steering Committee regularly reviews the overall trial accrual and may request information about a trial's accrual performance to better understand general accrual barriers or issues. Accrual and safety information will be presented to the RESCUE Data and Safety Monitoring Committee (DSMC) at regularly scheduled meetings thereof; the RESCUE DSMC may, at its discretion, re-evaluate the study with respect to feasibility or the need for additional participating institutions.

6.3.3 Safety Monitoring and Independent Clinical Event Adjudication Committee

Monitoring of study-specific adverse events (AEs) and all primary endpoint events—MACE and revascularization—will be conducted during the trial. ACRIN will centralize all AEs reporting for subsequent reporting to the RESCUE DSMC (and possibly to AHRQ). The medical monitor will review AEs on an on-going basis.

An adjudication committee will provide oversight for all reported MACE and revascularizations. Once MACE or revascularization has been reported, the site will be required to forward all medical and research records relating to these events to the ACRIN 4701 Lead Data Manager for review by the adjudication committee. An independent clinical event adjudication committee, comprising a minimum of three experts with clinical cardiovascular expertise, will be available to review and adjudicate medical records for all MACE and revascularization while blinded to study arm. The operation and procedures of the adjudication committee will be described in a separate document.

7.0 DATA MANAGEMENT/ONLINE REGISTRATION AND RANDOMIZATION

7.1 General

- 7.1.1** The ACRIN web address is www.acrin.org.
- 7.1.2** Data collection and management will be performed by the BDMC of ACRIN under the direction of Dr. Constantine Gatsonis. The Biostatistics Center (BC) is located at Center for Statistical Sciences at Brown University in Providence, RI, and the Data Management Center (DMC) is located at ACRIN in Philadelphia, PA.
- 7.1.3** Participant enrollment and data collection occurs through a series of programmed screens accessed through the ACRIN web site to register/randomize participants, collect participant data, and maintain calendars of data submissions for each participant. By using the World Wide Web, ACRIN has made participant registration, data entry, and updated calendar information available to clinical sites 24 hours a day, seven days a week. Each successful case registration is confirmed through receipt of an e-mail containing a registration/randomization confirmation and a case-specific calendar identifying timelines for data and image submission. If the confirmation e-mail is not received, the enrolling person should contact the DMC before attempting a re-registration. A DMC contact list is located on the ACRIN web site for each protocol.

7.2 Clinical Data Submission

- 7.2.1** Upon successful participant registration, a confirmation e-mail containing the registration and case-specific calendar is sent to the research staff enrolling the participant via the web. In addition, the investigator-designated research staff may download the participant specific data submission calendar, which lists all forms and designated reports required by protocol, along with the dates forms are due at the DMC. These calendars will be updated as the study proceeds to reflect data that have been received, deadlines to reply to queries about unclear data, deadlines for follow-up reports of AEs, or changes in the protocol that change the data being collected or the collection timeframe. Updated calendars for each participant can be obtained 24 hours a day from the ACRIN web site. The research associate (RA) may use the calendar as a case management tool for data submission and follow-up scheduling.
- 7.2.2** The investigative site is required to submit data according to protocol as detailed on each participant's calendar, as long as the case status is designated as open/alive or

until the study is terminated. The case is closed when all data have been received, reviewed, and no outstanding data query exists for the case.

7.2.3 To submit data via the ACRIN web site, the appropriate investigator-designated research staff will log onto the ACRIN web site and supply the pre-assigned user name and password. Case report forms (CRFs) will be available on the web site through a series of links. Each web form is separated into modules; each module must be completed sequentially in order for the internal programming to be accurate. The user selects the link to the appropriate form and enters data directly into the web-based form. As information is entered into the web form application, various logic checks will be performed. These logic checks look for data that are missing, data that are out of range, and data that are in the wrong format (e.g. character data in a field requiring numeric responses). Such errors will be detected as soon as the user attempts to either submit the form or move to the next data element. They must be corrected before the form is transmitted to the DMC. The user will not be able to finalize form transmission to the DMC until all data entered pass these logic checks. Forms that are not completed in one sitting can still be submitted and completed at a later date. The form will remain available on the web until the “Complete Form Submission” button is depressed.

7.2.4 Once data entry of a form is complete, and the summary form is reviewed for completeness and accuracy, the investigator or the research staff presses the “Complete Form Submission” button on the form summary screen and the data are transferred into the clinical database. No further direct revision of the submitted data is allowed after this point. E-mail confirmation of web data entry is automatically generated and sent to the site investigator or RA listing all of the data generated and just submitted. Should a problem occur during transmission and the e-mail confirmation of data submission is not received, the investigator or RA should contact the DMC for resolution of the submission.

7.2.5 If a temporary problem prevents access to the Internet, all sites are notified of the event and estimated down time through an ACRIN broadcast message. The investigative site should wait until access is restored to submit data. The site RA or investigator should notify the DMC of the problem and the DMC will give an estimated time when access will be restored. If access will be unavailable for an extended period, sites must seek another Internet Service Provider (ISP). On a short-term basis, the ACR can serve as an ISP.

7.3 Registration/Randomization Protocol

7.3.1 Registration

Once the patient has been found to be eligible to participate in the trial, the potential participant will be consented (see Informed Consent Form Template in Appendix I). Upon obtaining a signed ICF, the RA will register the participant by logging onto the ACRIN web site (www.acrin.org), and selecting the link for Data Center Login.

After completing the registration, the system assigns a participant-specific case number. The system then moves to a screen, which confirms that the participant has been

successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the participant's record.

7.3.2 Unsuccessful Registrations

Any problems or questions regarding registration of participants should be directed to the ACRIN DMC. Never re-register a participant as this may lead to duplicate case numbers.

7.3.3 Randomization

Study participants will be randomized to the two study arms in equal proportions. Blocked randomization will be used, stratified by gender and participating institution. Randomization will be done at the time of study enrollment using the web site of the ACRIN DMC. In the unlikely event that the web-based system is unavailable, send a fax to ACRIN to the attention of ACRIN 4701 RESCUE Lead Data Manager at: 215-717-0936. Please follow the fax with a call to the trial data manager at 215-574-3150 to help ensure the fax is seen as soon as possible. Should fax service be unavailable, call the ACRIN 4701 RESCUE Lead Data Manager at 215-574-3150 (assistance available 8:30 am to 5 pm ET, Monday through Friday).

7.4 Data Security

The registration and data collection system has a built-in security feature that encrypts all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of identification codes and passwords.

7.5 Electronic Data Management

7.5.1 Data received from the web-based forms are electronically stamped with the date and time of receipt by the ACRIN server. The data are then entered into the database. A protocol-specific validation program is used to perform more extensive data checks for accuracy and completeness. Complementary validation programs are initiated at the Brown BC and the DMC. The logic checks performed on the data at this point are more comprehensive than those built into the web-based data entry screens. They include checking that answers are logical, based on data entered earlier in the current form and the more thorough checks. Data elements that fail validation are followed up by the DMC. The validation program generated by BC produces a log of errors, which is sent to the DMC for resolution. The program is frequently updated to incorporate exceptions to rules so that subsequent validity checks minimize the time the DMC needs to spend resolving problems. Additional data review will take place once the data are transferred to the BC. The BC will run thorough cross-form validations, frequency distributions to look for unexpected patterns in data, and other summaries needed for study monitoring. Any errors found at the BC will be reported to the DMC for resolution. All BDMC communication with the participating sites is normally done through the DMC.

7.5.2 If checks at DMC or BC detect missing or problematic data, the DMC personnel assigned to the protocol sends a Request for Information (Z1 query letter) to the site RA or investigator specifying the problem and requesting clarification. The DMC updates the participant's data submission calendar with the due date for the site RA or investigator's response.

7.6 Missing and Delinquent Data Submission

In addition to providing the investigator a data collection calendar for each case, the DMC periodically prompts institutions for timely submission of data through the use of a Forms Due Report. Distributed at intervals via the electronic mail system directly to both the RA and the investigator at each site, this report lists data items (e.g., forms, reports, and images) that are delinquent and those that will be due before the next report date. In addition to prompting clinicians to submit overdue data, the Forms Due Report helps to reconcile the DMC's case file with that of the RA and/or investigator. Future Due Forms Report may be sent on an as needed basis in addition to past due reports. The site investigator or RA may use the Forms Due and Future Due Reports as a case management tool.

7.7 Data Quality Assurance

- 7.7.1** The BC at Brown University will maintain a study database at its site for monitoring data quality and for performing analyses. These data are drawn directly from the permanent database of the DMC. The transfer of data between the DMC and the BC has been validated through a series of checks consisting of roundtrip data verification in which data are sent back and forth to verify that the sent data are equivalent to the received data. These checks are repeated at random intervals during the course of a given study. Any discrepancies and other data quality issues will be referred to DMC for resolution, since only the DMC can correct the data file. No changes to the data will be made at the BC.
- 7.7.2** A goal of the monitoring of data is to assess compliance with the protocol and to look for unforeseen trends that may be indicative of procedural differences among clinical sites. If patterns are discovered in the data that appear to arise from causes specific to an institution, the BDMC will apprise ACRIN Headquarters and the site of the problem, and work with the site, along with ACRIN Protocol Development and Regulatory Compliance (PDRC) department, until the problem has been resolved. If the BDMC, along with the PDRC, cannot find a resolution to the problem, it will be brought to the ACRIN Quality Assurance (QA) Committee for further discussion and resolution.

8.0 STUDY PROCEDURES

Study-related procedures are detailed below. Important time points are:

- 1) The initial study visit for consenting, eligibility review, baseline quality-of-life (QoL) (US sites only) and lifestyle questionnaires, registration, randomization, diagnostic imaging appropriate to assigned study group, AE assessment, and treatment; and
- 2) Follow-up contacts—phone contact for participants with positive cardiac diagnostic findings at 2 weeks and 2 months; phone contact for all participants at 6-month intervals from enrollment for up to 24 months; and QoL assessment forms to a subset of participants—US sites only—at 12-months post-randomization.

Medical record collection will be required for adjudication for participants with a MACE or revascularization. Medical records will be abstracted for participants who report cardiac-related symptoms and care during follow-up contacts. In addition, medical records will be abstracted for those

participants with incidental findings on their CCTA or SPECT MPI examinations who self-report related care during trial follow up.

Sections 8.5 and 8.6 provide study procedures tables specific to site and participant activities. Figures 1 and 2 in Section 4.0 are flow charts of study procedures and medical records abstraction. Table 5 outlines distinctions in procedures by site (non-VA US sites, US VA sites, and foreign sites).

8.1 INITIAL VISIT AND ASSESSMENT

8.1.1 Phase I: Baseline Assessment

8.1.1.1 Obtain a signed informed consent form;

8.1.1.2 Perform baseline assessment to determine eligibility, comprising the following:

- Medical record review, especially to determine history of cardiac-related illness and testing—this may include a review of past medical history to determine cardiac or hypertensive tendencies at baseline;
- Query to participant regarding history of reaction to iodinated contrast agent;
- Query to participant regarding ability to hold breath for 15 seconds;
- Complete pregnancy test for women of childbearing potential;
- Collect blood for lab work to test renal sufficiency if not done within 28 days prior to enrollment;
- Assess for angina classification (CCS Class I to III), risk factors for CAD, CAD-specific morbidity, and comorbidity (Charlson Comorbidity);

8.1.1.3 Obtain contact information: two (2) phone numbers for participant (if possible), phone number for proxy, Social Security Number (for follow up access to Social Security Death Index [SSDI] as necessary), and self-addressed postcard completed by participant;

NOTE: VA and foreign sites may be exempt from submitting PHI for study purposes, depending on their local policy. Other sites may request exemption and will be considered on a site-by-site basis. See Sections 8.2 and 8.3 for additional details.

8.1.1.4 Collect ECG (originals are preferred, but color photocopies are sufficient; electronic submission or color photocopies by mail are sufficient), if performed within 30 days prior to diagnostic imaging; if not performed, unavailable, or completed within the 30 days prior to diagnostic imaging, the ECG should be completed at the time of diagnostic imaging (e.g., in the case of ECG during SPECT MPI);

8.1.1.5 Collect laboratory results, only if available, including LDL, HDL, and HbA1c (previous 28 days for each, or if available prior to diagnostic imaging) and highest-level troponin (previous 48 hours, or if available prior to diagnostic imaging);

8.1.1.6 Administer SAQ and SF-36 for participant to complete (assistance should be limited; research staff will be trained on appropriate responses to participant queries)—US sites only. Foreign sites are exempt from the QoL component of the trial.

8.1.1.7 Administer lifestyle questions (research staff will ask questions of participant to collect self-reported data).

8.1.2 Phase 2: Registration and Randomization

- 8.1.2.1** Register the eligible participant;
- 8.1.2.2** Receive randomization assignment to Group A (CCTA) or Group B (SPECT MPI/ICA);
- 8.1.2.3** Schedule CCTA or SPECT MPI/ICA to be completed within 2 weeks of consent.

8.1.3 Phase 3A: Group A—CCTA

- 8.1.3.1** Pre-treatment with heart-rate lowering drug and/or nitroglycerin depending on participant heart rate and imaging equipment (see Section 9.1.2.1);
- 8.1.3.2** Introduce intravenous (IV) catheter for contrast administration;
- 8.1.3.3** Administer iodinated contrast agent;
- 8.1.3.4** Complete CCTA per protocol specifications (see Section 9.1);
- 8.1.3.5** Assess for AEs.

NOTE: Should the left main be un-evaluable, the CCTA will be considered positive for study analysis. The research team recommends and encourages rescanning with CCTA using an additional bolus of contrast if possible, and otherwise leaves it to the treating physician to determine further diagnostic assessment. Data from both imaging studies will be collected.

8.1.4 Phase 3B: Group B—SPECT MPI/ICA

- 8.1.4.1** SPECT MPI and, if necessary based on extent of reversible defect, diagnostic ICA completed per institutional standard practices (see Section 9.2).

NOTE: Should the examination be un-evaluable, the SPECT MPI will be considered positive for study analysis. The research team recommends and encourages reviewing rest and stress images post-acquisition for quality before the participant is released from the scanner and rescanned, if necessary. For STRESS TI-201 imaging: If motion compromises a study, the benefit of rescanning is uncertain; the treating physician should determine further diagnostic assessment. Data from both imaging studies will be collected.

