AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK

ACRIN PA 4005

Randomized Controlled Study of a Rapid "Rule Out" Strategy Using CT Coronary Angiogram Versus Traditional Care for Low- to Intermediate-Risk ED Patients with Potential Acute Coronary Syndromes

Study Chair
Harold I. Litt, MD, PhD
Chief, Cardiovascular Imaging
Department of Radiology
University of Pennsylvania Health System
3400 Spruce Street, Silverstein 1
Philadelphia, PA 19104
Phone: 215-662-3043
Fax: 215-662-7868
Email: Harold.Litt@uphs.upenn.edu

Co-Chair
Judd Hollander, MD
Professor and Clinical Research Director in the
Department of Emergency Medicine
Hospital of the University of Pennsylvania
3400 Spruce Street
Philadelphia PA 19104-4283
Phone: 215-662-2767
Fax: 215-662-3953
Email: hollandj@uphs.upenn.edu

Study Statistician
Constantine Gatsonis, PhD
Center For Statistical Sciences
Brown University, Box G-S121-7
121 South Main Street
Providence, RI 02912
Phone: 401-863-9183
Fax: 401-863-9182
Email: gatsonis@stat.brown.edu

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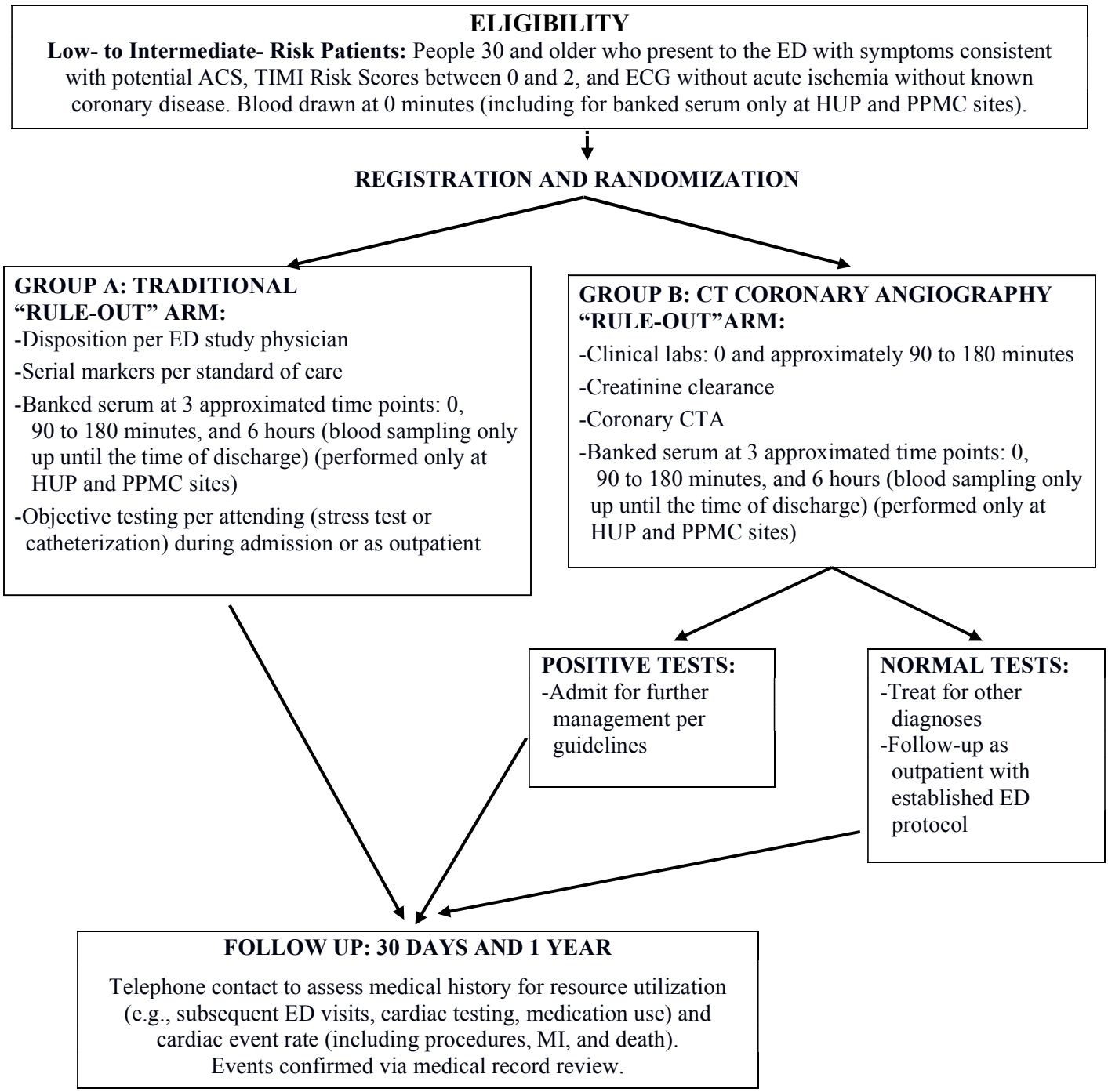
SCHEMA



SPECIFIC HYPOTHESIS

A randomized controlled trial of computed tomography (CT) coronary angiography (Group B) as compared to the traditional approach (usual care) (Group A) for low- to intermediate-risk chest pain patients.

1. To estimate the rate of major cardiac events (AMI or cardiac death) within 30 days in participants randomized to CT coronary angiography (Group B) who were found not to have significant coronary artery disease. "Significant" coronary artery disease is defined as greater than or equal to 50% stenosis of the left main, left anterior descending (LAD), left circumflex, right coronary artery (RCA), or their first order branches.

ELIGIBILITY *(see Section 6.0 for details)*

Patients presenting to the emergency department, who are at low- to intermediate-risk for an acute coronary syndrome by routine clinical assessment and meet the inclusion and exclusion criteria, will be candidates for participation in this study.

SAMPLE SIZE

Total of 1365 participants will be recruited for this trial; 455 will be randomized to the traditional usual-care "rule out" treatment and 910 will be randomized to a "rule out" strategy including CT coronary angiography. Accrual will be accomplished in 24 months.

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.

Of the nearly 6 million patients presenting annually in U.S. emergency departments (EDs) for evaluation of chest pain,[1] 55% to 70% do not have a cardiac cause for their symptoms.[2,3] However, given the prevalence and clinical significance of coronary artery disease (CAD), excluding a cardiac cause of chest pain remains a challenging clinical problem and often mandates extensive testing. There is little ambiguity in the management of high-risk patients: Patients with ST segment elevation myocardial infarction (STEMI) are treated expeditiously with primary percutaneous intervention (PCI) or fibrinolysis. Patients with unstable angina and non-STEMI are treated with antithrombin and antiplatelet agents with rapid transition to the catheterization laboratory. The management and disposition of patients with STEMI and non-STEMI are dictated by consensus expert guidelines.[4,5]

On the other hand, the management and disposition of low- to intermediate-risk patients is considerably less clear. Most of these patients are not ultimately diagnosed with acute coronary syndromes (ACS); yet the great majority is admitted to the hospital for "rule out MI [myocardial infarction]" protocols driving up health care costs. Moreover, these unnecessary hospital admissions lead to inpatient bed shortages, ED crowding, and prolonged ED stays, all of which lead to poor resource utilization.[6]

Current diagnosis of MI relies on the detection of certain biomarkers that are released into the serum after myocardial damage. However, laboratory tests more specific to MI do not become elevated until several hours after the initial event, while sensitive tests that become elevated rapidly do not have adequate specificity. Thus, low- to intermediate-risk patients often are admitted to the hospital to confirm that biomarkers remain normal after a 12- to 24-hour period. We believe that two recent complementary technological advances might help alleviate this predicament: They are computed tomography (CT) coronary angiogram and high sensitivity troponin assays.

2.0 BACKGROUND AND SIGNIFICANCE

Approximately 6 million patients present to the ED annually with the complaint of chest pain or other symptoms suggestive of myocardial ischemia,[1] the majority of whom are admitted to the hospital for evaluation and treatment of potential ACS. Despite this high admission rate, 2% to 4% of patients with acute myocardial infarction (AMI) are inadvertently discharged home from the ED.[2-3,7] Consequently, numerous studies have attempted to effectively risk stratify these patients in order to better identify those at risk for adverse outcomes and optimize care for all patients with ACS. These tools have employed a range and combination of variables such as historical information, clinical characteristics, markers of myocardial necrosis, ECG interpretations, computer algorithms and cardiac imaging.[2,3,7-18] However, not all variables or models previously studied are amenable to ED practice.

2.1 Clinical Risk Stratification

To have utility for the emergency practitioner, a risk-stratification tool needs to be simple, use information available during the initial presentation, and be easily applied early in the clinical course.

Current standard of care requires clinical risk stratification followed by cardiac markers and some form of imaging for most patients with potential ACS.