8.1.5 Phase 4: Post-CCTA or SPECT MPI/ICA, Treatment as Appropriate

- 8.1.5.1** Depending on diagnostic imaging study results, participant is prescribed OMT (see below), goes to diagnostic ICA for additional assessment, or may be discharged. All participants will be followed per Section 8.2.
 - Participants with CCTA findings of a stenosis $\geq 50\%$ in diameter will be treated with OMT unless the stenosis is in the left main coronary artery.
 - Participants with moderate-severe ischemia by SPECT MPI ($\geq 10\%$ reversible perfusion defect) or evidence of TID accompanied by ECG changes of ischemia will undergo diagnostic ICA to confirm no significant left main CAD ($< 50\%$ stenosis).

stenosis) and that the diagnosis is not a false positive. Participants with a stenosis \geq 50% in diameter on diagnostic ICA will be directed to OMT.

- Un-evaluable proximal and mid segments will be regarded as being positive for CAD for the purposes of the study and the participant directed to OMT.
- Participants with left main CAD (\geq 50% stenosis) found on CCTA will undergo diagnostic ICA.
- Participants with CCTA findings of stenosis $<$ 50% in diameter; SPECT MPI findings of reversible ischemia $<$ 10% of the myocardium; or SPECT MPI findings of \geq 10% reversible perfusion defect or evidence of TID accompanied by ECG changes of ischemia followed by ICA findings of $<$ 50% stenosis will be treated per institutional standard of care or discharged and followed per protocol for MACE and revascularization.

See also Figure 1 in Section 4.0.

8.1.5.2 Optimal Medical Therapy

OMT will be determined by the treating cardiologist, and a medical regimen to achieve OMT will be required. Specific medications, however, will not be required by the ACRIN 4701 RESCUE protocol. The following descriptions are based on the regimen used in the COURAGE trial³ and lipid lowering targets defined by the National Heart, Lung, and Blood Institute.⁴¹ The descriptions below should be considered a list of options to be applied to participants as appropriate to the individual participant's cardiac health requirements. The initial regimen and changes to the regimen (by participant or physician prescription) will be reported to ACRIN throughout the trial.

1. An antiplatelet such as aspirin, 81 to 325 mg each day, and/or clopidogrel, 75 mg per day if participant is aspirin intolerant, or prasugrel.
2. A statin such as atorvastatin, pravastatin, or rosuvastatin with target LDL cholesterol of 70 mg/dL.⁴¹
3. An anti-hypertensive/anti-anginal beta blocker, such as metoprolol, carvedilol, or atenolol, with a blood pressure goal of $<$ 130/80 mm Hg and reduced CCS angina class.
4. An additional anti-hypertensive, such as amlodipine or an ACE-inhibitor, as needed.
5. An additional anti-anginal, such as amlodipine or long-acting nitrate, as needed.
6. An ACE-inhibitor (lisinopril) or angiotensin II receptor antagonist (Losartan) if ACE-inhibitor not tolerated, for all participants with left ventricular ejection fraction \leq 40%.
7. Attempt to raise HDL cholesterol, $>$ 40 mg/dL in men and $>$ 50 mg/dL in women, with exercise, extended release niacin, or fibrates alone or in combination once LDL level is at goal.
8. Medications for diabetes control, with target HbA1c $<$ 7%.
9. Smoking cessation.
10. Exercise regimen appropriate to diagnosis.
11. Nutritional/dietary modification.

Adherence to the OMT regimen will be documented on CRFs during participant follow up and from medical records, including those from referring physicians.

8.1.5.3 Defining Worsening Angina and Subsequent Therapeutic Approaches

If a participant develops worsening or persistent angina after randomization, the following management guidelines will be used:

- a) For all but CCS Class IV participants, intensify medical therapy (increase doses of anti-ischemic drugs and/or add additional agents as needed clinically); if the participant subsequently stabilizes to CCS Class I to II, continue medical therapy indefinitely;
- b) If symptoms do not stabilize, or worsen to CCS Class III after 4 to 6 weeks of maximum medical therapy, it is recommended that the participant should undergo ICA for evaluation for revascularization.

8.2 FOLLOW UP: Telephone Contacts, Quality of Life Mailings, and Medical Records

Abstraction

8.2.1 Telephone Contact (2 to 6 Contact Time Points for Up to 24 Months)

Follow up at the site level will comprise telephone participant/proxy contact at 2 weeks and 2 months after enrollment **only** for participants who have positive cardiac findings on diagnostic CCTA or SPECT MPI. All participants (or their proxies) will be contacted by telephone for additional medical information at 6-month intervals after enrollment for up to 24 months.

Positive cardiac findings on diagnostic testing are defined as:

- 1) $\geq 50\%$ stenosis on CCTA or un-evaluable left main, or proximal and mid segments of all other epicardial arteries (right coronary artery, left anterior descending artery, or left circumflex artery); and
- 2) $\geq 10\%$ reversible defect on SPECT MPI or evidence of TID accompanied by ECG changes of ischemia.

Participants with positive cardiac findings on diagnostic testing will be contacted a minimum of four (4) times (2 weeks, 2-, 6-, and 12-months after enrollment). All participants will be followed for a minimum of two (2) time points (6- and 12-months) and a maximum of six (6) time points (2-weeks, and then at 2-, 6-, 12-, 18-, and 24-months) due to funding and trial timeline limitations. The following table presents this information again.

Participant Cohort	Minimum Follow-Up Time Points	Maximum Follow-Up Time Points
Only Participants With Positive Cardiac Findings on Diagnostic Testing	2 Weeks, 2 Months, 6 Months, and 12 Months After Enrollment	2 Weeks, 2 Months, 6 Months, 12 Months, 18 Months, and 24 Months After Enrollment
All Participants	6 Months and 12 Months After Enrollment	6 Months, 12 Months, 18 Months, and 24 Months After Enrollment

Ideally, contact to complete each follow-up CRF should occur no later than 14 days after each time point. However, this is a timing guideline. The form related to 6-month follow up, for example, should not be completed until contact has been made (four [4] attempts) or other confirmation of participant's vital status (e.g., record review or known death) has

been verified. As research staff attempt to make contact, a follow-up contact log will be maintained to document attempted contact.

8.2.1.1 Contact participant via telephone to obtain additional medical information. At each follow-up time point, the following information will be collected to assess angina, CAD, health status, and healthcare utilization:

- 8.2.1.1.1** Canadian Cardiovascular Society Angina Status;
- 8.2.1.1.2** Self-report for MACE, stroke, or revascularization;
- 8.2.1.1.3** Adherence to OMT;
- 8.2.1.1.4** Health status/medical utilization:
 - Outpatient providers;
 - Emergency departments;
 - Hospitals;
 - Specifically whether care was cardiac-related or related to care for incidental findings from the diagnostic assessment;
- 8.2.1.1.5** Healthcare-related time and travel;
- 8.2.1.1.6** Lifestyle questions (at 12-month follow-up only).

8.2.1.2 If the participant or proxy reports MACE or revascularization, the site then will conduct a review of the participant's medical records or the SSDI. RAs will need to prepare medical records per institutional standard practice to be delivered to ACRIN for adjudication in cases of MACE and revascularization (see Section 6.3.3).

8.2.1.3 Four (4) attempts should be made by research staff to contact the participant or proxy at each follow-up time point before completing the follow-up form. If participant vital status (e.g., known death) is verified, the site RA may complete the follow-up form. Attempts will be documented in a follow-up contact log. Participants should not be considered "lost to follow up" until the final month of follow up for the last participant who was enrolled.

8.2.1.4 If a participant or proxy is not contacted at the 6-month time point, for example, but is contacted at the 12-month time point, health information will need to be queried for the entire time period. However, the exception is administration of the lifestyle questionnaire—if contact cannot be made at the 12-month follow-up time point, the lifestyle questionnaire will not be administered at the 18- or 24-month follow up.

8.2.1.5 Medical record collection will be triggered by a combination of positive CCTA or SPECT MPI/ICA and/or participant self-report of MACE, stroke, revascularization, cardiac-related health care, or care for incidental findings from their study-related diagnostic evaluation. Medical record collection will be coordinated by the site RA or by ACRIN, depending on local institutional policy on release of PHI. Table 5 presents an overview by site type of the adjudication, abstraction, and QoL procedures.

Table 5. Overview of Adjudication, Abstraction, and QoL Procedures By Site Type			
	Standard non-VA US sites	US VA sites	Foreign sites
Records for adjudication (all MACE and revascularizations)	Sites send de-identified medical records to ACRIN upon request from ACRIN Data Management	Sites send de-identified medical records to ACRIN upon request from ACRIN Data Management	Sites send de-identified medical records to ACRIN upon request from ACRIN Data Management
Records for medical record abstraction for outcomes and for cost-effectiveness analysis (every 6 months only after participant-reported cardiac care)	Participant Contact Information sheets faxed to ACRIN. ACRIN obtains medical records from HIM departments or site coordinators, de-identifies, and prepares records for abstraction/coding	Sites shall obtain their own medical records and those of outside providers and forward de-identified records to ACRIN for subsequent abstraction/coding	Sites trained to abstract minimal required data themselves
Quality-of-Life (QoL) questionnaires (SF-36 and SAQ at baseline and at 1 year among a subset of participants)	Participant Contact Information sheets faxed to Brown. Brown coordinates distribution and collection of QoL at 1-yr follow up	VA sites may administer the QoL questionnaires to participants themselves. The VA sites will not be required to send Brown the Participant Contact Information sheets	Not done —foreign sites are exempt from conducting the QoL component of the trial
SSN for linking with Medicare data	SSN on Participant Contact Information sheets at ACRIN. Will be accessed only if needed for the cost-effectiveness analysis	Not done	Not done

8.2.2 QoL Questionnaires (At 12-Month Follow Up for Subset of Participants Only)

Depending on local policy for release of PHI, administration of the SAQ and SF-36 at 12 months will be coordinated by the site or by the ACRIN Outcomes and Economics Unit (AOEU) located within the ACRIN Biostatistics Center at the Brown University Center for Statistical Sciences, Providence, RI. Foreign sites are exempt from the QoL (quality-of-life) component of the trial.

Sites coordinating the QoL component of the trial will be responsible for follow up with the participant to encourage completion. For participants whose questionnaires are administered by the AOEU, the AOEU will maintain a database to monitor accrual of study participants for the QoL studies and the receipt of mailed questionnaires and telephone contacts. The originals will remain at Brown University.

8.2.2.1 A random sample of US participants from each arm of the trial will be selected for accrual into the QoL sub-study and will be asked to complete the 12-month follow-up questionnaires.

8.2.2.2 For sites able to release participant PHI only, Participant Contact Information Forms need to be faxed from the sites to the AOEU, where they will be received on a secure fax machine dedicated to studies conducted by the AOEU. The information will be entered in the AOEU database. AOEU personnel will contact the participant using participant contact information stored in the AOEU database.

8.2.2.3 For sites unable to release participant PHI only, site RAs may administer the questionnaires by mail (preferred; see procedures below), phone, or in-person. Site personnel will be responsible for management and administration of QoL tools if they choose not to have the AOEU assume this responsibility.

8.2.2.4 For participants whose questionnaires are administered by AOEU, AOEU personnel will mail copies of QoL tools to participants along with pre-addressed, stamped envelopes for return mailing to the AOEU. Participants will be provided with a toll-free number (which is answered by the AOEU or site RA) should they require assistance with reading questionnaires.

8.2.2.5 If the questionnaires are not received within 10 working days of the date of the mailing, the AOEU or site RA will telephone the participant to determine whether the questionnaires were received and completed. Participants who did not receive the questionnaires will have additional questionnaires sent by mail after confirming the correct mailing address. If questionnaires were received by the participant but never completed, the participant will be asked to complete and return them.

8.2.2.5 If questionnaires are not returned within 20 working days thereafter, the AOEU or site RA will attempt to complete the questionnaires in a telephone interview. Telephone interviews will be conducted only as a final measure to avoid any biases introduced by differences in the method of administration of the questionnaires, and the mode of administration of all such questionnaires will be documented in the trial database. The AOEU or site RA will not attempt to interpret a question; training will be provided to help ensure that the AOEU and site RAs facilitate completion of the QoL questionnaires in a standardized fashion.

8.3 MEDICAL RECORD ABSTRACTION

8.3.1 Triggering Medical Record Abstraction

8.3.1.1 Medical chart abstraction will be triggered by participant responses during telephone follow up. The selection process is detailed in Figure 2 (see Section 4.0) and described below.

8.3.1.2 All records relating to the following will be abstracted:

1. MACE, stroke, and revascularization events;
2. Medical care for cardiac issues;
3. Medical care for OMT, to include any results of monitoring of targets for OMT, such as LDL/HDL, HbA1c, blood pressure, and heart rate, if available;
4. ECG from follow-up cardiac-care visits (color photocopies are sufficient and may be submitted electronically or by mail);

5. Medical care related to incidental findings on the CCTA or SPECT MPI examinations. If during monitoring of the rate of incidental findings, the incidence is high, medical record abstraction may be conducted for only a subset of participants.

8.3.1.3 A separate document will be provided to the sites to explain their responsibilities in the process of medical record abstraction. Medical records will be de-identified to protect the identity of the participant. Participant informed consent will be obtained prior to trial participation to allow research staff to procure any medical records that need to be abstracted from institutions outside of the consenting institution (e.g., collection of medical records from physicians treating incidental findings).

8.3.2 Responsibilities and Participant Protections

8.3.2.1 Requests for medical records for adjudication and abstraction will be produced and mailed from ACRIN Headquarters based on response to follow-up contact and results of the diagnostic tests.

8.3.2.2 Medical records abstraction and coding will be performed by a single central medical record abstraction company. Centralizing the abstraction process with a single group of abstractors simplifies quality control, ensuring consistent and reliable coding of medical conditions and care.

8.3.2.3 All abstraction will be done directly onto electronic forms. These computer forms incorporate range checks and International Classification of Disease (ICD) and Current Procedural Terminology (CPT) look-ups which ensure that data are as error-free as possible.

8.3.2.4 Foreign sites will be expected to abstract medical records pertaining to the primary aim and are exempt from the QoL questionnaires component of the trial.

8.4 OFF-STUDY CRITERIA

This is an intent-to-treat trial; should a participant be registered, randomized, and subsequently be unable to complete the diagnostic test for any reason, the reason will be captured and the participant will be treated per the decision of the treating cardiologist as appropriate to the circumstance. The participant will remain on trial and will be followed per protocol.

8.5 STUDY PROCEDURES TABLE: SITE ACTIVITIES

Study Procedure	INITIAL VISIT AND ASSESSMENT			FOLLOW UP*†: 2 Weeks, 2 Months, and Then 6-Month Intervals From Enrollment for Up to 24 Months
	Phase I: Baseline Assessment	Phase 2: Registration and Randomization	Phase 3A or 3B: SPECT MPI/ICA or CCTA Within 2 Weeks of Consent (Per Randomization)	
Informed Consent Form	X			
Screening/Eligibility Review	X			
Medical History	X			
CCS Classification	X			X
Assess for CAD and Comorbidity	X			
Pregnancy Test, as Appropriate	X			
Serum Creatinine for GFR Measure (If Needed)	X			
Collect Contact Information	X			
Collect or Perform ECG (ECG Can Be Completed at Baseline Within 30 Days Prior to Diagnostic Imaging or at the Time of Diagnostic Imaging)	X			X (If Performed During Follow-Up Cardiac Visits)
Collect HbA1c, HDL, LDL, and Troponin Values (Only if Available; See Section 8.1.1.5)	X			X
Administer Questionnaires (QoL at US Sites Only)	X			
ACRIN Web Registration		X		
Randomization to CCTA or SPECT MPI		X		
GROUP A ONLY (CCTA)				
Pre-Medication, As Needed			X	
Intravenous Catheter and Iodinated Contrast			X	
Agent Administration			X	
CCTA			X	
GROUP B ONLY (SPECT MPI/ICA)				
SPECT MPI/ICA (per institutional standard)			X	
Prescribe Optimal Medical Therapy or Move to Invasive Coronary Angiography (as Appropriate to Diagnostic Results Per Protocol)			X	
Contact Via Telephone (See Section 8.6 Below)				X
Subset of Participants Complete QoL Questionnaires				X (at 12 Months)
Assess for AEs			X (CCTA Only)	

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- * ONLY participants with positive cardiac findings on diagnostic assessment will be contacted at 2 weeks and 2 months. Questions during participant contact at 2 weeks and 2 months will be limited to MACE, stroke, and revascularization. **All** participants will be contacted at 6-month intervals after enrollment. The 12-month follow-up contact will include an additional lifestyle questions.
- † Medical record collection for abstraction of medical care utilization and information used to obtain costs will be performed based on participant self-report during 6-month interval telephone follow up for MACE, stroke, cross-over to revascularization, cardiac-related care, and care for incidental findings as outlined in Section 8.3.

8.6 STUDY PROCEDURES TABLE: PARTICIPANT ACTIVITIES
(NOT ALL PARTICIPANTS WILL BE FOLLOWED FOR 24 MONTHS)

PARTICIPANT ACTIVITIES	Baseline	2 Weeks [‡]	2 Months [‡]	6 Months	12 Months	18 Months	24 Months
Entry Imaging Examination							
CCTA or SPECT MPI/ICA							
Within 2 Weeks After Consent	X						
Telephone Contact (In Person at Baseline)							
Confirm Contact Information and Collect Contact Information for Treating Physicians	X	X	X	X	X	X	X
Canadian Cardiovascular Society Angina Status	X			X	X	X	X
Risk Factors for CAD	X						
Diamond Forrester CAD Risk Analysis	X						
Charlson Comorbidity	X						
CAD-Specific Morbidity	X						
MACE	X	X	X	X	X	X	X
Stroke	X	X	X	X	X	X	X
Revascularization	X	X	X	X	X	X	X
Adherence/Changes to OMT				X	X	X	X
Health Status/Medical Utilization				X	X	X	X
Healthcare-Related Time and Travel				X	X	X	X
Questionnaires[§]							
SF-36 and Seattle Angina QoL Tools	X				X		
Lifestyle Questions	X				X		

[‡] ONLY participants with positive cardiac findings on diagnostic assessment will be contacted at 2 weeks and 2 months. **All** participants will be contacted at 6-month intervals after enrollment.

[§] Questionnaires will be completed in person at baseline. Completion of questionnaires at 12-month follow up will be coordinated through the site or the ACRIN Outcomes and Economics Unit (see Section 8.2.2 for details) and will include only a subset of participants. Foreign sites are exempt from administering the QoL tools.

9.0 IMAGING PROTOCOL

9.1 CCTA Imaging Requirements and Parameters

The CCTA core lab, the Cardiovascular Imaging (CVIC) Core Laboratory at the Massachusetts General Hospital, will assist ACRIN in the development of general and specific protocol recommendations. CCTA images from the first two study subjects at each site will be reviewed by the CCTA core lab, as well as a random sample of 10% of all cases thereafter. The ACRIN 4701 RESCUE Imaging Manual detailing imaging recommendations is available at www.acrin.org/RESCUE_imagingmaterials.aspx.

During the 18-month enrollment period, clinical interpretation of all tests will be performed by qualified local readers at qualified testing sites. This interpretation will inform patient management decisions and will be captured on test-specific CRFs using national reporting guideline standards and multimodality common data elements.^{48,49}

9.1.1 CCTA and ECG Gating

Participants will undergo contrast-enhanced CCTA following randomization to Group A for evaluation of suspected CAD. For CCTA, both retrospective and prospective ECG gating will be permitted. If retrospective ECG gating is performed, tube modulation is required. Calcium scoring is optional.

9.1.2 Image Acquisition Recommendations

The image acquisition protocol consists of the following two (2) steps:

- Image acquisition takes approximately 20 minutes;
- The participant will be transported to the CCTA suite and returned by qualified study personnel.

9.1.2.1 Participant Preparation

Participants will be instructed and trained in breath holding. ECG electrodes will be mounted on the chest to enable co-registration of image acquisition and ECG signal. With the exception of sites with a dual-source CT (DSCT) scanner, all participants with a heart rate > 65 beats per minute will receive a heart-rate lowering drug (usually a beta blocker), intravenously and/or orally, to optimize image quality and sublingual nitroglycerin to maximally dilate the coronary arteries unless their systolic blood pressure is < 100 mm Hg or other contraindications are present. At sites with a DSCT scanner, due to the improved temporal resolution, heart-rate lowering drugs are not required, and participants may receive only sublingual nitroglycerin if there are no contraindications.

9.1.2.2 Image Acquisition

All image acquisitions will be performed using a breath hold in inspiration. The CCTA imaging protocol will start with a topogram of the chest permitting the localization of the position of the heart. If standard care at the institution, a prospectively-gated low-dose non-contrast CT scan (120 kVp, 320 mA) to assess coronary calcium will be optional. Image acquisition will conclude with a contrast-enhanced CT scan to evaluate the presence of coronary atherosclerotic plaque and significant coronary artery stenosis.

For this scan, 80 mL of contrast, on average, will be injected as a bolus at a rate of 5 mL/s to attenuate the lumen of the coronary arteries, the aorta, and the left ventricle. Appropriate timing of the contrast bolus will be ensured by either the determination of the transit time or the bolus trigger technique.

Using ECG gating, the tube current will be reduced during systole according to each manufacturer's specific protocol to minimize radiation exposure. Sites may perform this with either prospective or retrospective ECG-gating. If retrospective gating is performed, the scan must be performed with radiation dose modulation or a minimum radiation dose protocol to reduce the tube current during systole.

The effective radiation exposure is between 5 and 12 mSv for a contrast-enhanced scan. See Section 9.3.1.3 for a description of patient-safety monitoring for radiation exposure.

9.1.2.3 Image Reconstruction

At least one data set that demonstrates the least cardiac motion will be reconstructed (a minimum 0.8 mm thick axial images, 50% overlap) from the contrast-enhanced CCTA scan for the detection of coronary plaque and stenosis (pixel matrix: 512 x 512, FOV: 25 cm).

9.1.2.4 Image Submission

The following should be included in the submitted data sets:

- Scout;
- Dose report;
- Calcium score series, if available;
- CCTA (1 or more phases);
- If retrospective ECG gating was used, a Multiphase series with 10 phases at 10% increments for single-source scanner or 20 phases at 5% increments for a dual-source scanner;
- If routinely reconstructed and assessed, a Full Field of View (FOV) series for incidental findings.

9.1.3 CCTA Reading for Stenosis

Central CCTA reads will be performed in the first two (2) cases from each site and subsequently in a random sample of 10% of cases to assess for stenosis. Local interpretation of the CCTA examination will determine patient care. Assessment will include each of the major epicardial vessels (left main, left anterior descending, left circumflex, and right coronary artery) and their side branches. Local CCTA reading CRFs will be used later for calculation of a modified Duke Prognostic Index and other indices. Central reader interpretations at the CCTA core lab (10% of CCTA examinations will be read centrally) will be used to assess the quality of the data obtained from local CCTA interpretations. A modified Duke Prognostic Index and other myocardial jeopardy scores based on the local read will be used, along with the outcomes data, to create a revised jeopardy score as described in Section 15.2.1.

9.1.3.1 Coronary Artery Stenosis

To allow a modified Duke Prognostic Index and other myocardial jeopardy/risk scores to be applied, stenoses—when present—will be graded as:

- None (0%);
- Very Mild (1% to 29% diameter);
- Mild (30% to 49% diameter);
- Moderate (50% to 69% diameter); or
- Severe ($\geq 70\%$ diameter).

Non-diagnostic coronary artery (proximal and mid) segments will be considered positive.

For CCTA questions related to image acquisition or interpretation, sites may contact the CCTA core lab at Massachusetts General Hospital via email or phone.

E-mail: rescuehelp@partners.org

Phone: 408-6RESCUE (408-673-7283)

9.2 SPECT MPI Recommendations

The SPECT MPI core lab at Tufts Medical Center, will assist ACRIN in the development of general and specific protocol recommendations. SPECT MPI images from the first two study subjects at each site will be reviewed by the SPECT MPI core lab at Tufts Medical Center, as well as a random sample of 10% of all cases thereafter. SPECT MPI studies will be performed per institutional standards in accordance with best practice standards, as delineated in the imaging guidelines of the American Society of Nuclear Cardiology (ASNC), by appropriately credentialed physicians. The ACRIN 4701 RESCUE SPECT MPI Imaging Acquisition Recommendations form is available online at www.acrin.org/RESCUE_imagingmaterials.aspx.

During the 18-month enrollment period, clinical interpretation of all tests will be performed by qualified local readers at qualified testing sites. This interpretation will inform patient management decisions and will be captured on test-specific CRFs using national reporting guideline standards and multimodality common data elements.^{48,49}

9.2.1 SPECT MPI Acquisition Recommendations

All site protocols will be reviewed and approved by the ACRIN core lab prior to the enrollment period in order to ensure optimal imaging techniques are performed. Participants will undergo radionuclide SPECT MPI following randomization to Group B for evaluation of suspected CAD. All image acquisitions for a particular participant during one visit will be performed on the same camera/computer system.

9.2.2 Recommended Method of SPECT MPI Interpretation

It is recognized that there are many appropriate ways to report findings for SPECT MPI, but in general it will be recommended that the report elements correlate with the following categories:

- 1) Normal scan;
- 2) Infarct (location) without inducible ischemia;
- 3) Inducible ischemia $< 10\%$ myocardium (location);
- 4) Inducible ischemia $\geq 10\%$ myocardium (moderate to severe ischemia, location);

- 5) Left ventricular function with quantitative ejection fraction:
Normal, global dysfunction, or regional dysfunction;
- 6) Uninterpretable study.

In order for the individual sites to interpret the SPECT MPI studies in accordance with the RESCUE guideline requiring cardiac catheterization for participants with $\geq 10\%$ of the left ventricle with a reversible defect (inducible ischemia), it will be necessary for the sites to have one of the standard commercially available analytic software packages (e.g., Emory Toolbox, 4DM SPECT Corridor, Cedars-Sinai QPS, etc.).

The ACRIN core lab will review one (1) sample SPECT MPI study from each site. Feedback from this sample study will be provided on an as-needed basis to discuss image quality issues or concerns. The feedback will occur via email and/or telephone call to the site's technologist during the study start-up period, prior to participant enrollment. During the trial, the SPECT MPI core lab at Tufts Medical Center will perform quality control on the first two (2) cases from each site and then a random sample of 10% of the SPECT MPI studies per site, with feedback provided as needed to the sites regarding image quality and analysis.

For Secondary Aim I, Section 3.2.1, determining a predictive SPECT MPI index, local reads of the SPECT MPI examinations will be performed to determine the percent reversible perfusion defect.

For SPECT MPI questions related to image acquisition or interpretation, sites may contact the SPECT MPI core lab at Tufts Medical Center via email, phone, or pager, to the attention of Deb Kinan, RTN.

Email: dkinan@tuftsmedicalcenter.org

Phone: 617-636-2357

SPECT Core Lab Hot Line: 617-604-4848 (pager)

9.3 Quality Control for CCTA and SPECT MPI Images

9.3.1 Ongoing Technical QC for CCTA and SPECT MPI Acquisition During Enrollment

9.3.1.1 Technical QC. ACRIN imaging research personnel will perform ongoing technical quality control (QC) review of all 4300 tests in RESCUE for quality and completeness of the diagnostic test dataset, adequate test protocol, proper data/image reconstruction, minimal radiation exposure for CCTA and SPECT MPI.

9.3.1.2 Site Communications. Quality improvement communications to sites will occur on an ongoing basis.

9.3.1.3 Participant Safety and Radiation Exposure. In addition, for participant safety, the ACRIN core lab will conduct a 100% QC of radiation exposure in CCTA and SPECT MPI. For the study-related CCTA imaging, sites will be contacted should radiation exposure exceed a mean of 15 mSv, to be assessed monthly by site and sites over the mean of 15 mSv based on the last 5 cases will be contacted by trial PIs. Sites whose performance repeatedly exceeds this criterion after repeated protocol review may be recommended to the ACRIN PDRC department for QA review and possible termination.

9.3.2 Ongoing QA During Enrollment: Central Reads

9.3.2.1 Expert Central Reads. The CCTA and SPECT MPI core labs will perform expert central reads (blinded to the local interpretations) and review overall image quality in approximately 10% of participant cases. To ensure protocol compliance early on and to account for sites with low accrual, the first two studies and a random sample of 10% of the remaining studies from each site will be read in each modality to assess quality of local reads. These 10% will be selected by block randomization stratified by testing site and test modality.