The Thrombolysis in Myocardial Infarction (TIMI) Risk Score was derived from a study of a population of patients with known unstable angina/non-STEMI.[19] Through a multivariate analysis of their ESSENCE and TIMI 11B databases, Antman et al. identified seven factors to create the TIMI Risk Score; these factors were independently predictive of the adverse outcomes of death, AMI, or recurrent ischemia at 14 days and documented increased risk with the addition of each positive risk factor. Further validation studies using the PRISM-PLUS[20] and TACTICS-TIMI 18[21] trials documented increased benefit from early, aggressive interventions for patients with higher TIMI Risk Scores. A modified version of the risk score applied to the TIMI III Registry[22] of admitted unstable angina/non-STEMI patients successfully predicted death, MI, and/or recurrent ischemia at both 6 weeks and 1 year.[23]

The TIMI Risk Score has now been "validated" in the ED patients with potential ACS. In a retrospective study conducted by our group, we enrolled 3,929 patients whose TIMI Risk Scores were determined at ED presentation.[24] The main outcome was the composite of death, AMI, and revascularization within 30 days. The TIMI Risk Score at ED presentation successfully risk stratified this unselected cohort of chest pain patients with respect to 30-day adverse outcome; adverse outcomes ranged from 2.1% of patients with a score of 0, to 100% with a score of 7. In a prospective study, conducted by University of Pennsylvania Health System investigators,[25] total of 1,490 eligible participants were enrolled and found that the incidence of 30-day death, AMI, and/or revascularization was highly related to the presenting TIMI Risk Score: TIMI 0, 1.7%; TIMI 1, 7.9 %; TIMI 2, 8.4%; TIMI 3, 16.5%; TIMI 4, 24.6%; TIMI 5, 37.5%; TIMI 6, 33.3% (p<0.001). Approximately two-thirds of patients enrolled in the study had a TIMI score of 0 or 1.

Since the TIMI Risk Score is simple, uses information available during acute presentation, and can be easily applied early in the clinical course, we have selected this as the primary risk stratification tool for this protocol. See Appendix III for the TIMI Risk Score Criteria.

2.2 Cardiac Markers

The utility of individual cardiac markers depends upon their ability to detect and risk-stratify patients with potential ACS. In the ED, the ideal marker will allow early detection of patients with ACS, enable optimal treatment pathways to be initiated, and assist with rapid patient disposition and treatment. The optimal use of cardiac markers depends upon the physician's intended use. Since up to 85% of patients who present to the ED with potential ACS do not ultimately have a cardiac etiology for their symptoms, a marker with a high negative predictive value is useful to allow expeditious evaluation and discharge from the ED. Markers with high positive predictive values are ideal to tailor aggressive care for patients at high risk of cardiovascular complications. To that end, a panel of cardiac markers may ideally provide for both a rapid "rule out" and for a rapid identification of patients at high-risk for ACS.

2.2.1 Cardiac Troponin

Cardiac troponin is more specific than other markers for identifying myocardial injury. Following AMI, first generation cardiac troponin assays became elevated at the same rate as CK-MB—peaking at 12 to 24 hours, and remaining elevated for 7 to 10 days. These cardiac troponin assay had a higher specificity for myocardial necrosis than CK-MB in selected subsets of patients with ACS, such as patients with recent surgery, cocaine use, chronic renal failure, and

skeletal muscle disease,[30-32] but in ED patients with potential ACS without these confounding conditions, they had similar sensitivity and specificity for detection of AMI as CK-MB.[32-34]

Although the early generations of cardiac troponins were useful for both diagnosis and risk stratification of patients with chest pain,[36] ACS, and/or AMI, cardiac-marker testing in the ED, they did not identify most ED patients that subsequently developed adverse events.[37,38] Thus, patients with negative initial markers still require evaluation and testing as dictated by their clinical presentation.

The latest generation of cTn assays have demonstrated 99th percentile values ranging from 0.012 to 0.06 µg/L equivalent to 12 to 60 pg/mL; with lower limits of detection to 6 pg/mL [39-41] It is believed that these assays can measure small increases in cTn within the first couple of hours following presentation. In one study, a high sensitivity commercial cTnI assay allowed the diagnosis of acute MI to be made using rising values, in over 80% of patients within 2 to 3 hrs of presentation.[42] This reduction from the typical time frame of 6 to 12 hours required to diagnose AMI may also allow targeted therapies to be administered more quickly. Other potential advantages of high sensitive cTn assays include earlier rule-out of non-cardiac chest pain and detection of patients that are currently labeled unstable angina.[43]

2.3 CT Coronary Angiogram

Electron beam CT (EBCT) for coronary calcium scoring is useful for detection of high-grade stenosis and occlusion with a sensitivity of 92% and specificity of 94%.[44] McLaughlin et al used EBCT to coronary calcium scoring stratify ED patients with chest pain without known CAD.[45] Only 1 of 48 patients with a negative test had a cardiac event.[45] Laudon et al found a 100% negative predictive value in 53 patients compared to other assessments for CAD.[46] Georgiou et al performed a prospective observational study of ED patients with chest pain.[47] They found the cardiovascular event rate to be 0.6% for 76 patients with a calcium score of 0 compared to 14% for patients with calcium scores greater than 400. Raggi et al studied 207 low- to intermediate-risk patients and found that EBCT for coronary calcium scoring has a sensitivity of 74% and a specificity of 89% for the presence of obstructive CAD.[48] These studies suggest that EBCT for coronary calcium scoring can provide valuable prognostic information for ED patients with chest pain. Further, in Raggi et al's Bayesian analysis, EBCT provided a cost savings of 45% to 65% over a pathway including treadmill testing.[48]

Coronary calcium scoring detects calcified atherosclerotic plaques but does not detect plaque without calcification. Studies in ED patients have demonstrated the safety of using the absence of coronary calcifications as criteria for risk stratification;[44-47] however, the addition of CT coronary angiography to coronary calcium scoring further enhances this diagnostic test by detecting both coronary calcification and coronary atherosclerosis (or plaque). Leber et al reported a specificity of 97%, indicating the utility of the method in identifying absence of CAD.[49] Raff et al compared invasive and CT coronary angiography in 70 patients; they analyzed 1,065 coronary artery segments and found a mean difference in percent stenosis of 1.3 ± 14.2%.[50] Specificity, sensitivity, positive and negative predictive values of CT coronary angiography for significant stenoses were: 86%, 95%, 66%, and 98%, respectively. This indicates the reliability of a negative CT coronary angiogram in excluding CAD.

Prior cardiac catheterization results are known to be exceedingly useful for risk stratification. Patients who have previously been documented to have minimal (<25%) stenosis or normal coronary

arteriograms have an excellent long-term prognosis with greater than 98% free from myocardial infarction 10 years later.[51] Repeat cardiac catheterizations an average of 9 years later found that approximately 90% of patients did not develop even single vessel CAD.[52] Thus, a recent cardiac catheterization with normal or minimally-diseased vessels almost eliminates the possibility of an ACS. These patients are routinely discharged from the ED without admission for further evaluation of potential ACS.

Based on this body of evidence, a combination approach has led the ED at the Hospital of the University of Pennsylvania (HUP) to commence utilization of the test in "real time" clinical practice, consistent with the standard of care, including:

- The outstanding negative predictive value of coronary calcium scoring, as documented in 3 studies of ED patients with potential ACS;[45,46,47]
- Documented correlation between CT coronary angiography and routine cardiac catheterization results;
- The ability to obtain both calcium scores and visualization of the coronary arteries with CT coronary angiography.

Continuous quality improvement initiatives have found that the test performance, in our patient population, performs as well as that reported in the literature.

Studies have demonstrated that CT coronary angiography can accurately identify or exclude coronary stenosis in low-,[53-55] intermediate-,[56-59] and high-risk[57,60,61] cohorts of patients with potential ACS. Most studies in high- and intermediate-risk patients have not used the test for clinical decision making. In these subgroups the test has been shown to be accurate, provide sufficient quality for diagnostic decision making,[60] and provide independent prognostic information over baseline clinical risk factors.[61] However, its greatest utility may lie in identifying patients without disease, since patients with ACS will still require further invasive testing and intervention. Studies of intermediate-risk patients also suggest the greatest utility of CT coronary angiography may be in the subset of patients without disease. Schuijf et al[59] found that CT coronary angiography provided accurate information that was complementary to myocardial perfusion imaging. Hoffman et al[62] studied 103 admitted intermediate-risk patients and found that patients without significant coronary disease on CT coronary angiography had a 100% negative predictive value for ACS during index hospitalization as well as for major adverse cardiac events after 5 months. Similarly, Rubinshtein et al[63] found a 100% negative predictive value for the ED diagnosis of ACS in 58 patients. Thirty-five patients without obstructive coronary disease were discharged to home after negative serial troponin measurements without any deaths or MI during the 15-month follow-up period.[63]

At the low risk end of the spectrum, studies have suggested the safety of CT coronary angiography for clinical decision making.[53-55,61] Gallagher et al[54] compared the accuracy of CT coronary angiography with myocardial perfusion imaging for detection of ACS or 30-day major adverse cardiac events following an observation unit admission to rule out ACS. All patients underwent rest and stress myocardial perfusion imaging and CT coronary angiography. Although the 85 patients were not managed based on CT coronary angiography results, the sensitivity of CT coronary angiography was comparable to myocardial perfusion imaging (86% vs 71%), as was the specificity (92% vs 90%).

Goldstein et al[55] studied 197 patients admitted to an observation unit. Patients were randomized to either standard evaluation or CT coronary angiography. The patients with minimal disease on CT coronary angiography were discharged to home. Compared to the standard evaluation, the use of CT coronary angiography resulted in reduced length of stay and lower costs. Although this study was too small to comment conclusively on safety, no patient in either group died or had an AMI.

Chang et al[64] compared direct and indirect costs of 4 different strategies to evaluate patients with potential ACS and found that immediate CT coronary angiography was more cost effective and was associated with a shorter length of stay than: observation unit management with CT coronary angiography, observation unit management with stress test, and admission with hospitalist-directed care. Although the strategy of immediate CT coronary angiography appeared to be as safe as the other strategies, the cohorts were small, preventing definitive conclusions. Khare et al performed decision analysis comparing CT coronary angiography to other strategies and found it to be cost effective in this model. [65]

We have conducted an observational cohort study that extends this prior work and suggests that CT coronary angiography could be safely used to discharge low-risk patients to home from the ED. [66] Like Goldstein et al[55] we had a cohort of patients who received CT coronary angiography after a brief observation unit stay. The low event rate in 265 patients,[66] along with the larger size of our cohort, allows us to conclude that such patients will have a 1% or lower 30-day risk of cardiovascular death or MI, thus demonstrating the utility of CT coronary angiography in rapidly identifying patients without disease.

Unlike prior studies, our work allowed us to extend this approach to patients without mandating an overnight stay in the observation unit.[66] In the 285 patients who received immediate CT coronary angiography after just an initial serum creatinine measurement, we were able to discharge the great majority (75%) safely without any cardiovascular deaths or MIs.[66] Our study shows that the use of CT coronary angiography produces outcomes similar to those reported with inpatient admission and observation unit stays, while avoiding the majority of admissions and shortening the duration of time required to determine the patient is safe for discharge.

None of the 508 patients with a maximal stenosis less than 50% on CT coronary angiography were found to have reversible ischemia on stress test or significant CAD on cardiac catheterization.[66] Although not all patients received further testing, none had a cardiovascular death or MI within 30 days. Conversely, there were no patients with high-grade (>80%) lesions on CT coronary angiography with negative stress tests or catheterizations. As might be expected, patients with coronary stenosis between 50% and 70% on CT coronary angiography had positive or negative stress test results—confirming that anatomy alone cannot always predict physiology, particularly in patients with intermediate degrees of stenosis.

Therefore, based upon the work by the University of Pennsylvania Health Care System research team and others, we plan to incorporate CT coronary angiography into this rapid "rule out" protocol. CT coronary angiography has been available and used in the HUP ED since 2005. It has been available at the Penn Presbyterian ED since 2007. Recent American Heart Association (AHA) guidelines have made it a Class IIa recommendation for evaluation of low risk patients with potential ACS. It is now a standard-of-care procedure.[67]

3.0 STUDY OBJECTIVES/SPECIFIC AIMS

In this study, eligible participants with potential ACS will be randomized to traditional "rule out" care (Group A) or a rapid "rule out" strategy comprising CT coronary angiography (Group B).

3.1 Primary Aim

3.1.1 To estimate the rate of major cardiac events (AMI or cardiac death) within 30 days in participants in Group B, who were found not to have significant coronary artery disease by CT coronary angiography. "Significant" coronary artery disease is defined as greater than or equal to 50% stenosis of the left main, left anterior descending (LAD), left circumflex, right coronary artery (RCA), or their first order branches.

3.2 Secondary Aims

3.2.1 To estimate and compare the rates of significant coronary artery disease detected within the index visit in participants across the two study groups.

3.2.2 To compare hospital length of stay across the two study groups. Hospital length is defined as the time interval from the triage time in the Emergency Department to discharge from the hospital.

3.2.3 To compare health care utilization and cost of care in the two study groups during the index hospitalization.

3.2.4 To compare cardiac health care utilization and cost of care in the two study arms during 1 year post randomization. Health care utilization components will include cardiac-related lab tests, diagnostic (imaging) tests, interventions, repeat ED visits that for cardiac related problems, and repeat hospitalizations for potential cardiac pain.

3.2.5 To compare the two study groups in terms of the respective rates of major cardiac events (cardiac death, AMI, and revascularization) within 1 year post randomization, experienced by participants who were not found to have significant coronary disease at the index visit.

4.0 STUDY OVERVIEW

This is a randomized, controlled trial of the traditional "rule out" approach based on institutional standard of care (Group A) as compared to a CT coronary angiography–based "rule out" strategy (Group B) for low- to intermediate-risk chest pain participants. In the traditional-care arm (Group A), all management and disposition decisions will be made by the healthcare providers caring for the participant. Participants will receive disposition (admit to hospital, admit to cardiac diagnostic unit, or discharge to home), diagnostic testing (none, stress testing, or cardiac catheterization), and treatment according to the team caring for the participant.

In the study CT coronary angiography–based rapid "rule out" arm (Group B), participants will receive initial cardiac troponin and creatinine tests. Upon return of normal laboratory values (including a

calculated creatinine clearance), the participants will receive a CT coronary angiography an estimated 90 minutes following the initial values assessment. Participants with negative test results will be discharged and follow up will comprise telephone interviews 30 days and 1 year after enrollment. Participants with positive test results will be admitted to the hospital for further management, which will be dictated by the admitting team.

For both Group A and B participants enrolled at the University of Pennsylvania Health System (Hospital of the University of Pennsylvania and Penn Presbyterian Medical Center), participants will have serum banked for future research. In order to conduct future research for analysis of cardiac markers, blood samples will be collected at three (3) approximated time points: 0 minutes (time of blood draw), 90 to 180 minutes, and 6 hours, or up until the time of discharge. The blood samples will be collected and stored at University of Pennsylvania Health Care System (See Appendix V for details). There will be no results from these blood tests available to the healthcare providers.

5.0 PARTICIPANT SELECTION/ELIGIBILITY CRITERIA

Patients who present in the Emergency Department (ED) with a chief complaint consistent with potential ACS may be eligible for participation in this trial. If the potential participant meets the inclusion/exclusion criteria, he/she will be randomized to one of the two arms of the study, the traditional standard-of-care arm or the study arm. Randomization will occur after the initial ECG. If the patient has low creatinine clearance, they will be subsequently removed from the study. If an elevated troponin level is discovered after randomization but prior to CT coronary angiography or stress testing, the patient will be treated according to institutional standard of care and will remain in the study for the intent-to-treat analysis. If after randomization, but prior to CT coronary angiography or stress testing, the participant is discovered to have had CT coronary angiography or normal catheterization results within the year prior to presentation, then the participant will be treated according to institutional standard of care and will be included in the analysis for intent to treat.

5.1 Inclusion Criteria

- **5.1.1** Participant is 30 years of age or older;
- **5.1.2** Participant presents with complaints consistent with potential ACS (e.g., chest pain, shortness of breath, other);
- **5.1.3** Participant requires admission or objective testing to exclude ACS;
- **5.1.4** Participant with initial ECG result without acute ischemia;
- **5.1.5** Participant with an initial Thrombolysis in Myocardial Infarction (TIMI) Risk Score of 0 to 2 (see Appendix III);
- **5.1.6** Participant is willing to provide a written informed consent.

5.2 Exclusion Criteria

- **5.2.1** Patients who present with symptoms that are clearly not cardiac in origin (e.g., chest pain secondary to herpes zoster, obvious pneumonia, or recent trauma);
- **5.2.2** Patients with no initial ECG performed in the ED;
- **5.2.3** Patients with ST-elevation myocardial infarction (STEMI);

5.2.4 Patients with existing co-morbidity that requires admission regardless of presence of ACS (e.g., uncontrolled diabetes);

5.2.5 Patients with contraindications to CT coronary angiography:

5.2.5.1 Iodinated contrast allergy;

5.2.6 Patients who are known to have had CT coronary angiography in the year prior to presentation;

5.2.7 Patients who are known to have normal catheterization results (no or minimal, <25%, stenosis) in the year prior to presentation;

5.2.8 Patients who are pregnant;

5.2.9 Patients with known renal insufficiency (e.g., creatinine clearance < 60 mL/min/1.73 m^2);

5.2.10 Patients with no telephone or cell phone numbers (preventing follow up);

5.2.11 Patients unwilling to provide a written informed consent.

5.3 Recruitment and Screening

The research team at each participating site includes the ED attending physician, CT technologist, and research associate(s). The investigator and the research staff will be responsible for the screening, review of participant medical records and investigator-designated data submission.

5.4 Inclusion of Women and Minorities

The ACRIN participating institutions will not exclude potential participants from participating in this or any study solely based on ethnic origin or socioeconomic status. Every attempt will be made to enter all eligible participants into this protocol and therefore address the study objectives in a patient population representative of the entire English-speaking population at risk for ACS treated by the institution.

Women of all ethnic groups are eligible for participation in this study.

6.0 SITE SELECTION

6.1 Institution Requirements

The potential sites for this study are ACRIN-participating institutions, predominantly in Pennsylvania but also including other sites in the United States with ED research programs, that meet qualifications for participating in this study. Each institution must complete a Protocol Specific Application (PSA) (available online at www.acrin.org/4005_protocol.aspx) and have the cardiac CT scanner approved prior to the institution participating in the study (Appendix II).

Detailed information for CT Qualification Procedures and its application to become qualified, as well as the PSA can be accessed at www.acrin.org/4005_protocol.aspx. All qualification documentation must be submitted to ACRIN Headquarters for review and approval.

6.2 CT Reader Qualifications

6.2.1 All CT coronary angiography readers must meet American College of Cardiology/ American Heart Association level 3 cardiac CT training guidelines.

6.3 IRB Approval and Informed Consent Form

The study will be approved by the appropriate institutional review boards (IRBs) and the appropriate institutional review committees. All study participants will provide written informed consent (ICF).

All institutions must have site-specific IRB approval for the protocol and ICF for this study. (The ICF is included in this protocol as Appendix I.) 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 at the institution. A copy of the IRB approval letter and a copy of the IRB-approved, site-specific ICF must be submitted to the ACRIN study monitor for review and to keep on file at ACRIN Headquarters (fax: 215-717-0936, ATTN: ACRIN PA 4005 Study Monitor) prior to registering the first participant.

6.4 Accrual Goals and Monitoring

The ACRIN Biostatistics and Data Management Center (BDMC) will monitor participant accrual. Total target accrual for this study is 1365 participants. During the first year, the accrual goal will be 700 participants. If the target is not reached, a review will be conducted with the intention of discovering and resolving any recruitment barriers.