9.3.2.2 Site Communications. Feedback to sites will occur on two levels:

- 1) Reports of site data benchmarked against all other sites including severity of disagreement; and
- 2) Re-education and training of sites and readers as necessary.

9.4 Image Submission

Each participating site is required to submit all acquired CCTA and SPECT MPI images of study participants to the ACRIN core laboratory. The image transfer method is via TRIAD-OA, a software application that includes a rich client and a site server (DICOM file cache). ACRIN will provide TRIAD software for electronic image submission and anonymization to participating institutions. Images can be transferred to the ACRIN central archive by inserting a CD or DVD in the drive of a PC with the TRIAD rich client installed. The TRIAD software anonymizes, encrypts, and applies lossless compression to the images before they are transferred to the ACRIN image archive in Philadelphia, PA.

Prompt submission of all image data within five (5) days of completion of imaging is essential to ensure adequate QC. Images should be transmitted along with an Imaging Transmittal Worksheet (ITW) that can be found on the ACRIN 4701 RESCUE web site at: www.acrin.org/RESCUE_imagingmaterials.aspx. For support in sending the images via the Internet using TRIAD, contact the representatives of the core lab via email at Triad-Support@acr.org or by phone: 215-940-8820.

Instructions for image submission and anonymization, as well as information regarding QC of images, are available at www.acrin.org/RESCUE_imagingmaterials.aspx.

10.0 ADVERSE EVENTS REPORTING

10.1 Definition of Adverse Event

An **Adverse Event** (AE) is any untoward medical occurrence in a participant that does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory or physiological finding), symptom, or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). Abnormal results of diagnostic procedures are considered to be AEs if the abnormality:

- Results in study withdrawal
- Is associated with a serious adverse event (SAE)
- 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

10.2 Definition of Serious Adverse Event

A **Serious Adverse Event** (SAE) is defined as any untoward medical occurrence that:

- Results in death, or
- Is life-threatening (at the time of the event), or
- Requires inpatient hospitalization or prolongation of an existing hospitalization, or
- Results in persistent or significant disability or incapacity, or
- Is a congenital anomaly/birth defect, or
- Requires intervention to prevent any of the above, per the investigator/sponsor.

Life-Threatening Adverse Event: A life-threatening AE is any adverse event that places the study participant, in the clinical opinion of the investigator, at immediate risk of death.

10.3 Adverse Event Grading

Grade denotes the severity of the AE. An AE is graded using CTEP Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, or the following categories (if the term does NOT appear in the CTEP CTCAE v 4.0):

- 1 – Mild
- 2 – Moderate
- 3 – Severe
- 4 – Life-threatening or disabling
- 5 – Fatal

10.4 Adverse Event Attribution

Attribution determines whether an AE is related to a study treatment or procedure.

Attribution categories are:

- Definite – AE is ***clearly related*** to the study treatment or procedure.
- Probable – AE is ***likely related*** to the study treatment or procedure.
- Possible – AE ***may be related*** to the study treatment or procedure.
- Unlikely – AE is ***doubtfully related*** to the study treatment or procedure.
- Unrelated – AE is ***clearly NOT related*** to the study treatment or procedure.

10.5 Potential Expected and Unexpected Adverse Events

AEs may be **expected** or **unexpected**:

- An **expected AE** is one that is described in the protocol, the ICF, or the investigator's clinical brochure.
- An **unexpected AE** is one that has not been described in the protocol, the ICF, or the investigator's clinical brochure.

10.6 Expected Study-Related Adverse Events

Any AE that is a result of standard of care practice (e.g. related to stress testing or cardiac catheterization) will be reported and managed per the institution's policies and procedures.

Only AEs that are considered **possibly**, **probably**, or **definitely** related to the study-related CCTA scan procedures require reporting to ACRIN. Please refer to your local IRB's policies regarding AEs.

10.6.1 Expected Adverse Events Associated with Iodinated Contrast Agent

Likely

- Flushing;
- Pallor.

Rare

- Low-grade fever;
- Nausea;
- Vomiting;
- Hives;
- Rash;
- Extravasation.

Rare, but potentially life threatening

- Kidney failure;
- Allergic-like reaction (including anaphylaxis or asthma).

A history of contrast allergy excludes potential participants from this study. The injection may cause discomfort and irritation. The iodine-containing contrast used for CT scanning may cause significant contrast reactions in about one in a thousand (1:1,000) participants. Severe reaction is seen in as low as 4:10,000 to as high as 2:1,000 depending on the type of contrast used. Fatal reactions are exceedingly rare and have been reported in 1:170,000 irrespective of the type of contrast used. The risk of death is less than 1:10,000.

10.6.2 Expected Adverse Events Associated with IV Needle Placement

- Hemorrhage (hematoma at the injection site);
- Infection (catheter related infection) at the injection site;
- Minor discomfort/pain;
- Fainting;
- Bleeding;
- Bruising.

10.6.3 Expected Adverse Events Associated with Radiation Risks

The radiation dose from a \geq 64 slice CCTA study of the coronary arteries varies widely depending upon patient size, scanner used, technique used (prospective triggering vs. retrospective gating), and the use of available methods for dose reduction. All studies performed for this protocol will be performed with application of all available methods for dose reduction, including but not limited to:

1. ECG-modulated tube current reduction during systole to at least 20% of the nominal value;
2. Z-axis and in-plane topogram density modulated tube current variation (e.g. CareDose4D, SmartDose, etc.);
3. Low kVp acquisition for smaller participants, if technique is available on scanner;
4. Prospective ECG-triggered technique for selected patients at sites with relevant hardware, software, and experience with this technique.

The radiation dose associated with this protocol will range from approximately 5 to 12 mSv. Recent publications have modeled the risk of cancer induction related to this dose using the linear no-threshold assumption. These studies have suggested that for young women who receive doses at the highest end of the range above, there would be an approximately 1% to 2% increase in their lifetime risk of cancer, with lower increases in cancer risk seen for older women and all men. However, this range of doses is similar to that received during other studies performed for evaluation of suspected CAD, including coronary catheterization (4 to 10 mSv) and stress myocardial perfusion imaging using SPECT MPI (10 to 20 mSv).^{50,51}

10.6.4 Expected Adverse Events Associated with CCTA Scan

- Reactions to medications administered as part of the CCTA procedure (e.g., heart-rate lowering drugs, nitroglycerine), including hypotension, syncope, headache, arrhythmia, palpitations;
- AEs related to procedures or treatments following incidental findings from the CCTA;
- *Rare:* Malfunction of worn or implanted electronic medical devices. It has been reported by the FDA that CT scans may rarely cause the malfunction of electronic implanted medical devices, including drug pumps and pacemakers.

10.6.5 Expected Adverse Events Associated with Standard Practice

ACRIN will not collect any AEs related to standard-of-care SPECT MPI or ICA procedures. Sites will follow institutional policies and procedures for any reported side effects for procedures other than the experimental CCTA component of the trial.

10.7 Recording of Adverse Events

Prompt reporting of AEs is the responsibility of each investigator, clinical RA, and/or nurse engaged in clinical research. Please refer to Sections 10.8 and 10.9 for specific details about reporting. Anyone uncertain about whether a particular AE should be reported should contact ACRIN Headquarters at 215-574-3150 for assistance. However, an AE report should be submitted if there is a reasonable suspicion that the AE may be related to the study procedures.

Routine reporting is defined as documentation of AEs on source documents and the AE CRF, and submission to ACRIN for preparation of a report for RESCUE DSMC review, and the final study report.

Expedited reporting is defined as immediate notification of ACRIN within the specified timeframe outlined in the protocol. Routine reporting requirements also apply.

Information on all serious and non-serious, expected and unexpected AEs considered **possibly, probably, and/or definitely** related to the study components of the ACRIN 4701 RESCUE trial with the severity level of grades 3, 4, or 5 should be recorded immediately into the source document (e.g. [AE Log](#) and/or progress notes of the study participant's chart) and retained at the site. These AEs will also be recorded in the AE CRF and reviewed by the site principal investigator in real time to determine grade and attribution of the event. If the AE meets the criteria for serious and requires expedited reporting, an ACRIN SAE Report will be completed (refer to Section 10.9 for detailed instructions).

AEs already documented in an AE CRF (i.e., at a previous assessment) and designated as 'ongoing,' should be reviewed at subsequent visits as necessary. If these have resolved, the documentation in the AE CRF should be completed including an end date for the event and not the date of the visit. If an adverse experience increases in frequency or severity during a study period, an up-to-date record of the experience will be documented. Each AE should be followed until resolution, stabilization, or until it has been determined that the study procedure or study participation is not the cause. Any SAE that occurs after the study period and is considered to be possibly related to the study procedures or study participation should be recorded and reported immediately.

10.8 When to Report

It is the responsibility of the investigator to document all AEs (as identified in Section 10.6) that occur during the course of the study including any unexpected AEs with grades 3, 4, and 5 with attributions of **possible, probable, and definite**. At each designated visit, the investigator will evaluate for any AEs. AEs not previously documented in the study will be recorded within the study participant's chart to identify any potentially related to any study procedures. The nature of each event, date and time (when appropriate) of onset, outcome, frequency, maximum intensity, action taken, and attribution will be recorded.

10.8.1 When to Report

You must use the following AE reporting criteria for all protocol-specific AEs/SAEs:

1. Grade 3 unexpected AEs with hospitalization that are **possible, probable, or definite** require a complete SAE report to be submitted within **10 calendar days** of first knowledge of the event. **Routine reporting procedures also apply.**
2. Grade 3 expected AEs with hospitalization that are **possible, probable, or definite** will be reported by **routine reporting procedures only.**
3. Grade 3 unexpected and expected AEs without hospitalization that are **possible, probable, or definite** will be reported by **routine reporting procedures only.**
4. Grade 4 unexpected and expected AEs that are **possible, probable, or definite** require a complete SAE report to be submitted within **10 calendar**

days of first knowledge of the event. **Routine reporting procedures also apply.**

5. Grade 5 unexpected and expected AEs that are **possible, probable, or definite** will be reported via phone report within a **24-hour** time period to ACRIN by the investigator or investigator-designee. In addition, a complete SAE report is due within **10 calendar days** of the initial 24-hour telephone report. **Routine reporting procedures also apply.**
6. Expedited AE reporting must be completed within 10 working days of first knowledge of the event.

10.8.2 Assignment of grades and attribution for each AE/SAE must be completed by the site principal investigator. All AEs/SAEs should be documented in the study participant's chart and CRFs. For expedited SAE reports, a copy of the report must be kept at the site. Significant new information on any on-going SAE should be promptly reported to ACRIN.

10.9 How to Report

10.9.1 An expedited AE report requires submission to ACRIN using the ACRIN SAE Report.

10.9.2 Completed expedited reports should be sent to:

ACRIN AE Coordinator
Re: Serious Adverse Event Report
ACRIN 4701 RESCUE
1818 Market Street, 16th Floor
Philadelphia, PA 19103

10.9.3 A copy of all SAE reports should be sent to ACRIN by fax at 215-940-8819. All deaths should be reported by telephone within 24-hours of first knowledge of the event. To make a telephone report to ACRIN, call 215-717-2763, available 24 hours a day (recorder available Monday through Friday from 4:30 PM to 8:00 AM Eastern Time and on weekends).

10.9.4 All expedited AE reports should be sent to your local Institutional Review Board (IRB). Please refer to your local IRB's policies regarding AEs.

11.0 ETHICAL CONSIDERATIONS

This study is to be conducted according to International Conference of Harmonisation [ICH] guidelines, U.S. federal regulations, standards of Good Clinical Practice, and ACRIN research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or IRB 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 ACRIN before implementation of the study.

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The investigator will provide ACRIN with the institution's Federalwide Assurance (FWA) number, along with the IRB approval letter and copy of the IRB-approved ICF. The investigator will provide a copy(s) of IRB approval letter(s) for any amendment(s) and copy(s) of annual renewal(s).

All potential participants invited to join this study will be given an IRB-approved, site-specific ICF describing the study and providing sufficient information for participants to make informed decisions about their participation in this study (see Appendix I for an ICF template). The ICF will be submitted along with the protocol for review and approval by the EC/IRB. The study participant MUST be consented with the EC/IRB-approved ICF before the participant is subjected to any study procedures. The approved ICF MUST be signed and dated by the study participant or legally acceptable representative and the investigator-designated research staff obtaining the consent. Any revisions to the ICF at any time during the trial will need to be submitted to the local IRB for approval and to ACRIN PDRC for review and filing.

12.0 CONFLICT OF INTEREST

Any investigator and/or research staff member who has a conflict of interest with this study (such as patent ownership, royalties, or financial gain greater than the minimum allowable by their institution) must fully disclose the nature of the conflict of interest in accordance with [ACRIN Conflict of Interest policies](#) and applicable federal, state, and local laws and regulations.

13.0 PUBLICATION POLICY

Neither complete nor any part of the results of the study obtained under this protocol, nor any information provided to the investigator for the purposes of performing the study, will be published or passed on to any third party without the consent of the ACRIN Publications Committee. Any investigator involved in this study is obligated to provide ACRIN with complete test results and all clinical data obtained from the participants in this protocol. Investigators will follow the ACRIN Publication Policy (available online at www.acrin.org/PublicationsPolicy.aspx).

14.0 INSTITUTIONAL MONITORING AND AUDITS

The investigator will permit study-related monitoring and auditing inspections of all study-related documents by the EC/IRB, government regulatory agencies, and ACRIN. The investigator will ensure the capability for inspection of all participating sites' study-related facilities (e.g. imaging centers, satellite sites). The investigator will allocate adequate time for these activities, allow access to all study-related documents and facilities, and provide adequate space to conduct these visits.