Monitoring of study-specific adverse events (AEs) and cardiac-related deaths and AMIs will be conducted by various oversight committees and individuals. The medical monitor will review AEs on an on-going basis. An adjudication committee will provide oversight to the reported cardiac-related deaths and AMI. In addition, accrual and safety information will be presented to the ACRIN PA (Pennsylvania) Data and Safety Monitoring Board (DSMB) at regularly scheduled meetings thereof; the PA DSMB may, at its discretion, re-evaluate the study with respect to feasibility or the need for additional participating institutions.

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 Biostatistics and Data Management Center (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 and randomization to Group A or Group B, 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 form due dates at the DMC. These calendars will be updated as the study proceeds to reflect data that have been received, reply deadlines for queries about unclear data, deadlines for follow-up reports of adverse events, or changes in the protocol that change the data being collected or the timeframe. Updated calendars for each participant can be obtained 24 hours a day from the ACRIN web site. The research associate 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. For additional details on Clinical Data Collection Criteria, see Appendix IV. 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 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 is 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 research associate 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 research associate 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, ACRIN can serve as an ISP.

7.3 Registration/Randomization Protocol

Once the investigator-designated research staff (i.e. the Research Associate [RA]) has completed the eligibility checklist (Appendix II) and the participant has been found to be eligible to participate in the trial, the potential participant will be consented. Upon obtaining a signed informed consent form, the RA will register the participant by logging onto the ACRIN web site (www.acrin.org), and selecting the link for Data Center Login. **Randomization will not occur until after the initial ECG is available but may occur prior to the availability of creatinine and cardiac troponin results.** If, after randomization, the participant is found to have an initially low creatinine clearance, they will be removed from the study. If an elevated troponin level is discovered after randomization but prior to CT coronary angiography or stress testing, the patient will be treated according to institutional standard of care and will remain in the study for the intent-to-treat analysis.

The registration screen begins by asking for the date on which the eligibility checklist was completed, identification of the person who completed the checklist, whether the potential participant was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

After completing the registration, the system assigns a participant-specific case number and a randomization group. The system then moves to a screen, which confirms that the participant has been successfully enrolled/randomized. This screen can be printed so that the registering site will have a copy of the registration/randomization for the participant's record.

Participants will be randomized into study group assignments (to Group A—traditional care—or Group B—CT coronary angiography) in 1 to 2 ratio based upon blocked assignment in groups of 30. To avoid duplicate randomizations, do not re-register or re-randomize a participant; contact the DMC regarding any questions or problems.

7.3.1 Unsuccessful Registrations/Randomization:

In the unlikely event that the ACR web registration site is not accessible, sites will be able to use sequential numbered opaque sealed envelopes (SNOSE) to randomize participants. Randomization envelopes must always be opened sequentially (next highest number). Prior to opening the envelope, the research associate should write the date and her/his signature on the front of the envelope. When the ACRIN web site is accessible the RA should register the participant using the envelope randomization option.

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

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 research associate. 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 is 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 the 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

Upon presentation to the emergency department with complaints symptomatic of potential ACS, the principal site investigator (or designee) at the participating emergency department must confirm that the potential participant meets the eligibility criteria (see Section 5.0). Medical eligibility will be determined as detailed in the inclusion and exclusion criteria section of the protocol. This will require thorough review of cardiac risk factors, symptom characteristics, blood test results, etc, as detailed below for baseline Visit 1. Upon registration and randomization of the participant to Group B (CT coronary angiography "rule out" arm) or Group A (traditional standard-of-care "rule out" arm), participant will proceed with either CT coronary angiography per protocol as outlined in Section 9.1 or institutional traditional standard-of-care "rule out" strategies.

For both Group A and B participants enrolled at the University of Pennsylvania Health System (Hospital of the University of Pennsylvania and Penn Presbyterian Medical Center) will have serum banked for future research. In order to conduct future research for analysis of cardiac markers, blood samples will be collected at three (3) approximated time points: 0 minutes (time of blood draw), 90 to 180 minutes, and 6 hours, or up until the time of discharge. The blood samples will be collected and stored at University of Pennsylvania Health Care System (see Appendix V for details). There will be no results from these blood tests available to the healthcare providers.

8.1 VISIT 1: Baseline Visit—Eligibility & Randomization

8.1.1 Phase 1 of Visit 1

Baseline assessment to determine eligibility will comprise of the following:

- Obtain a signed informed consent form;
- Obtain medical history and conduct physical examination, including:

  - Demographic characteristics, including personal contact information for follow up, proxy contact, and Social Security Number;
  - Cardiac risk factors;
  - Chest pain characteristics;
  - Associated symptoms;
  - Obtain clinical blood sample results from initial blood work to check creatinine clearance prior to CT coronary angiography, and cardiac troponin (if available);
  - Medications (including use of aspirin, statins, and anti-platelet medications);
  - Initial vital signs (pulse, temperature, blood pressure, resting heart rate, and oxygen saturation level);
  - Previous treatment (when, where, and what, including out-patient cardiac testing such as catheterization, echocardiographic stress testing, SPECT myocardial perfusion imaging, percutaneous coronary interventions [PCIs], coronary artery bypass graft [CABG], and chest x-rays);
  - Disposition;
- Obtain blood samples for blood collection at three (3) approximated time points: 0 minutes, 90 to 180 minutes, and 6 hours or immediately prior to discharge (blood banked for future use—see Appendix V for blood banking instructions)—if participant consents to blood collection (performed only at HUP and PPMC sites);
- Obtain resting ECG assessment: ST segment deviation, T and Q wave morphology, presence of bundle branch block(s);
- Assess TIMI Risk Score (see Appendix III);
- Register the eligible participant;
- Assign randomization code to CT coronary angiography "rule out" arm (Group B) or traditional standard-of-care "rule out" arm (Group A).

8.1.2 Phase 2 of Visit 1: After Registration and Randomization

8.1.2.1 Traditional Standard-of-Care "Rule Out" Arm (Group A)

- Determine the disposition of participant to hospital, to cardiac diagnostic unit, or discharge to home;
- Conduct diagnostic testing: stress testing, cardiac catheterization, or other testing as dictated by healthcare providers per standard of care;
- Initiate treatment for participant per standard of care;
- Obtain blood samples at three (3) approximated time points: 0 minutes, 90 to 180 minutes, and 6 hours or immediately prior to discharge (blood banked for future use—see Appendix V for blood banking instructions) (performed only at HUP and PPMC sites).

8.1.2.2 CT Coronary Angiography "Rule Out" Arm (Group B)

- Obtain clinical blood sample approximately between 90 to 180 minutes after initial blood work to check repeat cardiac troponin (optional if participant already has had two clinical blood draws [e.g., if participant is randomized from an observation unit]);
- Conduct diagnostic testing: stress testing, cardiac catheterization, or other testing as dictated by healthcare providers per standard of care;

- Obtain clearance and order for CT coronary angiography after normal values have been confirmed;
- Confirm negative pregnancy status on all female participants of childbearing potential via urine or serum pregnancy test prior to imaging;
- Perform CT coronary angiography within approximately 90 minutes following the return of initial values or as soon as possible once CT coronary angiography is available (see Section 9.0 for imaging details);
- Obtain blood samples at three (3) approximated time points: 0 minutes, 90 to 180 minutes, and 6 hours or immediately prior to discharge (blood banked for future use—see Appendix V for blood banking instructions) (performed only at HUP and PPMC sites);
- Assess for AEs related to the CT coronary angiography.

8.1.3 Phase 3 of Visit 1: For Group B ONLY, CT Coronary Angiography "Rule Out" Arm Only—Post-CT Coronary Angiography

The results of the cardiac CT scan, including the presence and extent of coronary atherosclerotic plaque, coronary artery stenosis, global and regional LV dysfunction, and noncoronary findings will be provided to the ED treating physicians immediately.

8.1.3.1 Negative CT Coronary Angiography Results

- Discharge participant from the hospital unless other indications for admission per standard of care, such as elevated biomarkers or noncoronary disease requiring admission.

8.1.3.2 Positive CT Coronary Angiography Results

- Admit participant to the hospital for further management as dictated by the admitting healthcare team per standard of care.

8.1.4 Phase 4 of Visit 1: At End of ED or Hospital Stay, Confirm Treatments and Outcomes

8.1.4.1 Confirm ED measures for participants in Groups A and B with treating resident or attending physician or medical record review.

8.1.4.2 Contact the treating resident or attending physician or review the medical record to collect:

- Treatments details (e.g., medications, stress test, CT coronary angiogram, chest CT);
- Chest x-ray results;
- ED disposition;
- Discharge medications;
- Initial creatinine clearance.

8.2 VISIT 2: FOLLOW UP—After 30 Days From Enrollment Date

Follow up will comprise of a telephone contact with the participant or proxy for additional medical information up to 30 days from the time the participant presented in the emergency department for evaluation chest pain. The telephone contact should occur after 30 days from the enrollment date. Ideally, contact should occur no later than 14 days after the 30 days from the

enrollment date. However, this is a timing guideline. The form related to 30-day follow up should not be completed until contact has been made or other confirmation of participant's status (e.g., record review or known death) has been verified via medical record, contact with participant or proxy, or SSDI. As research staff attempt to make contact, a screening log will be maintained to document attempted contact.

8.2.1 Contact participant via telephone to obtain additional medical information. If the participant or proxy responds that a cardiac event or hospitalization related to cardiac symptoms has occurred, the site then will conduct a review of the participant's medical records or the Social Security Death Index (SSDI).

8.2.2 No fewer than three (3) attempts should be made by research staff to contact the participant or proxy. Ideally, attempts will continue until contact is made. Attempts will be documented in a screening log. Participants should not be considered "lost to follow up" until the final month of follow up for the last participant who was enrolled.