14.1 Monitoring

Monitoring ensures protocol and regulatory compliance, participant's welfare and safety, and provides resources to sites for clarification to the protocol and guidance in completion of the CRFs. Monitoring of the protocol is implemented after the activation of the trial, and once participants have been enrolled into the study at each site. Each site will be informed when the monitoring of the protocol is implemented. Monitoring instructions will be sent to the site prior to the implementation of monitoring to aid in preparation for the monitoring. The instructions will specify regulatory documents and participant case records scheduled to be monitored. The ACRIN QA Monitor will review CRFs and source documents at several different time points: after first few participants enrolled and during the conduct of the trial, including staff changes at the participating sites. The QA Monitor will review the initial, annual, and any

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revised regulatory documents during each monitoring phase. **Please refer to the study-specific monitoring guidelines for details. The study-specific monitoring guidelines supersede the protocol's monitoring description.**

14.2 Audits

All participating institutions that enroll participants will be audited. The timing of the initial on-site audit will depend upon several factors, including the rate of accrual (both study-wide and site-specific), the number of evaluable participants enrolled at an individual site, the status of the protocol and pending amendments, and monitoring status. Generally, audits will be conducted after the number of evaluable participants reaches 10% of targeted accrual, either study-wide and/or site-specific. Audits are typically scheduled to occur at least 3 months after an institution has been monitored, providing that monitoring did not identify issues that mandate immediate auditing. This schedule may be altered in the event of pending protocol amendments. Closure of the study to accrual will trigger auditing of all participating institutions not yet audited. Additionally, site-specific circumstances may prompt an audit at any time.

Subsequent audits will be scheduled per the outcome of the initial audit. The audits will be conducted per federally-mandated procedures established by the Department of Health and Human Services. Instructions for preparation for the audit visit will be sent to the site prior to the scheduled audit visit. These instructions will specify which participant case records will be reviewed during the audit. On-site records will be verified against the submitted form, and the findings will be recorded on specially-prepared audit reports. Major discrepancies will be forwarded to the appropriate oversight body within ACRIN. IRB procedures, approvals, and ICFs will also be reviewed at the time of the audit visit. The ACRIN Audit Manual is available online at www.acrin.org. **Please refer to the study-specific audit guidelines for details. The study-specific audit guidelines supersede the protocol's audit description.**

To help sites prepare for monitoring and audits and to assure that the investigator and the research staff maintain records appropriately, ACRIN Headquarters will offer training to sites. This training will cover all aspects of data collection, including special instructions to obtain and file the various source documents needed to verify the accuracy of submitted data for this trial.

14.3 Source Documents

Source data are found in all information, original records of findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documents represent the first recording of any observations made or data generated about a study participant while he or she is enrolled in a clinical trial. Source documents for each study participant substantiate the data that are submitted to ACRIN.

Source documents must verify the eligibility criteria and data submitted on all CRFs. If an item is not mentioned (e.g., history and physical examination alluding to a condition, but no mention of a psychological condition), it will be assumed it is not present.

Research records for each case should contain copies of the source documents for the data collected and reported to ACRIN. If data are abstracted from medical charts that are not filed at the investigative sites (e.g. hospital charts), copies of these records should be filed in the research chart. Every attempt must be made to obtain all records/charts that were used to abstract any study data for this protocol. This will prevent any discrepancies and the inability to verify the document and the data reported.

14.4 Case Report Forms

CRFs, both web-based and paper forms, are the primary data collection instruments for the study. The paper CRFs are provided as tools to the sites; they are not mandated to be used on site. If sites do use ACRIN-supplied CRFs, then 1) make sure they are complete; 2) ensure medical records are copied even if data are extracted from the medical records; 3) and use “N/D” and “N/A” appropriately. All data requested on the CRFs must be recorded, and any missing data must be explained. If a space is left blank on paper CRFs because the procedure was not done or the question was not asked, “N/D” must be noted. If the item is not applicable to the individual case, “N/A” must be noted. All entries on paper CRFs must be printed legibly in black ink on the paper CRFs. In the event of any entry errors, corrections must be made by drawing a **single straight line** through the incorrect entry, writing **the initials of the person making the correction, recording the date** when the correction is being made, and entering the correct data above the strike through. Do not use white out or an eraser. Please refer to [ICH Good Clinical Practice Guidelines](#).

Data elements that are extracted from the medical record (such as participant history or official clinical interpretations of images, pathology, or surgery results) and recorded on the CRFs will be reviewed against the appropriate component of the medical record. Data elements gathered from signed participant questionnaires must be available for review. Required study image interpretation data that are more detailed in information than the image and not typically documented in the standard radiology report may be documented on the CRF and are acceptable source documentation **if signed by the Investigator**. At the time of audit, the auditor will verify the occurrence of the imaging examination, the reader, and the date of the exam(s) from the medical record(s).

If the paper CRFs are to be used as source documentation at the time of data collection, then 1) a Note to File should indicate that the CRF is the source document and 2) the paper CRF must be signed and dated by the person who filled out the form. If data are directly entered into the electronic CRF, the confirmation sheet should be printed out, signed and dated by the person completing the electronic CRF, and filed as a source document. Any use of approved CRFs as source documentation require a signature and date on the CRF with a reference to the information source (participant questionnaire, CT, MR, etc.). Any use of CRFs as source documentation when the protocol has designated the source data will be medical record documentation will be considered a major protocol deficiency.

14.5 Institutional Review Board/Ethics Committee

Sites must obtain initial, full-board, local IRB approval to participate in ACRIN trials. Prior to participant registration, a copy of the IRB approval letter for the protocol and the ICF must be sent to ACRIN, along with a copy of the IRB-approved, site-specific ICF. Any study-related materials for patients must be IRB reviewed and approved prior to distribution; approval notifications and other IRB correspondence should be delivered to ACRIN PDRC. Investigator will provide a copy(ies) of IRB approval letter(s) for any amendment(s), and copy(ies) of annual renewal(s). International sites may use an Ethics Committee instead of an IRB.

15.0 STATISTICAL CONSIDERATIONS

A total of 4300 patients being evaluated for stable angina or angina equivalent will be randomized to either CCTA or SPECT MPI/ICA for diagnosis. All participants who are diagnosed as having obstructive CAD will be initially treated with OMT, allowing participants with persistent or worsening symptoms to later undergo revascularization. All participants will be followed for MACE and cross-over to revascularization (see Appendix IV for definitions), as well as cardiac-related care and care related to incidental findings from the diagnostic evaluations. QoL questionnaires will be administered at baseline and to a subset of participants at 12 months after enrollment. Lifestyle questions will be administered at baseline and 12-months among all participants contacted at that time point. Participant angina class will be assessed on entry into the study (CCS I-III, Canadian Cardiovascular Society)⁶ and at 6-month intervals for up to 24 months. The data will be analyzed in terms of non-inferiority. Sub analyses will be performed to assess outcomes by age, gender, co-morbidities, and angina class at presentation.

Participants will be enrolled and randomized in equal proportions to the two study arms (Group A—CCTA—and Group B—SPECT MPI/ICA). As noted earlier, randomization will be stratified by gender and participating institution. Participants will be enrolled over a period of 18 months. Participants with positive cardiac-related findings on their CCTA or SPECT/MPI will be followed a minimum of four times (at 2 weeks and 2, 6, and 12 months) and a maximum of six times over 24 months (adding 18 and 24 months). For participants with negative cardiac-related findings on their CCTA or SPECT MPI, the first enrolled participants will be followed at four time points (6, 12, 18, and 24 months) and the last enrolled participants for two time points (6 and 12 months).

15.1 Study Design and Endpoints

15.1.1 To compare outcomes of participants with symptoms of stable angina or angina equivalent evaluated with an anatomic imaging strategy using CCTA as initial method of CAD diagnosis (Group A) to a combined functional and anatomic imaging strategy of SPECT MPI/ICA (Group B) as a guide to OMT.

The primary endpoint of the study is a combined endpoint of occurrence of MACE, comprising cardiac-related death or acute MI, and revascularization. We will calculate differences in the combined MACE/revascularization endpoint between the CCTA and SPECT MPI arms. Time to the primary endpoint will be measured from randomization to the first occurrence of any of the component events. Definitive data regarding the primary endpoint will be collected via chart abstraction. All reports of MACE or revascularization will be reviewed by the outcomes adjudication committee (see Section 6.3). In order to account for the variable length of follow up of study participants, we will use methods from survival analysis to compare event rates in the two arms. Cases that have not reached the endpoint or have dropped before the end of the follow-up period will be considered as “censored”.

In the first step of the analysis, we will use graphical techniques to examine the distribution of time to the primary endpoint and will derive Kaplan–Meir curves for each arm, overall, and by subsets of interest (defined by gender, age, and major risk factors). The primary analysis will be conducted from an intent-to-treat perspective and will compare time to endpoint events in the two arms using a logrank test for the hypothesis of non-inferiority of the CCTA arm.^{52,53}

In secondary analyses, we will compare the two study arms separately on the basis of the two main components of the composite endpoint, namely MACE and revascularization. We also will use Cox regression models to examine the difference between the two arms in participant groups defined by characteristics of interest, including gender, age, major comorbidities, pre-existing CAD, and inpatient or ER status. Of primary interest in this regression analysis will be the interaction of participant covariates with the indicator of study arm. The Cox regression analysis will be performed for the composite primary endpoint and for MACE and revascularization separately. The results of these secondary analyses will be exploratory in nature and will be reported as such.

To help with the clinical understanding of the comparisons in this aim, we will also perform a secondary analysis of data on angina symptom status assessed using the CCS Angina Status scale. The CCS Angina Status ordinal scale result will be assessed for each participant at baseline and at six-month intervals thereafter. We will first perform a graphical exploration of the data by examining the distribution of the results at each time point. We will use regression modeling for longitudinal ordinal data to compare the two arms and to examine potential effects of participant characteristics known at baseline, such as gender, race, and comorbidity.⁵⁴ In these models, the interactions of covariates with indicator of study arm will be of primary interest. We will approach the handling of missing data and dropout using pattern mixture modeling, with sensitivity analysis to assess the effect of assumptions on patterns of missingness.^{55,56}

15.2 Secondary Aims

15.2.1 To evaluate the ability of available prognostic indices to predict revascularization or MACE using CCTA information and to develop new indices using the RESCUE trial data.

In this aim, we will examine the ability of indices to predict whether a study participant will experience MACE or will undergo revascularization within a period of 12 months from the time of study entry. For analysis purposes, the response will be a binary indicator of whether MACE or revascularization occurred in this 12-month period. Per study protocol, all participants will be followed for at least 12 months.

In the first part of the analysis we will evaluate a modified Duke Prognostic Index to predict MACE or revascularization for participants in the CCTA arm. The index will be computed for each participant in the CCTA arm, and a receiver operating characteristic (ROC) curve will be developed with the reference standard being the binary indicator of whether the participant underwent revascularization or had MACE within 12 months from study entry as determined by the outcomes adjudication committee. We will develop next other new modifications of the Duke index adapted to the context of predicting MACE or revascularization using CCTA. We will use multivariate binary regression modeling to examine the relation between the binary response to the multidimensional vector of predictors used in a modified Duke index. Multiple imputation will be used to handle missing observations, if necessary. We will use cross-validation to limit the potential for overfitting and to derive realistic estimates of the predictive performance of the model.⁵⁷ We also will consider Ridge regressions, which impose penalty on the least squares to improve the predictive stability, to reduce the impact of collinearity in the predictors. The cross-validated area under the ROC curve for

the new index will be compared to the area under the curve estimated earlier for a modified Duke index. A non-parametric approach will be taken to the analysis of these ROCs.⁵⁸ We will estimate and compare the areas under the curves using bootstrap methods, in order to account for the correlation in the index values arising from the fact that the indices will be evaluated on the same participants.

In the second part of the analysis for this aim, we will use the CCTA assessments of the American Heart Association model of the coronary arteries to develop a new index for the prediction of revascularization or MACE. First, we will develop an index using the information of the maximum degree of stenosis (grade: none, very mild, mild, moderate, severe) in each segment. The analytic approach will be based on multivariate binary regression modeling as described above and will also incorporate clinical input and judgment for defining predictor variables. The cross-validated area under the ROC curve for the new index will be compared to the areas under the curve for the other indices discussed earlier in this section. We will also consider other, more recently developed measures of predictive performance based on reclassification.⁵⁹

The predictive index for SPECT MPI will be the measurement of size of the reversible perfusion defect on SPECT MPI. We will develop an ROC curve for this index as predictor of revascularization or MACE within 12 months and will estimate the area under the curve. We will use the ROC curve to estimate threshold values of the index that correspond to desirable values of sensitivity and specificity. We also will compare the areas under the ROC curves across the two arms using methods appropriate for independent curve comparisons.

15.2.2 *To determine the cost, effectiveness, and incremental cost-effectiveness of CCTA versus SPECT MPI/ICA in the evaluation of participants with symptoms of stable angina.*

The analysis will be performed from the societal perspective. Costs will be measured in terms of US dollars while effectiveness will be measured in terms of life years and quality adjusted life years (QALYs). It is expected that the results from this study will provide the United States public and medical community with a scientific and economic basis for the production of imaging guidelines in the diagnosis and management of stable angina and will provide additional evidence for the evolution to initial treatment by OMT as the new standard of care.

15.2.2.1 *Health Care Utilization and Comparative Cost Analysis*

We will obtain information on health outcomes and health care utilization from medical records. Medical record abstraction will be coordinated centrally by staff at the Center for Statistical Sciences (CSS) at Brown University and at ACRIN. This group currently manages the chart abstraction process for the ACRIN arm of the National Lung Screening Trial (NLST). We will model our approach on that used for the NLST. In this multi-stage process to obtain medical records, study participants will complete a Health Status and Medical Utilization Questionnaire (in order to provide information on medical care received from outpatient providers, ERs, and hospitals) and a Patient and Caregiver Costs Related to Time and Travel Questionnaire (to document

healthcare-related time and travel since the last questionnaire completion) at 6-month intervals for up to 24 months.

Participants will be asked to provide information on whether the care was cardiac-related or related to medical follow-up of incidental findings on the CCTA or SPECT MPI examination, as well as contact information for each provider. Site RAs will obtain copies of the medical records based on information provided by the participant. Medical records abstraction will be performed by a central medical record abstraction company. Centralizing the abstraction process with a single group of abstractors simplifies quality control, ensuring consistent and reliable coding of medical conditions and care. All abstraction will be done directly onto electronic forms online. These computer forms incorporate range checks and ICD and CPT look-ups which ensure that data are as error-free as possible.

15.2.2.2 Cost-effectiveness Analysis

We will perform a cost-effectiveness analysis (CEA) comparing the two arms within RESCUE using data from all participants recruited within the United States.^{60,61} We will attempt to access international medical records, and recognize that it may not be feasible at all participating international sites. The primary analysis will be performed assuming a societal perspective and lifetime time horizon.⁶² The effectiveness of each arm will be measured in terms of life years and QALY. In-trial life years and QALYs will be based on in-trial ascertainment of deaths and utilities. Utilities will be based on SF-36 assessments at baseline and 12 months with conversion to Quality of Well Being scores.⁶³ Life years beyond the trial will be based on Framingham survival estimates based on age, sex, and cardiovascular events.⁶⁴ QALYs beyond the trial will be based on utilities assessed at 1 year, with downward adjustments to account for aging.

The costs in each arm will be measured in terms of 2010 US dollars using the medical component of the consumer price index to adjust for the timing of the costs.⁶⁵ The computation of costs will include direct and indirect medical costs, the latter of which will include time and travel expenses for participants and caregivers in each arm. Direct medical costs will be based on hospitalizations, outpatient care, and drugs assessed by medical chart abstraction blinded to randomization arm. Costs of hospitalizations will be based on diagnosis-related groups coding and average Medicare reimbursement rates obtained from the Medicare Part A (MEDPAR).⁶⁶ Costs of outpatient care, including initial and subsequent cardiac testing and physician visits, will be based on current procedural terminology coding and the Medicare fee schedule⁶⁷ while costs of cardiac drugs will be based on *Red Book* average wholesale prices. Finally, costs related to time and travel expenses for participants and caregivers will be based on in-trial questionnaires. Costs beyond the trial will be based on total annual personal age-specific healthcare costs per capita⁶⁸ with adjustment for year.⁶⁵

Life years, QALYs, and costs will be reported for both arms for in-trial, beyond trial, and lifetime time horizons. We will estimate incremental cost-effectiveness ratios (ICERs) for life years and QALYs over the lifetime time horizon along with 95% confidence intervals for the ICERs using nonparametric bootstrapping methods.⁶⁹ Uncertainty surrounding cost effectiveness will be displayed with scatter plots of incremental cost versus incremental effectiveness and cost-effectiveness acceptability curves.⁶⁹ In addition, we will perform one-way sensitivity analysis on key variables, including those used to project survival beyond the trial and various costs.

15.2.3 To compare angina symptoms and self-reported health status of participants with symptoms of stable angina undergoing CCTA as initial method of CAD diagnosis to SPECT MPI/ICA as a guide to OMT.

15.2.3.1 Quality-of-Life Assessment

The COURAGE study measured angina symptoms using the Seattle Angina Questionnaire (SAQ). In addition, Dougherty³² has reported that differences in angina severity were related to selected subscales of the Short Form-36 (SF-36). The SF-36 is useful because participant responses may be used to derive health utilities³¹ that may be used to inform cost-effectiveness analyses.

In RESCUE, we propose to monitor angina symptoms and impact of those symptoms on participant QoL by administering the SAQ to all participants at baseline and to a subset of participants, stratified by diagnostic examination, at 12 months after enrollment for all sites within the United States. The total time to complete both questionnaires is approximately 20 minutes.

At Baseline. To establish a baseline for angina symptoms and the QoL assessment, all participants will be asked to independently complete the SAQ and the SF-36 at the baseline visit. QoL assessment at baseline will be completed prior to randomization.

At 12 Months. Administration of the SAQ and the SF-36 at 12 months will be coordinated by the sites or ACRIN Outcomes and Economics Unit (AOEU) located within the ACRIN Biostatistics Center at the Brown University Center for Statistical Sciences, Providence, RI, for a subset of participants. See Section 8.2.2 for details of administration procedures.

We will use the SAQ to assess whether participants are angina-free at 12 months, as well as to determine whether participants report a clinically meaningful improvement in any of the SAQ scales between the baseline and 12-months assessments. Participants will be classified as angina-free if their SAQ score is 100, indicating no angina symptoms.

We will use the SF-36 to derive eight profiles of functional health and well-being. Physical health is measured by the Physical Functioning (PF), Role-Physical (RP), Bodily Pain (BP), and General Health (GH) scales. Mental Health is described by the Vitality (VT), Social Functioning (SF) Role-

Emotional (RE), and Mental Health (MH) scales.^{28,70} We will compare the change in each of these subscales between the baseline and the 12-month assessments for participants in each arm of the study.

15.2.3.2 Statistical Analysis

Measures of health status as measured by SAQ and SF-36 will be computed for selected participants. We will first perform a graphical exploration of the data by examining the distribution of each scale at the two time points and the change in the scale between the two time points. We will use regression modeling for longitudinal data to compare the two arms.⁵⁴

In these models, the interactions of covariates with indicator of study arm will be of primary interest. In addition to the overall comparison between the arms, the regression analysis will be used to examine potential effects of participant characteristics such as gender, race, and comorbidity. As described earlier in the analysis of the CCS longitudinal data on angina status, we will use pattern mixture models to address participant drop out and missing assessments. The clinical implications of potential effects identified in the analysis of the scale measures computed from SAQ and SF-36 will be examined using published guidelines.⁷¹

15.3 Sample Size/Accrual Rate and Power Considerations

The planned sample size is 4300 participants at up to 80 institutions, to be accrued over 18 months.

15.3.1 Primary Aim

15.3.1.1 *To compare outcomes of participants with symptoms of stable angina or angina equivalent evaluated with an anatomic imaging strategy using CCTA as initial method of CAD diagnosis (Group A) to a combined functional and anatomic imaging strategy of SPECT MPI/ICA (Group B) as a guide to OMT.*

We used reported data on MACE and revascularization from the COURAGE trial and combined this information with data from our clinical experience to formulate the range of necessary assumptions for sample size and power considerations for the primary endpoint. The computations were performed using the subroutine for logrank test for non-inferiority in the software package PASS.⁷²

In particular, we assumed that about 1% of participants will experience a MACE within 12 months from study entry and that an additional 5% will undergo revascularization within the same period. Thus we assumed a combined rate of 6% within 12 months for the primary endpoint (hazard rate=0.0052, assuming an exponential survival distribution). We also assumed that about 5% of participants will drop out during a 12-month period from each arm and about 1% will switch from each arm to the other. The accrual time was set at 18 months and the additional follow-up time at a minimum of 12 months. The following table shows the power of a test of non-inferiority for a test at level 0.05 and the indicated non-inferiority hazard ratio.

Power	Total Sample Size	Hazard Ratio for Non-Inferiority
0.7438	4300	1.25
0.8548	4300	1.30
0.9254	4300	1.35
0.9651	4300	1.40

The above computations of power are performed under the assumption that the actual hazard rates are identical in the two arms. The table indicates that if the hazard ratio for non-inferiority is 1.3 and above, a total sample size of 4300 would provide adequate power under the above assumptions about 12-month rate for the combined primary event rate, drop out, drop in, and non-compliance. If the 12-month rate of MACE or revascularization is higher than 6%, the power would increase. For example, if the 12-month event rate was 7% and all other assumptions were kept unchanged, the power is about 90% for hazard ratio equal to 1.3 and is about 80% for hazard ratio equal to 1.25.

15.3.2 Secondary Aims

15.3.2.1 *To evaluate the ability of available prognostic indices to predict revascularization or MACE using CCTA information and to develop new indices using the RESCUE trial data.*

Statistical power for the comparison of areas under the ROC curves envisioned in this aim depends crucially on the relatively small number of participants expected to be revascularized or have MACE within 12 months. In line with information used in the primary aim, we assumed that about 6% (or approximately 129 participants) will have MACE or undergo revascularization within 12 months in each arm. We also assumed the correlation between index values is 0.5. The following table shows estimates of power to detect the indicated difference in areas under the curve, using a test of level 0.05.

Power	Area 1	Area 2	Area Difference
0.8147	0.8000	0.8700	0.0700
0.9087	0.8000	0.8800	0.0800
0.9624	0.8000	0.8900	0.0900
0.9873	0.8000	0.9000	0.1000
0.9965	0.8000	0.9100	0.1100
0.9992	0.8000	0.9200	0.1200

The power will decrease if control for multiple comparisons is implemented. For example, if the level of the test is set at 0.01, the minimum difference between the two areas under the curve needs to be at least 0.08 in order to achieve 80% power. Computations of power for these comparisons were made using PASS.⁷²

15.3.2.2 To compare angina symptoms and self-reported health status of participants with symptoms of stable angina undergoing CCTA as initial method of CAD diagnosis to SPECT MPI/ICA as a guide to OMT.

We used data from the OMT arm of the COURAGE study³³ to guide us in the choice of assumptions needed in the power computations for this aim. For example, for the QoL score from the SAQ, we assumed that the standard deviation at each time point is about 25 and the average, within arm, change between baseline and 12 months is about 20. The following table shows estimates of the power to detect a difference in the change from baseline between the two arms of the study using a two-sided test of the indicated level. The lower level was chosen to indicate power while control for multiple comparisons. Two values of the correlation were used and the sample size was adjusted for the projected drop out by 12 months. Computations were performed using the PASS software subroutine for means in repeated measures designs.⁷²

Power	Difference Between Arms	Correlation	Level of Test
0.83542	2.000	0.500	0.050
0.99273	3.000	0.500	0.050
0.99995	4.000	0.500	0.050
0.77578	2.000	0.750	0.050
0.98287	3.000	0.750	0.050
0.99975	4.000	0.750	0.050
0.64055	2.000	0.500	0.010
0.96621	3.000	0.500	0.010
0.99951	4.000	0.500	0.010
0.55652	2.000	0.750	0.010
0.93334	3.000	0.750	0.010
0.99788	4.000	0.750	0.010

We performed similar computations for other subscales that will be computed in the study. Overall, the proposed design can provide adequate power to compare QoL changes in the two arms.

15.4 Reporting Guidelines

15.4.1 Routine Reporting

Routine reports for this protocol will be included in the ACRIN Biostatistics Center Mid-Year and Year-End Updates and will be provided to oversight bodies, including RESCUE DSMC for review during each of its twice-yearly meeting.

Routine reports will include:

- Accrual and participant characteristics;
- Timeliness and completeness, eligibility and protocol compliance, and outcome data;
- All reported AEs.

15.4.2 Interim Analysis

Beside the data analysis as described in the analysis plan and standard monitoring for AEs and data quality at study terminal, we will conduct interim monitoring analyses at 6-month intervals (i.e., at 12, 18, and 24 months) after the beginning of participant enrollment. Given the projected accrual rates at the three interim looks, we expect to have recruited 1075, 2150, and 3225 participants from whom we will have collected the baseline and at least one follow-up data. The interim analysis will assess efficacy and safety. The results will be presented to the RESCUE DSMC.

15.4.2.1 Efficacy Monitoring

Efficacy monitoring will be done by comparing the two arms on the basis of the time to occurrence of the primary endpoint, which is MACE, comprising cardiac-related death or acute MI, and revascularization. For the primary endpoint, a group sequential rule with a spending function corresponding to an O'Brien-Fleming boundary will be used to determine the nominal significance levels to which interim p-values will be compared.⁷³

15.4.2.1 Safety Monitoring

The RESCUE DSMC will review regular summary reports on AEs and more detailed information on SAEs. In addition the RESCUE DSMC will receive regular reports on events relevant to participant safety (including cardiac deaths or acute MIs). The timing and content of the reports will be decided during the first meeting of the RESCUE DSMC. The RESCUE DSMC may recommend special measures to be taken or the study to be stopped based on information about safety issues and other unanticipated concerns.

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APPENDIX I

ACRIN 4701

INFORMED CONSENT FORM TEMPLATE

**Randomized Evaluation of Patients with Stable Angina
Comparing Utilization of Diagnostic Examinations: RESCUE**

<<Note: The American College of Radiology Imaging Network (ACRIN) complies with the privacy measures put forth by the Health Insurance Portability and Accountability Act (HIPAA). However, ACRIN does not monitor compliance with HIPAA; that is the responsibility of the local institutions and their Institutional Review Boards (IRBs). Local IRBs may choose to combine the authorization elements in the informed consent.>>

DISCLAIMER: “RESCUE” stands for Randomized Evaluation of Patients with Stable Angina Comparing Utilization of Diagnostic Examinations. RESCUE is the acronym for the study title and does not indicate any health benefit related to your decision to participate in the trial.

<<Depending on institutional practices related to protected health information (PHI) and the release of PHI for trial conduct (that is, medical record collection), sections of the trial description may need to be deleted, such as reference to collecting the patient’s Social Security Number and the authorization document for medical records collection. Content related to the quality-of-life questionnaires at baseline and at 12-month follow up will need to be removed from all foreign-site questionnaires. If you need assistance in revising the ICF Template for your institution, contact the ACRIN 4701 RESCUE trial monitor.>>

This is a clinical trial, a type of research study. Research staff will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your treating doctor, the study doctor, or other research staff for more explanation. If you decide to participate in this study, you will be asked to sign and date this form.

You are being asked to be in this trial because you have symptoms of chest pain that your treating doctor thinks may be related to your heart health. Your treating doctor would like to perform some tests to find the cause of your pain. This trial will determine which diagnostic test you have and how you will be treated will depend on the results of the diagnostic test.

WHY IS THIS STUDY BEING DONE?

Your treating doctor believes your symptoms are related to heart disease. If you decide to join the trial, you will be randomly assigned to either the current standard of care for diagnosis of your symptoms or to the study-related imaging for diagnosis. You should get information about the standard-of-care practice from your institution, but this informed consent form provides basic information since you will be randomly assigned to the standard-practice group or to the experimental group.

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The current standard practice is a nuclear medicine cardiac stress test to see how your heart works during exercise or while using medications to excite the heart. You would undergo this cardiac stress test, or a similar study, even if you did not join the trial.

The experimental group uses imaging is called coronary computed tomography (CT) angiography, which takes pictures of your heart after a dye is injected into your blood stream.

If you are diagnosed with a heart condition, your treatment will depend on your diagnosis and amount of heart disease. You will either 1) be treated with medication and lifestyle change without additional procedures or 2) undergo testing that may involve additional procedures.

The purpose of this research is to:

- Compare patient outcomes after diagnosis with either coronary CT or nuclear medicine cardiac stress test results;
- Determine the appropriate use of medication and lifestyle change in clinical care; and
- Compare costs associated with these approaches to care.

The study doctors are hoping to be able to correctly diagnose heart disease and reduce the need for diagnostic tests and treatments while safely treating the condition. Previous research has shown that treatment with medicine and lifestyle change is safe and may reduce the need for additional diagnostic testing or surgery.