8.2.3 The following data (and test results) will be obtained and reviewed at these time points:

- Death;
- Heart attack/acute MI;
- Repeat ED visits;
- Subsequent hospitalization for cardiovascular presentation;
- Revascularization (e.g., PCI or CABG);
- Cardiac testing (such as CT coronary angiography, echocardiogram, stress testing, cardiac MRI, and nuclear imaging);
- Cardiac catheterization;
- Visit(s) to cardiologist(s);
- Medication use (especially use of aspirin, statins, and anti-platelet medications).

8.3 VISIT 3: FOLLOW UP—After 1 Year From Enrollment Date

Follow up will comprise telephone contact with the participant or proxy for additional medical information up to 1 year from the time the participant presented in the emergency department for evaluation of chest pain. The telephone contact should occur after 1 year from the enrollment date. Ideally, contact should occur no later than 14 days after the 1 year enrollment date. However, this is a timing guideline. The form related to 1-year follow up should not be completed until contact has been made or other confirmation of participant's status (e.g., record review or known death) has been verified via medical record, contact with participant or proxy, or SSDI. As research staff attempt to make contact, a screening log will be maintained to document attempted contact.

8.3.1 No fewer than three (3) attempts should be made by research staff to contact the participant or proxy. Ideally, attempts will continue until contact is made. Attempts will be documented in a screening log. Participants should not be considered "lost to follow up" until the final month of follow up for the last participant who was enrolled or 3 months after the due date, whichever is later.

8.3.2 Contact participant via telephone to obtain additional medical information. If the participant or proxy respond that a cardiology visit, cardiac event, ED visit for cardiac symptoms, or hospitalization related to cardiac function have occurred, the site then will

conduct a review of the participant's medical records or the Social Security Death Index (SSDI). The following data (and test results) will be obtained and reviewed at these time points:

- Visit(s) to cardiologist(s);
- Outpatient cardiac testing (such as CT coronary angiography, catheterization, echocardiographic stress testing, SPECT myocardial perfusion imaging, PCIs, and CABG,);
- Medication use (especially use of aspirin, statins, and anti-platelet medications);
- New CAD or ACS diagnosis;
- Cardiovascular events (e.g., acute MI);
- Repeat ED visits;
- Subsequent hospitalization for cardiovascular presentation;
- Revascularization (e.g., PCI or CABG surgery);

8.4 Off-Study Criteria

Participants will be removed from the study and will need to be replaced to ensure target enrollment for the following reasons:

- Previously-unknown creatinine clearance levels contraindicating use of the contrast agent (creatinine clearance < 60 mL/min/1.73 m^2) at any time prior to CT coronary angiography;
- Previously-unknown positive return of D-dimer levels prior to CT coronary angiography that causes participants to have protocol violation, due to testing for PE.

8.5 Study Procedures Table

Study Procedures For Both Groups A & B, Unless Otherwise Specified	VISIT 1				VISIT 2 TELEPHONE FOLLOW UP: After 30 Days From Enrollment Date	VISIT 3 TELEPHONE FOLLOW UP: After 1 Year From Enrollment Date
	Phase 1: Baseline Visit	Phase 2: After Registration and Randomization	Phase 3: Group B Only	Phase 4: At End of Stay, Confirm ED Visit Treatments and Outcomes		
Informed Consent Form	X					
Medical History (see Section 8.1)	X					
Physical Examination/Vital Signs	X					
Blood Tests, Including for Cardiac Biomarkers	X	X				
Blood Sample Collection As Appropriate	X	X		X		
Resting Electrocardiogram	X					
TIMI Risk Score	X					
Eligibility/Registration	X					
Randomization to Group A or B	X					
Urine or Serum Pregnancy Test, As Appropriate, Immediately Prior to CT Scan **(Group B Only)**		X				
CT Scan **(Group B Only)**		X				
CT Scan Results Assessment **(Group B Only)**: Negative Results = Discharge Positive Results = Admission to Hospital			X			
Diagnostic Testing As Appropriate		X				
Treatment As Appropriate		X				
Contact Treating Resident or Attending Physician to Confirm Stay Details				X		
Assess for Adverse Events **(Group B ONLY)**		X				
Assessment of Cardiac-Related Visits, Medications, Treatments, Etc					X	X
Medical Records Review					X	X

9.0 IMAGING PROTOCOL

9.1 CT Coronary Angiography

Participants with elevated heart rates will be given oral or intravenous metoprolol to reduce the heart rate according to local practice, when not contraindicated. CT coronary angiography will be performed using a 64 or greater slice CT scanner with the ability to perform retrospectively ECG-gated cardiac studies. The study will begin with a pre-contrast ECG-triggered acquisition through the entire chest (or as much of the chest as breathholding permits) for the purpose of calcium scoring, and to evaluate lung abnormalities. This will be followed by an intravenous injection of 80 to 120 mL of non-ionic iodinated contrast with bolus tracking in the descending aorta, and a saline flush. A dual-phase or three-phase injection may be utilized depending upon local practice. Nitroglycerin, either sublingual tablet or spray, may be used to improve coronary artery visualization according to local practice. Patients with known sensitivity to nitroglycerin, hypotension (generally systolic blood pressure < 100 mm Hg), and those with a recent history of phosphodiesterase inhibitor use should not receive nitroglycerin.

After the appropriate scan delay, an ECG-gated acquisition from the carina to the base of the heart will be performed. The use of radiation dose reduction techniques, including ECG-gated tube current modulation and low kVp scanning in smaller patients, is strongly encouraged. Sites with hardware and software allowing prospectively ECG-triggered acquisitions, as well as appropriate clinical experience with this technique, may choose to use it in selected cases for dose reduction according to their clinical routine. Image data will be reconstructed at multiple phases of the cardiac cycle and will be post-processed on a 3-D workstation using a variety of tools and applications depending upon local practice and availability. The imaging test will be considered positive if the participant has an equal to or greater than 50% stenosis of the right coronary, left main, left anterior descending, or circumflex arteries or of their first-order branches. Results will be communicated to the responsible ED staff immediately upon interpretation. Reporting of studies will be according to the AHA coronary segment model and will also include an assessment of global and regional cardiac function (when available), calcium score, mass, and volume, and additional cardiac and non-cardiac findings.

The imaging protocol described above is the suggested imaging approach for this trial; however, sites with experience in CT coronary angiography may perform the scan according to their own protocol as long as both a pre-contrast acquisition for calcium scoring and a post-contrast acquisition for coronary angiography are obtained. For applicable purposes, the decision to perform contrast-enhanced imaging in the presence of a large amount of calcium should be made according to the procedures for CT coronary angiography at each individual site. Studies must be reported according to the format found in the ACRIN data submission forms.

The protocol required images must be in DICOM format on CD/DVD-ROM or submitted via the Internet using secure File Transfer Protocol (sFTP), and transmitted along with an Imaging Transmittal Worksheet (ITW) which can be found on the ACRIN PA 4005 web site (www.acrin.org/4005_protocol.aspx). The required images must be submitted to ACRIN Imaging Core Lab. ACRIN can provide electronic image submission and anonymity utilities for participating institutions via TRIAD software. For support in sending the images via the internet using TRIAD, contact the representatives of the Image Management Center (IMC) via email at Triad-Support@phila.acr.org or via phone: 215-940-8820.

Monitoring of radiation dose will be a part of the image quality assurance program for this trial, and sites with higher average doses will be given feedback by the core lab and PI concerning methods to reduce dose.

9.2 Image Submission

If required and part of the protocol, images maintained at ACRIN Headquarters Image Archive may be distributed to other participating sites, using sFTP, or CD-ROM where appropriate, for purposes of secondary review.

9.2.1 Removal of Confidential Participant Information: The header record on DICOM formatted image data, which often contains information identifying the participant by name, MUST be scrubbed before the images are transferred.

This involves **replacing** the following:

- Participant Name tag with the ACRIN Institution ID or number;
- Participant ID tag with the ACRIN case number; and
- Other Participant ID tag with ACRIN Study Number.

9.2.2 sFTP Transfer: Digitally generated image files in DICOM v3.0 format can be transmitted to the ACRIN IMC via sFTP directly to the image archive. This can be performed using a customized software program or by using TRIAD software available from ACRIN. An ITW must be faxed at the time images are transmitted. Contact the ACRIN IMC for additional details at Triad-Support@phila.acr.org

9.2.3 Please fax the ITW to:

ACRIN Core Lab at (215) 923-1737, ATTN: ACRIN PA 4005 Imaging Specialist

9.2.4 In the event that the transfer of scrubbed image headers is not available, images may also be sent on a CD/DVD-ROM to the ACRIN IMC for transfer to the image archive. Please contact ACRIN prior to sending the media to confirm compatibility.

9.2.5 Images and the ITW may be mailed to:

American College of Radiology Imaging Network
MR/CT Core Laboratory
Attn: ACRIN PA 4005
1818 Market Street 16th floor
Philadelphia, PA 19103

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.

10.3 Adverse Event Grading

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

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

(For terms listed in the CTEP Active version of the CTCAE, the grade is still recorded as 1, 2, 3, 4, or 5; however, the definition of the various grades will be specific to the term being used.)

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 GROUP A: Expected Adverse Events Associated With Standard of Care Practice

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.

10.7 GROUP B: Expected Adverse Events Associated With CT Angiography

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

10.7.1 Expected Adverse Events From Iodinated Contrast Agent

Rare

- Nausea;
- Vomiting;
- Hives;
- Rash.

Rare, but potentially life threatening

- Kidney failure;
- Allergic reaction (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 most common reactions are nausea, vomiting, hives, or rash. The risk of death is less than 1:10,000.