Experimental Group: About Coronary CT Angiography (Group A)

Coronary CT angiography is a heart-imaging technique that allows doctors to see your heart without having to put any tubes in the blood vessels near your heart (you will still need an arm vein IV). Coronary CT is a type of x-ray that can take as little as about 10 minutes. Your study doctor may wish to give you one or more medications to slow your heart rate and make the coronary arteries larger to improve the images. You will not be given these medications if you have any medical condition or are taking other medications that may cause problems. Please let your study doctor know if you have a history of asthma or other lung disease, allergic reactions to any medication, or if you have recently taken medications such as Viagra, Cialis, Levitra, or something similar.

The coronary CT pictures show where blockages have built up in the coronary arteries. These materials, called plaques, can block the flow of blood needed to keep the heart healthy. If untreated, the muscle of the heart can be damaged or die.

About Contrast Agents (Group A)

Contrast agents are liquid-like dyes that go into the body to help imaging machines create pictures of the body's organs and bones. The agent used with coronary CT in this trial contains iodine. If you have had a previous reaction to contrast agents with iodine, be sure to let your treating or study doctor know.

Standard Practice Group: About Nuclear Medicine Cardiac Stress Testing (Group B)

Currently, people with symptoms like yours are evaluated using nuclear medicine stress testing. This test is used because it is good at accurately diagnosing and can be used in almost all patients. It involves gathering information about your heart health by having a scan of your heart at rest and another scan after you've stressed your heart. In order to stress your heart, your heart rate is increased by either

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walking on a treadmill, or if you are unable to walk on the treadmill, you can receive medications to increase your heart rate as if you've been exercising.

About Radiotracers (Group B)

For nuclear medicine cardiac stress testing on a treadmill, a small amount of radioactive material, called a *radiotracer*, is injected into the blood stream using an intravenous catheter that goes into a vein in your arm. The radiotracer gives off energy that can be collected to create a picture of how the heart is working.

About Diagnostic Invasive Coronary Angiography (Group B)

You may need to have an additional diagnostic test called *invasive coronary angiography*. It will depend on the results of your nuclear medicine cardiac stress test. This test is part of standard care. A catheter—a small tube—is woven up from a blood vessel, usually in the upper thigh, through the body, and into the arteries that run outside of the heart. A dye made of iodine is injected through the catheter and makes pictures of the inside of the arteries. These pictures inform the doctors of where additional treatment may be needed.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

A total of 4300 people will take part in this study at up to 80 institutions internationally.

HOW LONG WILL I BE IN THE STUDY?

You are being asked to join the study for up to two years (24 months). A member of the study staff will contact you or someone you designate (a proxy) by phone about your heart and other health up to six times, and you may be asked to complete questionnaires for the study.

This trial is expected to end after all participants have completed the study-related follow-up calls and all information has been collected. This study may be stopped at any time by your study doctor, ACRIN, Food and Drug Administration (FDA), or Agency for Healthcare Research and Quality (AHRQ) without your consent because:

- Your health or safety may be at risk;
- You have not been following study instructions;
- Of an administrative decision by ACRIN, the study doctor, FDA, or AHRQ.

These actions do not require your consent, but you will be informed of any of these decisions if such a decision is made.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor and your treating doctor first. Choosing to withdraw from the study will not interfere with your future care.

WHAT AM I BEING ASKED TO DO IN THE STUDY?

If you take part in this study, you will have one of two diagnostic tests (either the coronary CT or the nuclear medicine cardiac stress test study) and your treatment will be determined by your diagnosis.

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After one year, you may be asked to complete questionnaires related to your health and quality of life. You will be contacted by telephone up to six times, depending on your diagnosis and when you join the trial.

The research staff will ask you questions about your health, including treatments related to your heart, care for non-heart-related findings from your diagnosis, visits to your treating doctor(s), and even the time and effort you have put into taking care of your heart (driving distances, amount of time). You may want to keep track of these details to make it easier for you to remember.

<<Depending on institutional practices related to protected health information (PHI) and the release of PHI for trial conduct, sections of the trial description may need to be deleted, such as reference to collecting the patient's Social Security Number and the authorization document for medical records collection. Content related to the quality-of-life questionnaires at baseline and follow up will need to be removed from all foreign-site questionnaires.>>

When You Join the Trial ...

The following tests and procedures will be performed to determine if you qualify to take part in this study:

- Review of your medical history including your history of heart-related illnesses, trends in heart health (such as your blood pressure), and recent blood test results.
- Blood collection to check your kidney health, if not checked within the past 28 days (this may mean a vial of blood has to be drawn for the test).
- Pregnancy test if you are a woman who may be able to become pregnant. The result of the pregnancy test must show that you are not pregnant for you to qualify to participate in the study.
- You will be asked to sign a separate authorization to release some or all of your medical records for review and collection in this study.

If you qualify to participate in this research study and if you decide to join the study, you will be asked to:

- Provide your contact information, including your mailing address, Social Security Number, and phone number(s), and the name of another person or doctor(s) we can contact who knows about your heart health should you be unavailable.
- Have an electrocardiogram (also called an ECG) at the time of your diagnostic imaging—but only if you have not had an ECG in the 30 days prior to diagnostic imaging that can be sent to ACRIN.
- Complete three (3) questionnaires that describe your health and quality of life. These questionnaires will take a total of about 25 minutes for you to complete them.

Diagnosis: Randomized to One of Two Groups ...

If you qualify to participate in this research study, you will be randomly assigned by chance to one of the two following study groups:

- Experimental Group A: The study-related coronary CT imaging for diagnosis of your symptoms. (Your heart, blood pressure, and oxygen levels will be checked during the imaging study.)
- Standard Practice Group B: The current standard care, nuclear medicine cardiac stress testing for diagnosis of your symptoms.

You will have an equal 50/50 chance of being assigned to either of the study groups. Neither you nor the study doctor or study staff will choose what group you will be in. If you are randomized to a diagnostic test and cannot complete it, your study doctor and treating doctors will decide how to diagnose and treat your chest pain. You will still complete the study follow-up procedures.

Treatment

Depending on your diagnosis, your study and treating doctors have agreed to a specific treatment approach for this trial. You may be discharged from the hospital; receive a prescription for medication(s) and lifestyle changes; or you may need surgery for your condition.

Follow Up: Phone Contact, Questionnaires, and Medical Record Review

If you are diagnosed with heart disease during the study, a member of the study staff will contact you by telephone a minimum of four times (at 2 weeks, 2 months, 6 months, and 12 months after you join the study). You may also be contacted at 18 and 24 months after you join the study.

If you are not diagnosed with heart disease during the study, a member of the study staff will contact you by telephone, a minimum of two times (at 6 months and 12 months after you join the study). You may also be contacted at 18 and 24 months after you join the study, for a possible total of 6 times that someone may contact you for the study.

You will be asked to provide information about your heart-related and other health treatment and who has been treating you and where. With your permission and signed authorization of release of medical records form which you signed at the beginning of the study, the study staff will contact your treating doctors to request medical records for any treatment you may have received.

You also will be asked about the time and effort you have put into taking care of your heart (driving distances, amount of time). You may want to keep track of these details to make it easier for you to remember.

At 12 months after you join the trial, you may be asked to complete the same two questionnaires asking about your health and quality of life that you filled out at the beginning of the trial. People who receive the questionnaires will be randomly chosen. If you receive them, you will need to fill these out again and return them to research staff or in the envelope provided. These two questionnaires will take a total of about 20 minutes to complete.

Medical Records Collection

At the baseline assessment, your study doctor will ask you to sign a separate document called “authorization to disclose/release medical records” to obtain some or all of your medical records from your doctor. A separate authorization is needed for the research doctors to collect and review the information regarding your heart health and treatments you have received. Your medical records will be collected and sent to ACRIN. The study staff will remove information that can identify you from your medical records. Your medical records will continue to be collected until the end of the study unless you withdraw your authorization in writing, as described in the separate authorization to release medical records.

A study chart follows. It explains what is expected of you at each study time point.

STUDY CHART**INITIAL VISIT AND ASSESSMENT:**

Phase 1 – Eligibility and Randomization to Group A or Group B	<ul style="list-style-type: none"> • Read and sign the informed consent form; • Provide contact information for yourself (your Social Security Number, mailing address, and phone number[s]) and for another person or doctor(s) who can be contacted regarding your heart health; • Provide medical history; • Have a pregnancy test, as appropriate; • Have about a vial of blood collected to check your kidney health, if not checked within the past 28 days before enrollment; • Have an ECG if you have not had one within 30 days prior to diagnostic imaging; • Complete three questionnaires (about 25 minutes total).
Phase 2 – Registration and Randomization	After you join the trial, you will be randomly assigned to Group A (coronary CT) or Group B (nuclear medicine cardiac stress test) for diagnosis.
Phase 3A – GROUP A Diagnostic Coronary CT Test	<ul style="list-style-type: none"> • Receive pre-treatment medications, depending on your heart rate and the equipment being used at your institution; • Have an intravenous (IV) catheter placed; • Receive iodinated contrast agent; • Have a coronary CT.
Phase 3B – GROUP B Diagnostic Nuclear Medicine Cardiac Stress Test	The nuclear medicine cardiac stress test will be performed per standard practice at <i><<the institution>></i> .
Phase 4 – After Diagnosis ... Treatment Based on Results	<p>Depending on the results of your diagnostic test, you will:</p> <ul style="list-style-type: none"> • Be allowed to go home; OR • Receive a prescription for medication(s) and lifestyle changes; OR • Undergo surgery to further diagnose and/or treat your heart disease.

FOLLOW UP:

Telephone Contact: Positive Diagnostic Test— At 2 Weeks and 2 Months Everyone—Every 6 Months for Up to Two (2) Years After Entering the Study	<ul style="list-style-type: none"> • Provide medical information after 2 weeks and 2 months (only for positive cardiac findings) and (all participants) at 6 months and every six (6) months for up to 24 months (up to six times total) from the time of your initial visit. <p>NOTE: You will definitely receive follow-up phone calls at 6 and 12 months, but you may not be called at 18 and 24 months; the length of follow up depends on when you joined the trial.</p>
Questionnaires at 12 Months After Entering the Study (Only A Subset of US Participants Will Receive Questionnaires)	<ul style="list-style-type: none"> • Complete and return two (2) questionnaires (about 20 minutes total) that you may receive by mail at approximately 12 months after you join the study. Not everyone will receive this mailing. Some participants may be asked to complete the questionnaires at their institution or by phone. Those who do will be randomly chosen.

Depending on how you respond to follow-up questions about your heart health and treatment, research staff may need to access your medical records from other institutions and at facilities outside of this one. In order to request your medical records, these professionals will need access to your contact information.

WHAT ARE THE POSSIBLE RISKS OR DISCOMFORTS OF THE STUDY?

While on the study, you may be at risk for these side effects if you are randomly assigned to the study-related coronary CT test. You should discuss these with your study and/or treating doctor(s). There may be other side effects that we cannot predict. Many side effects go away shortly after the coronary CT scan is stopped, but in some cases side effects can be serious, long lasting, or permanent.

Risks For Group A: Experimental Component

Risks Associated With Intravenous (IV) Catheter Placement for Coronary CT Contrast Agent

Likely

- Minor discomfort;
- Bruising;
- Pain in the injection site.

Rare

- Fainting;
- Bleeding;
- Infection.

Risks Associated With the Contrast Agent for the Coronary CT Scans

Likely

- Flushing;
- Paleness.

Rare

- Low-grade fever;
- Nausea;
- Vomiting;
- Hives;
- Rash;
- Leaking from your IV into the soft tissue of your arm.

Very Rare, Potentially Life Threatening

- Allergic-type reaction;
- Kidney failure.

When you receive the contrast during the coronary CT scan, you may experience a warm or hot sensation and/or a metallic taste in your mouth. These are normal reactions and are not dangerous.

If you experience an allergic-type reaction, with the coronary CT contrast agent, you will be treated for the reaction. If you have allergies or have had an allergic reaction to contrast in the past, please notify your treating doctor, the study doctor, and research staff.

Risks Associated With Coronary CT Scans

Likely

- Headache, if nitroglycerin is given to you under your tongue.

Less Likely

- Detection of abnormalities unrelated to your chest pain may occur in 10% to 20% of people undergoing coronary CT. Most often, small non-cancerous findings will be detected in the lung, and this could lead to an additional CT scan. Less likely, you will receive additional treatment. Your treating physician will be notified of any findings on imaging studies related and unrelated to your chest pain.

Rare

- Malfunction of worn or implanted electronic medical devices;
- Reaction to a medication given to you as part of the coronary CT procedure (such as a heart-rate lowering drug), including low blood pressure, passing out, headache, and abnormal or fast heart rate.

If you wear or have electronic medical devices implanted such as a pacemaker or a drug pump, please make sure you tell your treating doctor, the study doctor, and research staff. It was reported by the FDA that CT scans may cause the malfunction of electronic implanted medical devices.

<<Sites are encouraged to revise this section of the Informed Consent Form Template to conform risks-related language to their institution's specifications for consenting patients to SPECT MPI and/or ICA.>>

Risks for Group B: Standard Practice Component

NOTE: If you do not join this trial, you will be undergoing these or similar procedures as standard practice at your institution.

Risks Associated With Intravenous (IV) Catheter Placement for the Radiotracer

Likely

- Minor discomfort;
- Bruising;
- Pain in the injection site.

Rare

- Fainting;
- Bleeding;
- Infection.

Risks Associated With the Radiotracer for the Nuclear Medicine Cardiac Stress Test

Very Rare, Potentially Life Threatening

- Allergic-type reaction.

If you experience an allergic-type reaction related to the radiotracer, you will be treated for the reaction. If you have allergies or have had an allergic reaction to radiotracers in the past, please notify your treating doctor, the study doctor, and research staff.

Risks Associated With Nuclear Medicine Cardiac Stress Tests (With Pharmacologic Stress Agent)

Likely

- Fast heart rate;
- Flushing;
- Headache;
- Chest pain;
- Shortness of breath.

Less Likely

- Low blood pressure;
- Irregular heart rhythm;
- Dizziness.

Rare

- Difficulty breathing (bronchospasm);
- Transient (temporary) heart block;
- Slow heart rate.

Very Rare

- Death.

Risks Associated With Nuclear Medicine Cardiac Stress Tests (With Exercise)

Likely

- Chest pain.

Less Likely

- Irregular heart rhythm.

Rare

- Heart attack;
- Dizziness;
- Low blood pressure.

Very Rare

- Death.

Other Risks

Detection of abnormalities related to your chest pain is uncommon, but can happen during your nuclear medicine cardiac stress test examination. Your treating doctor will be notified of any findings on imaging studies related and unrelated to your chest pain.

Risks Associated With Diagnostic Invasive Coronary Angiography

Less Likely

- Changes in your heart beat;
- Heart attack;
- Stroke;

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- Bleeding.

Rare

- Internal bleeding (retroperitoneal hematoma);
- Death.

Radiation Risks

<<Each site may need to modify this section to quote the correct CT dosimetry for its own cardiac CT scanner in accordance with its own institutional policies and procedures. The following language and dosing range is an example only.>>

For example:

Coronary CT. If you are assigned to the coronary CT, there are some risks from the scan used to evaluate your heart health in this study. This research study involves exposure to radiation from the coronary CT and therefore you will receive a radiation dose. Radiation dose associated with this study will range from approximately 5 to 12 mSv. At doses much higher than you will receive, radiation is known to increase the risk of developing cancer after many years. The dose that you will receive will very likely have no effects at all, but there is a very low risk that even at these doses, you may be at increase risk for developing cancer. Measures are taken to ensure that you are an appropriate candidate for these tests and that the risks to you are minimal.

Nuclear Medicine Cardiac Stress Test. If you are assigned to the nuclear medicine cardiac stress test, there are some risks from this test used to evaluate your heart health in this study. The nuclear medicine radiotracer in the trial will bring a small dose of radiation into your body. The radiation dose associated with this test will range from approximately 10 to 20 mSv. This test is currently one of the most widely used tests for diagnosing heart disease. At doses much higher than you will receive, radiation is known to increase the risk of developing cancer after many years. The dose that you will receive will very likely have no effects at all, but there is a very low risk that even at these doses, you may be at increase risk for developing cancer. Measures are taken to ensure you are an appropriate candidate for these tests and that the risks to you are minimal.

Reproductive Risks

Because possible exposure to radiation can damage an unborn baby, you will need to inform your study doctor or research staff if you are pregnant or suspect that you may be pregnant. If you are pregnant, you will not be able to participate in this study. If you are unsure, you will need to have a negative pregnancy result per the usual standard of care prior to enrolling and/or prior to imaging in this trial.

For more information about risks and side effects, ask your study doctor.

WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART IN THE STUDY?

Taking part in this study may or may not make your health better. The results of your study-related diagnostic test will be shared with your treating doctor. The information from this study will help doctors decide diagnostic testing and treatment for people with chest pain in the future. The researchers hope the findings from this study will help reduce the need for a surgical procedure for some patients and will show the value of medical treatment before surgery.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT WANT TO PARTICIPATE?

You may choose not to take part in this study. If you choose not to participate, there will be no penalty and your treatment/medical care will not be affected. Your treating doctor can tell you the different available treatments for your chest pain or heart condition.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?

We will do our best to make sure that your personal information will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. Records of your participation on this study, your progress, and images submitted (such as CCTA) while you are on the study will be kept in a confidential form at <<*Institution*>> and in a computer file at the headquarters of the American College of Radiology Imaging Network (ACRIN) in Philadelphia. All data sent to ACRIN over the Internet will be coded so that other people cannot read it. All personal identifiers are removed and replaced with a unique identifying number.

You further understand and agree that authorized representatives of ACRIN, the FDA, AHRQ and its agents and contractors, the Institutional Review Board (IRB) of <<*Institution*>> and other groups or organizations that have a role in this study may, without obtaining additional consent from you, have access to and copy both your medical and research records, including the results of your participation in this study. This access is necessary to ensure the accuracy of the findings, the completion of the study, and your safety and welfare. If any publication or presentations result from this study, you will not be identified by name. Results will be reported in a summarized manner in which you cannot be identified.

All personal identifiers will be removed and replaced with a unique identifying number to protect your identity. Your test results and clinical data important for the trial results will be kept permanently on file at ACRIN and may be used for future research. Any publications based on future research will not contain any identifying details or names. These images will not contain any identifying information and may be used for radiologist training and/or future research.

WILL I BE PAID FOR BEING IN THIS STUDY?

You will receive no payment for taking part in this study.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

You will not be billed for the costs of any examinations or treatments that are considered part of the study and not part of standard care, such as the coronary CT and contrast agent used if you are randomly assigned to Group A. However, you and/or your health insurance will be charged for any portion of your care that is considered standard care (that is, if these expenses would have happened even if you were not in the study), such as the nuclear medicine cardiac stress test used in Group B. You may be responsible for any co-payments and deductibles that are standard for your insurance coverage. You and/or your insurance company will be billed for continuing medical care and/or hospitalization, including emergency medical care.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

It is important that you tell your study doctor, <<*insert name*>>, if you feel that you have been injured because of taking part in this study or if any medical emergency, injury, or illness occurs during this study. You can tell the study doctor in person or call him/her at <<*insert telephone number*>>.

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In the case of medical emergency, injury, or illness during this study, emergency medical treatment is available but will be provided at the usual charge. You and/or your insurance will be responsible for the cost of the medical care of that illness or injury. There is no financial compensation that has been set aside to compensate you in the event of injury.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is your choice. You may choose not to take part in the study. If you decide to participate, you are free to leave the study at any time. No matter what decision you make, there will be no penalty to you, and you will not lose any of your regular treatment and medical care options now or in the future. You can still get your medical care from our institution.

During the study, we may find out more information that could be important to you. A Data and Safety Monitoring Committee (an independent group of experts) will be reviewing the data from this research throughout the study. This includes information that might cause you to change your mind about being in the study. If information becomes available from this or other studies that may affect your health, welfare, or willingness to stay in this study, we will tell you about it as soon as possible.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

(This section must be completed)

This document explains your rights as a study participant. If you have any questions regarding your participation in this research study or you have any questions regarding your rights as a research participant, do not hesitate to speak with your treating doctor, the study doctor, or anyone listed below.

You can talk to your treating doctor and the study doctor about any questions or concerns you have about this study. Contact the study doctor, <<insert name>>, at <<insert telephone number>>.

For additional information about your health or medical emergency, you may contact: <<Usually the name of the local hospital information is provided and with instructions to study participants to inform the ER doctor of their participation in a clinical trial.>>

Name

Telephone Number

For information about this study, you may contact:

Name

Telephone Number

For questions about your rights while taking part in this study, call the <<insert name IRB contact person>> at <<insert name of the IRB>> Institutional Review Board (a group of people who review the research to protect your rights) at <<insert telephone number>>.

<<Provide the name of a local IRB contact person.>>

Name

Telephone Number

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WHERE ELSE CAN I GET MORE INFORMATION?

More information on CT scans can be found in the “Patients” section of the ACRIN web site: www.acrin.org. You or your doctor can print a description of CT scans from this web site.

ACKNOWLEDGEMENT

When you sign this document, you are agreeing to take part in this study. This means you have read all the above information, asked questions regarding your participation, and received answers that you understand to all your questions. You also may have the opportunity to take this consent form home for review or discussion if you would like. A copy of the signed consent will be given to you.

You willingly give your consent to participate in this study.

Printed Name of Study Participant/
Legal Representative

Signature

Date

APPENDIX II

ACRIN 4701

AUTHORIZATION TO RELEASE/DISCLOSE MEDICAL RECORDS TEMPLATE:
HIPAA COMPLIANT RELEASE OF PATIENT INFORMATION
PURSUANT TO 45 CFR 164.508

FROM: American College of Radiology Imaging Network (ACRIN)
ACRIN 4701—Record Procurement Unit
1818 Market Street, Suite 1600
Philadelphia, PA 19103

RE: Patient Name: _____
Date of Birth: _____

I authorize and request any and all of my healthcare providers to disclose my protected health information to ACRIN for the purpose of review and evaluation of the cost-effectiveness and healthcare utilization for diagnosis of cardiac-related symptoms for the ACRIN 4701 trial, entitled *Randomized Evaluation of Patients with Stable Angina Comparing Utilization of Diagnostic Examinations*.

I am authorizing release of all medical records pertaining to cardiac-related care and incidental findings care identified during trial-related diagnostic assessment and disclose full and complete protected medical information to ACRIN and its representatives.

- All medical records, meaning every page in my record, including but not limited to: office notes, face sheets, history and physical, consultation notes; inpatient, outpatient, and emergency room treatment; all clinical charts, reports, order sheets, progress notes, nurses' notes, clinic records, treatment plans, admission records, discharge summaries, requests for and reports of consultations; medication administration reports; documents, test results, statements, questionnaires/histories; and records received by other medical providers.
- All physical, occupational, and rehab requests and related consultations.
- All laboratory, histology, cytology, pathology, autopsy, immunohistochemistry records, and specimens reports; radiology records and images, including (but not limited to) CT, MRI, MRA, PET scans; echocardiogram and cardiac catheterization results.

I understand the medical records to be released or disclosed may include information relating to sexually transmitted diseases, acquired immunodeficiency syndrome (AIDS), or human immunodeficiency virus (HIV), and alcohol and drug abuse and that this information will be used in the trial analysis only if they have any impact on my cardiac health. I have the option to refuse to release this type of medical information. I understand that if I check the "Yes" box below and add my initials, I am authorizing the release or disclosure of this type of information.

Yes _____ (Initials) No

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I understand the following: See CFR §164.508(c)(2)(i-iii)

- a. The healthcare providers who will receive this authorization are unknown at this time.
- b. By signing this authorization form, I am permitting the release of medical records to ACRIN by my treating doctors on past, present, and future treatments for the trial.
- c. ACRIN will contact my treating doctors with my permission to request and continue to collect my medical record until the trial is completed, regardless of whether I decide to actively participate or not to actively participate in the trial (called withdrawing from the study).
- d. I have a right to revoke this authorization at any time. I understand that to revoke this authorization, I must do so in writing and present my written revocation to ACRIN and the health care providers who previously received my authorization. I understand that the revocation will not apply to information that has already been released in response to this authorization.
- e. The information released will be de-identified and will be disclosed to other ACRIN representatives for the purpose of the clinical trial, or as required by law.
- f. My treatment or payment for my treatment will not be impacted by the signing of this authorization.
- g. I will receive a copy of this authorization.

Any facsimile, copy or photocopy of the authorization shall authorize you to release the records requested herein to ACRIN and its representatives.

Your organization will be reimbursed for copies of the medical record upon receipt of an invoice. If you require prepayment or have questions concerning reimbursement, please contact ACRIN at <*phone #*>.

Printed Name of Patient or Legally Authorized Representative

Signature of Patient or Legally Authorized Representative
(See 45CFR § 164.508(c)(1)(vi))

Date

Name and Relationship of Legally Authorized Representative to Patient
(See 45CFR §164.508(c)(1)(iv))

Witness Signature

Date

APPENDIX III

ACRIN 4701

SUPPLEMENTAL MATERIALS AVAILABLE ONLINE

Supplemental materials that support the conduct of the trial are available on the ACRIN web site at the ACRIN 4701 RESCUE Protocol web page (www.acrin.org/RESCUE_protocol.aspx). Types of materials posted online include:

- Application and protocol activation documents (General Qualifying and Protocol Specific Applications, Form FDA 1572, protocol activation checklist, etc.);
- Data forms;
- Imaging materials (Image Transmittal Worksheet, imaging parameter charts, image submission instructions, and scanning and image qualification instructions), available directly via www.acrin.org/RESCUE_imagingmaterials.aspx;
- Recruitment and education materials;
- Regulatory resources, available directly via www.acrin.org/pdrc.aspx;
- Participating site list.

For more information related to the trial, contact the ACRIN 4701 RESCUE Contact Personnel link on the above-mentioned web page for a list of protocol team members at ACRIN Headquarters and their roles.

APPENDIX IV

ACRIN 4701

ENDPOINT-RELATED DEFINITIONS

Primary Endpoint Definition

The primary endpoint will have been reached if either MACE or revascularization occurs.

MACE comprises:

1. Cardiac-related death;
2. Acute myocardial infarction (AMI).

Cardiac-related death: Any sudden cardiac death, death due to AMI, and death due to heart failure/cardiogenic shock. In addition, any death without a clear non-cardiovascular cause or a death without known cause will be presumed cardiovascular death. Cardiac-related death is determined by adjudication of all-cause mortality.

Non-fatal acute myocardial infarction: Defined as evidence of myocardial necrosis/loss of viable myocardium in a clinical setting consistent with myocardial ischemia. MI events will be classified using the categories—type 1 to 5—defined by the *Universal Definition of Myocardial Infarction*.¹

- 1) Spontaneous/non-procedure-related MI (types 1, 2):
 - No recent cardiac intervention (e.g.: prior 72 hours).
 - Abnormal levels of cardiac biomarkers, which are defined as values above the decision threshold considered diagnostic of MI at the local laboratory. Cardiac troponin is the preferred biomarker, and takes precedence over CK-MB. When troponin levels are unavailable, then CK-MB mass is the preferred biomarker and takes precedence over CK-MB activity. In the event that only CK-MB activity is available, abnormal is defined as total CK > 2 upper limit of normal and MB > 5% of total CK.

AND one of the following:

- Ischemic symptoms within the prior 48 hours;
- Imaging evidence of loss of viable myocardium;
- New ECG findings (or presumed new if no prior ECG available as defined in the ACC Universal MI definitions).¹

- 2) Procedure-related MI events (types 4, 5) will be considered a primary end-point and are further defined in ancillary documentation provided to the adjudication committee.

Revascularization is defined as an attempted CABG and PCI, whether the procedure is successful or not, to include plain balloon angioplasty, stent placement, brachytherapy, atherectomy, laser, or rotational ablations. Coronary revascularization procedures for restenosis or as part of a staged PCI will be considered a subcategory of coronary revascularization.

Reference

1. Thygesen K, Alpert JS, White HD, et al; the Joint ESC/ACCF/AHA/WHF Task for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. Published jointly in: *Eur Heart J*. 2007;28:2525–2528; *J Am Coll Cardiol*. 2007;50:2173–2195; and *Circulation*. 2007;116:2634–2653.