10.7.2 Expected Adverse Events From IV Needle Placement

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

10.7.3 Expected Adverse Events Associated With Radiation Risks

The radiation dose from a 64 or greater slice CT 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 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 patients, 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

Utilizing these techniques, the radiation dose associated with this protocol will range from approximately 2 to 21 mSv (for obese participants). This corresponds to approximately 0.6 to 7 times the yearly background radiation dose in most regions of Pennsylvania. 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 as 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 ACS, including coronary catheterization (4 to 10 mSv) and stress myocardial perfusion imaging using SPECT (10 to 20 mSv).[68,69]

10.7.4 Expected Adverse Events From CT Scan

- Discomfort;
- Claustrophobia.

10.8 Recording of Adverse Events

Prompt reporting of AEs is the responsibility of each investigator, clinical research associate (RA), and/or nurse engaged in clinical research. Please refer to Sections 10.9 and 10.10 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 case report form (CRF), and submission to ACRIN for preparation of a report for DSMB 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.

At each contact (site visit and/or telephone) with the study participant, the investigator or investigator-designee must seek information on AEs through discussion and, as appropriate, by examination. 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 PA 4005 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 principal site 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 10.10 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.

10.9 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.

10.9.1 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.

10.9.2 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.

10.10 How to Report

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

10.10.2 Completed expedited reports should be sent to:

ACRIN AE Coordinator
Re: Serious Adverse Event Report
ACRIN PA 4005
1818 Market Street, 16th Floor
Philadelphia, PA 19103

10.10.3 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).

10.10.4 All expedited adverse event reports should be sent to your local Institutional Review Board (IRB). Please refer to your local IRB's policies regarding adverse events.

11.0 ETHICAL CONSIDERATIONS

This study is to be conducted according to US and international standards of Good Clinical Practice (International Conference of Harmonisation [ICH] guidelines), applicable government regulations, and ACRIN research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB) for formal approval of the study conduct. The decision of the 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.

The investigator will provide ACRIN with the institution's federal wide assurance (FWA) number, along with the IRB approval letter and copy of the IRB-approved informed consent form (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 study participants in 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 local IRB. The study participant MUST be consented with the EC/IRB-approved ICF before the participant is subjected to any study procedures. The IRB-approved ICF MUST be signed and dated by the study participant or legally acceptable representative and the investigator-designated research staff obtaining the consent before the participant is subjected to any study procedures. Any revisions to the ICF at any time during the trial will need to be submitted to the IRB for approval and submission to ACRIN PDRC.

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 ACRIN, the Study Chair, and/or the ACRIN Publication 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 auditing and inspections of all study-related documents by the 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.

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. **Please refer to the study-specific protocol and study-related documents for details.**

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 case report forms (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. CRFs and source documents of selected study participants enrolled at each site will be reviewed. In addition, the initial regulatory documents and any revised regulatory documents will also be monitored.

The ACRIN QA Monitor will review case report forms 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. In addition, the QA Monitor will review the initial and annual regulatory documents and any revised regulatory documents.

14.2 Auditing

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 20% 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. Audits can be completed more frequently and conducted on a yearly basis depending on the outcome of the audit and monitoring. The audits will be conducted per procedures established by ACRIN 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.

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)

CRFs, both web-based and paper forms, are the primary data collection instruments for the study. 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). 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

Sites must obtain initial 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. Investigator will provide a copy(s) of IRB approval letter(s) for any amendment(s), and copy(s) of annual renewal(s).

15.0 STATISTICAL CONSIDERATIONS

15.1 Study Design and Endpoints

Study participants will be recruited among those presenting in the Emergency Department with symptoms consistent with ACS. Participants will be randomized to either a traditional "rule out" approach based on institutional standard of care (Group A) or to a CT coronary angiography-based "rule out" strategy (Group B). Participants will be followed for one year after their index hospitalization to collect data on medical outcomes, health care utilization, and cost.

15.1.1 Primary Endpoint

15.1.1.1 The primary endpoint will be major cardiac event (cardiac death or AMI) within 30 days from randomization, as determined by participant follow up and medical records review. This endpoint will be assessed for each participant. However, the primary aim of the study will examine the endpoint only in participants in Group B, who were found not to have significant coronary artery disease. "Significant" coronary artery disease is defined as greater than or equal to 50% stenosis of the left main, left anterior descending (LAD), left circumflex, right coronary artery (RCA), or their first order branches.

15.1.2 Secondary Endpoints

15.1.2.1 Significant coronary artery disease detected within index hospitalization as assessed by medical record review.

15.1.2.2 Lengths of hospital stay during the index admission.

15.1.2.3 Health care utilization and cost incurred during the index admission and during a 1 year interval post randomization. For the index admission, health care utilization includes all inpatient care. For the 1 year interval, utilization will include all inpatient or outpatient visits, imaging, and laboratory testing

as applicable. Standard Medicare reimbursement rates will be used to compute costs.

15.1.2.4 Major cardiac events experienced during 1 year post randomization, as assessed by participant follow up and medical record review.

15.2 Specific Aims and Analysis Plans

15.2.1 Primary Aim

To estimate the rate of major cardiac events (AMI or cardiac death) within 30 days in participants in Group B, who were found not to have significant coronary artery disease by CT coronary angiography.

The primary aim addresses the safety of the CTA strategy, as implemented in Group B of the study. For this analysis, major cardiac events will be defined as the occurrence of AMI or cardiac death. The analysis will estimate the proportion of patients in Group B who were not found to have significant coronary artery disease during the initial workup but experienced a major cardiac event within 30 days from their index admission. An exact confidence interval for this proportion will be derived and the hypothesis that the proportion exceeds 1% will be tested using a one-sided exact test. In a secondary analysis, factors possibly related to occurrence of major cardiac events will be examined using exact logistic regression modeling.

15.2.2 Secondary Aims

15.2.2.1 *To estimate and compare the rates of significant coronary artery disease detected within the index visit in participants across the two study groups.*

The analysis for this secondary aim will be performed from the intent-to-treat perspective. Diagnosis of significant coronary artery disease will be determined via review of medical records. Rates of significant CAD will be estimated for each study Group and will be compared.

15.2.2.2 *To compare hospital length of stay across the two study groups. Hospital length is defined as the time interval from the triage time in the Emergency Department to discharge from the hospital.*

The analysis for this secondary aim will be performed from the intent-to-treat perspective. Length of hospital stay (LOS) for each participant will be computed based on medical record information. After a graphical exploration of the data using Kaplan Meier curves, LOS will be compared across the two study arms using a non-parametric procedure.

15.2.2.3 *To compare health care utilization and cost of care in the two study groups during the index hospitalization*.

The analysis for this secondary aim will be performed from the intent-to-treat perspective. Health care utilization will be assessed using medical record review. The main components of health care utilization will be cardiac-related lab tests, diagnostic imaging tests, interventions, repeat ED visits for cardiac related problems, and repeat hospitalizations for cardiac pain. Cost of care will

be assessed using standard Medicare reimbursement rates and will be aggregated for each patient over the entire length of the index hospitalization. Measures of key components of utilization will be compared across the two study groups using procedures appropriate for each measure (rate or count). Costs will be compared non-parametrically between the two study groups.

15.2.2.4 *To compare cardiac health care utilization and cost of care in the two study arms during 1 year post randomization. Health care utilization components will include cardiac-related lab tests, diagnostic (imaging) tests, interventions, repeat ED visits that for cardiac related problems, and repeat hospitalizations for cardiac pain.*

The analysis for this secondary aim will be performed from the intent-to-treat perspective and will parallel the analysis for Secondary Aim #3. Utilization and cost will be assessed during over a full year period from the index hospitalization.

15.2.2.5 *To compare the two study groups in terms of the respective rates of major cardiac events (cardiac death, AMI, and revascularization) within 1 year post randomization, experienced by participants who were not found to have major coronary disease at the index visit.*

The analysis for this secondary aim will be performed from the intent-to-treat perspective but will include participants who were found not to have major coronary disease at the index visit. The occurrence of major cardiac events will be assessed via patient follow up and medical chart review. Note that the definition of major cardiac events for this aim includes revascularization, in addition to cardiac death and AMI. The primary analysis for this aim will be performed at the patient level by determining whether any major cardiac event occurred or not. Event rates will be estimated and compared between study groups using exact procedures. In a secondary analysis, the rates of each type of major cardiac event will be examined separately.

15.3 Sample Size/Accrual Rate

Study participants will be recruited and randomized in 1:2 ratio between Group A and Group B. A total of 1365 participants will be enrolled over an accrual period of 24 months at least 4 institutions.

15.4 Power Consideration

15.4.1 Primary Aim

The primary aim of the study is to estimate the rate of major cardiac events (cardiac death or AMI) within 30 days from the index admission in Group B participants who were not found to have significant coronary artery disease during their index admission. An important question in this context is whether the rate of major cardiac events exceeds 0.01. Because the primary aim is focused on Group B patients, the randomization will be done in a 1:2 ratio between groups A and B.

The following table presents estimates of the sample size of participants without major coronary artery disease required in order to achieve power of 90% for testing the null hypothesis that rate of major cardiac events exceeds 0.01. The calculations are based on an exact one-sided test of the null hypothesis at level 0.05.

Power	Sample Size	True rate of major cardiac events
0.9179	473	0.0010
0.9286	**773**	**0.0020**
0.9314	1182	0.0030
0.9173	1693	0.0040
0.9052	2546	0.0050
0.9052	4293	0.0060

Based on prior experience we expect that up to 10% of participants will be found to have significant coronary artery disease. We also expect that the true rate of major cardiac events will be very low and not higher than 2/1000. Under these assumptions, a sample size of 860 evaluable participants in Group B would provide power at least 90% to reject the null hypothesis if the true rate is 2/1000. Allowing for a 5% attrition from the originally enrolled population, we arrived at a final sample size of 910 participants in Group B and 455 participants in Group A, *or a total of 1365 participants*.

The choice of sample size was based on the needs for the primary aim of the study. The planned sample size will also permit reasonable statistical precision for addressing secondary aims of the study. In particular, for the comparison of cost of care during the index visit, we expect the difference in average cost to be at least $600 and more likely about $1000 between the two arms and the standard deviation in each arm to range from $2500 to $3500. Under these assumptions, the proposed sample size will provide power at least 83%, using a two-sided test of size 0.05. The power will be very high (above 99%) to detect a difference in average cost of $1,000.

Also, for the comparison of rates of major cardiac events during one year from the index admission, we expect that the rate in Group A will be from 2% to 5% and in Group B about 1%. The following table presents power estimates for the comparison of the indicated rates.

The computations are based on a two-sided test of level 0.05, using the un-pooled estimate of the variance. The proposed sample size will provide power of about 76% to compare the two groups if the rates are 0.04 and 0.01, respectively. The power will increase to 90% if the rate in Group A will be 0.05. If the rate in Group A falls below 0.04, the needed sample size to ensure power 80% will be considerably higher than the projected sample size for the study.

Power	Group A	Group B	Group A	Group B
0.90	968	1936	0.03	0.01
0.80	742	1483	0.03	0.01
0.90	555	1110	0.04	0.01
0.80	427	853	0.04	0.01
0.76	386	773	0.04	0.01

0.90	386	773	0.05	0.01

15.5 Reporting Guidelines

Routine reports for this protocol will be provided to oversight bodies, including the ACRIN PA DSMB, for review during each of its twice-yearly teleconferences.

Routine reports will include:

- Accrual and participant characteristics
- Timeliness and completeness, eligibility and protocol compliance, and outcome data
- All reported adverse events

15.6 Trial Monitoring

This trial will be monitored and may be stopped for safety. Based on previous experience we expect that the rate of AMI or cardiac death in study participants who were not found to have significant CAD during their index visit will be very close to zero. If the true rate of AMI or cardiac death among such patients was 0.002 in the combined study groups, the probability of observing more than 5 such events for the combined study groups would be less than 0.04. Each death or AMI within 30 days in such patients will be recorded and examined promptly.

The DSMB will review all deaths and AMI that occurred within 30 days of the index visit. All patients randomized to either coronary CT angiography or usual care will be treated in accordance with the standard of care. Predetermined stopping criteria will include an excess of 5 or more cardiac deaths within 30 days in the coronary CT angiography arm compared with the standard-of-care arm. DSMB will monitor adverse events and have the ability to stop the study based upon other unanticipated concerns.

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CONFIDENTIAL

APPENDIX I

ACRIN PA 4005

SAMPLE CONSENT FOR RESEARCH STUDY

Randomized Controlled Study of a Rapid "Rule Out" Strategy Using CT Coronary Angiogram Versus Traditional Care for Low- to Intermediate-Risk ED Patients with Potential Acute Coronary Syndromes

[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.]

The American College of Radiology Imaging Network (ACRIN) is conducting a research study known as a clinical trial. Clinical trials include only people who choose to take part. Please take your time in deciding whether you want to be involved in the clinical trial. You are encouraged to discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you should ask your study doctor for more explanation. If you decide to do this study, you will be asked to sign and date this form.

You are being invited to participate in this research study because you may have a heart condition. The treating doctor who is caring for you in the Emergency Department believes you might have acute coronary syndrome, a heart condition that can cause chest pain and other symptoms because the heart is not getting enough blood. Acute coronary syndrome is caused by the build-up of plaque in arteries that deliver blood to the heart; this plaque can cause the pathways to narrow or be completely blocked. Heart attacks, also called *myocardial infarctions* or *MIs*, can be caused by acute coronary syndrome.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to determine if an imaging procedure called computed tomography (CT) coronary angiography, or simply called CT angiography, can safely and rapidly determine whether or not a person's chest pain is related to a heart problem. Your study doctors want to see if the CT scan can safely provide enough information to Emergency Department doctors to send people at low- to intermediate-risk for acute coronary syndrome home without having to stay overnight in the hospital.

This study will compare the effects—good and bad—of two different ways of diagnosing heart disease in the Emergency Department. People who agree to join this study will be randomly selected to receive a CT scan or to undergo routine care. In the one year that follows this Emergency Department visit, your study and treating doctors will check to see if you need other tests and/or treatment for your heart after you leave the Emergency Department.

About CT Coronary Angiography

CT coronary angiography is a heart-imaging technique that allows doctors to see your heart without having to put any tubes in the body. It is a type of x-ray that can take as little as about 10 minutes. A

contrast agent containing iodine is injected into your veins to help create clear and detailed pictures. Your study doctor may also wish to give you one or more medications to slow your heart rate and make the blood vessels larger to improve the CT images. You will not be given these medications if you have any medical condition or are taking other medications which may cause problems with giving these medications. 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, or similar.

The pictures the CT angiogram show where the fat and the calcium have built up around and in the heart. These materials, called plaques, build up and 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 the Contrast Agent

In order to better distinguish healthy tissues(s) from disease on the CT angiogram, an intravenous (IV) contrast agent will be used. The contrast agent (dye) used in CT, although very safe, has been associated with allergic reactions. Allergic reactions to these types of contrast agents are rare and most are mild, but some can be life threatening. Every effort will be made to screen you for allergies before an agent is given.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 1365 people with possible acute coronary syndrome will take part in this study. This study will be conducted at least four emergency departments.

HOW LONG WILL I BE IN THE STUDY?

You will be directly in the study for about one (1) year, starting with the day you come to the Emergency Department. This may include contacting outside institutions and treating doctors caring for you to request access to your medical records from during this year period. Whether you are admitted to the hospital or allowed to leave the same day of your Emergency Department visit, your study doctors will want to gather information about your heart health. The study team will contact you about 30 days and one (1) year after you are released from the hospital. The trial will continue for about two (2) to three (3) years.

This study is expected to end after all study participants have completed the visits and all the information has been collected. The study may be stopped at any time by your study doctor or by ACRIN without your consent for the following reasons:

- Your health or safety may be at risk;
- You have not been following study instruction;
- A study administrative decision has been made by ACRIN or your study doctor.

These actions do not require your consent, but you will be informed of any of these decisions.

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

WHAT AM I BEING ASKED TO DO IN THE STUDY?

If you agree to take part in this study and determined to be eligible by your study doctor, you will be asked to read and sign this consent form before you are enrolled to participate in this trial and before any study procedures are performed. When you are enrolled into the study, you have the following tests and procedures. *<<Next sentence for the blood banking procedure will only apply for institutions that are participating in the blood banking component of the trial. Those who are not participating, please remove.>>* As part of this study and if you agree, blood samples will be taken and will be sent and stored at Hospital of University of Pennsylvania for future correlative research.

See the Study Chart at the end of this section for a visit-by-visit outline of what will be expected of you if you decide to participate in this trial.

Standard medical procedures that are part of regular standard of care and would probably be done even if you do not join the study:

- A review of your medical history;
- A physical examination, including vital signs;
- Blood tests;
- Electrocardiogram (ECG) to test the heart's electrical pattern;
- Blood pressure tests.

Medical procedures that are being done specifically because you are in this study (these may or may not be done if you were not in this study):

- Blood samples collection and storage for future research (optional);
- Pregnancy test for female participants of childbearing age, as appropriate, immediately prior to CT angiography;
- CT angiography;
- Telephone follow up to discuss your heart health at 30 days and 1 year from the time you enter the study;
- Medical record review, as needed to confirm heart-related testing and treatment, at 30 days and 1 year after entering the study.

Blood sample collection – this is an optional procedure:
<<Following language for the blood collection procedure will only apply for institutions that are participating in the blood banking component of the trial. Those institutions who are not participating, please remove.>>

If you are a patient at the Hospital of the University of Pennsylvania or Penn Presbyterian Medical Center, your study doctors would like to collect and store your blood that may be later used to look for changes in blood associated with acute coronary syndrome. This is an optional procedure in this study, so you may choose to be in the study but not to have the blood sample collection. Time may not allow for all of the blood samples to be taken, so you may not have three blood draws. If you agree, the blood

specimens will be collected, stored, and used in future research to learn more about other diseases. All your personal information will be removed from the sample before it is shared and stored.

If you agree, you are being asked to have one (1) tube of blood taken at the following times:

- When you get your 1st blood test as part of your treatment;
- About 90 to 180 minutes after your 1st blood test;
- About 6 hours after your 1st blood test or prior to being discharged from the hospital.

The blood sample will be given only to the approved researchers and will not be sold. The research done on the blood will also be reviewed and approved by the researcher's institutional review board (IRB). The research done with your blood will probably not help you but it may help other people who have a heart condition in the future. Reports about the research done with your blood will not be given to you or your treating doctor. These reports will not be put into your medical records and it will not have an effect on your care.

I agree to participate in the blood sample collection and storage for future research portion of this study.

☐ **YES** ☐ **NO** _____ **Participant's Initials**

If you agree to participate in this study, you will be assigned to one of two different study groups. It is important to know that the study doctors and staff who are conducting this trial will not choose which of these two groups you will be placed into. Instead, you will be placed randomly into one of the groups. The study group (A or B) that you will be assigned will be determined randomly like a coin flip. In this study, the "coin flip" will make you twice as likely to be in Group B than in Group A (see descriptions below).

For Group A (Standard Care)

If you are put into Group A (what is know as the control group), you will receive standard of care as determined by your study and treating doctor, which includes a blood test and ECG. Your treating doctors may determine that no additional testing is needed per standard of care; or, may find it necessary to test your heart with a cardiac stress test or cardiac catheterization.

In addition, if you agree to the blood collection, you will have one tube of blood taken from a vein in your arm (about 1 tablespoon of blood) three times over the first 6 hours of your visit. Your blood sample will be stored at the Hospital of the University of Pennsylvania for future research.

For Group B (Standard Care + CT Scan)

If you are put into Group B, you will receive standard of care as determined by your study and treating doctor, which includes a blood test and ECG. After the results of your 1st blood test, you will receive a CT scan of your chest/heart.

If your CT scan results come back negative, you will be released from the hospital to go home. If your CT coronary angiography results come back positive, then you will be admitted to the hospital and your

treating doctors will decide what is best for you. The clinical information about your symptoms and condition while in the hospital will be recorded for this study.

In addition, if you agree, you will have another tube of blood taken from a vein in your arm (about 1 tablespoon of blood). You will have blood taken about two (2) other times over the first 6 hours of your visit. Your blood sample will be stored at the Hospital of the University of Pennsylvania for future research.

Both Groups A and B

Regardless of which group you are in, your treating doctor(s) will want to gather information about your heart health, including what tests and treatments you have had and whether you've returned to the hospital, after you leave the Emergency Department. We will ask you to provide your contact information, including your mailing address, and the name of another person or doctor(s) we can contact who knows about your health should you be unavailable to provide any information. We may need to access your medical records at facilities outside of this one. Whether you are admitted to the hospital or allowed to leave the same day of your Emergency Department visit, the research staff will contact you and your treating doctor(s) about 30 days and about one (1) year after the date you entered the trial.

An outline of the study follows …

STUDY CHART

VISIT 1: **Phase 1 – Eligibility and Randomization to Group A or Group B**	• Read and sign the informed consent form; • Provide contact information for yourself, including your mailing address, and for another person or doctor(s) that can be contacted regarding your heart health to collect information about your care from one (1) year following your entrance into the trial; • Have a physical examination, including vital signs; • Provide medical history; • Have blood test(s) for clinical and/or collection (if you are eligible and volunteer); • Have an ECG.
Phase 2 – After Registration and Randomization: GROUP A	• Have diagnostic treatment and testing; OR • Be discharged per standard of care as your treating doctor(s) recommends; • Have a blood sample collected, if you volunteer.
Phase 2 – After Registration and Randomization: GROUP B	• Have diagnostic treatment and testing per standard of care as your study and treating doctors recommend; • Have a clinical blood test (unless two blood tests have already been collected during observation); • Have a pregnancy test, as appropriate; • Have a CT angiogram; • Have a blood sample collected, if you volunteer.
Phase 3 – CT Scan Results: GROUP B ONLY	Depending on the results of your CT angiogram: • If negative, you will be discharged from the hospital; • If positive, you will be admitted to the hospital.
Phase 4 – Discharge From the Hospital	• Obtain and confirm treatments with your treating doctor.
VISIT 2: **Telephone Contact After 30 Days From Entering the Study**	• Provide additional medical information from time of your ED visit up to 30 days after regarding your heart health.
VISIT 3: **Telephone Contact After 1 Year From Entering the Study**	• Provide additional medical information from time of your ED visit up to 1 year after regarding your heart health.

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 have the following procedures. You should discuss these with your study and/or treating doctor(s). There also may be other side effects that

we cannot predict. Many side effects go away shortly after the CT scan is stopped, but in some cases side effects can be serious, long lasting, or permanent.

Risks Associated With Intravenous (IV) Catheter Placement for Contrast Agent and/or Blood Collection

Likely

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

Rare

- Fainting;
- Bleeding;
- Infection.

Risks Associated With the Contrast Agent for the CT Scans

Rare

- Nausea;
- Vomiting;
- Hives;
- Rash.

Very Rare, Potentially Life Threatening

- Allergic reaction;
- Kidney failure;
- Malfunction of worn or implanted electronic medical devices.

When you receive the contrast during the 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 reaction, with the 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 study doctor and research staff who are explaining this study.

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

Risks Associated With CT Coronary Angiography Scans (CT Scans)

Likely

- Discomfort from lying still on the enclosed scanning table;
- Claustrophobia;

Risks Associated With Blood Collection

Likely

- Minor discomfort.

Rare

- Fainting;
- Bleeding.

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:

There are some risks from the CT scans used to evaluate your heart health in this study. This research study involves exposure to radiation from the CT angiogram and therefore you will receive a radiation dose. Radiation dose associated with this study will range from approximately 2 mSv to 21 mSv. This is often less than the radiation (10–22 mSv) a patient is exposed to when they have images taken before and after a stress test, called a nuclear stress test, which 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. Measures are taken to ensure that 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 potential benefit to you may be that your treating doctors are able to determine faster whether or not your symptoms are related to your heart. This may decrease time and money for you and other patients with similar issues. We hope the information learned from this study will benefit other patients with potential heart problems in the future.

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 or loss of benefits to which you are otherwise entitled. Please talk with your study and/or treating doctor(s) about this and other options.

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 (CT Angiography scans) 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 Pennsylvania Dept. of Health, 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.

Your research records and images will be kept permanently on file at ACRIN and may be used for future research. All personal identifiers are removed and replaced with a unique identifying number. The information that may be done with the information will not specifically help you. But, it might help people in the future who have a heart condition and other diseases.

WILL I HAVE TO PAY FOR ANYTHING?

Taking part in this study may or may not lead to added costs to you or your insurance company. Please ask your study doctor about any expected added costs or insurance problems.

You and/or your health insurance will be charged for any portion of your care that is considered standard care or if your insurance agrees in advance to pay. You and/or your insurance company will be charged for continuing medical care and/or hospitalization. You may be responsible for any co-payments and deductibles that are standard for your insurance coverage.

You or your insurance company will not be charged for the following part of this research study:

- Blood samples collected for future research;

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

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 your study doctor in person or call him/her at *<<insert telephone number>>*.

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 to or not to take part in the study. If you decided 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 benefits. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. Your decision whether or not to participate in this study will not interfere with your future care. 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 Board (an independent group of experts) may 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.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

(This section must be completed)

You can talk with your study doctor(s) about any questions or concerns you have about this study. Contact your study doctor *<<insert name>>* at *<<insert telephone number>>*.

This document explains your rights as a study participant. It 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 study doctor or anyone listed below.

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 emergency care doctor of their participation in a clinical trial.*

_____	_____
Name	Telephone Number

For information about your rights as a research subject, you may contact *<<Institution Name>>* Institutional Review Board (a group of people who review the research to protect your rights):
(Provide the name of local IRB contact person)

_____	_____
Name	Telephone Number

WHERE CAN I GET MORE INFORMATION?

For more information, you may also visit the American College of Radiology Imaging Network web site, **www.acrin.org**.

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 willingly give your consent to participate in this study. A copy of this signed informed consent form will be given to you.

Printed Name of Study Participant/ Legal Representative	Signature	Date

<Insert other signature and date lines as appropriate per local IRB policies and procedures>

APPENDIX II

ACRIN PA 4005

SUPPLEMENTAL MATERIALS AVAILABLE ONLINE

Supplemental materials that support the conduct of the trial are available on the ACRIN Web site at the ACRIN PA 4005 Protocol Web page (www.acrin.org/4005_protocol.aspx). Types of materials posted include:

- Application and protocol activation documents (General Qualifying and Protocol Specific Applications, protocol activation checklist, etc.);
- Data forms;
- Imaging materials (Image Transmittal Worksheet);
- Recruitment and education materials;
- Regulatory resources;
- Participating site list.

For more information related to the trial, contact the ACRIN PA 4005 Contact Personnel link on the above-mentioned Web page for a list of protocol team members at ACRIN Headquarters and their roles.

APPENDIX III

ACRIN PA 4005

TIMI RISK SCORE CRITERIA

The Inclusion Criteria (see Section 5.1) for this protocol mandates that participants must have a TIMI risk score of 0 to 2 based on the following parameters. One point is awarded for each of the following:

- Age > 65 years (1 point)
- Documented prior coronary artery stenosis ≥ 50% (1 point)
  On prior cath.CTA, PCI, CABG, or prior AMI
- 3 or more conventional cardiac risk factors (1 point)
  HTN, DM, Cholesterol, FH, Tobacco use
- Aspirin (prescribed) taken in past week (1 point)
- 2 or more anginal events in the past 24 hours (1 point)
- ST-segment elevation or depression > 1 mm (1 point)
- Elevated troponin (1 point)

APPENDIX IV

ACRIN PA 4005

CLINICAL DATA COLLECTION CRITERIA

Patients will have a structured history and physical examination performed at the time they present to the Emergency Department. Information will be collected in accordance with Standardized Reporting Guidelines[70] and Key Definitions.[71] Demographic characteristics, cardiac risk factors, chest pain characteristics, associated symptoms, medications, initial vital signs, treatment, and disposition will be collected.

Electrocardiograms will be interpreted by treating clinicians according to seven categories outlined in the Standardized Reporting Guidelines.[66] Additional information regarding ST segments deviation, T and Q wave morphology, and the presence of bundle branch block(s) will be documented. Clinical information will be obtained directly from the treating physician, when possible. Trained research assistants will be present in the Emergency Department from 7 am to midnight, 7 days per week, to enroll patients with potential ACS.

Admitted participants will be followed daily during hospitalization for cardiovascular complications including death, MI, development of heart failure, dysrhythmias, and other specific cardiovascular complications. Determination of the presence or absence of each of these events will be made during daily communication between the investigators and the healthcare team. Discharged and admitted participants will be contacted by telephone at 30 days and 1 year to assess main outcomes.

CT Coronary Angiography:
Participants with an elevated heart rate will be given oral or intravenous metoprolol to reduce the heart rate according to local practice, when not contraindicated. CT coronary angiography will be performed using a 64 or greater slice CT scanner with the ability to perform retrospectively ECG-gated cardiac studies. The study will begin with a pre-contrast ECG-triggered acquisition through the entire chest (or as much of the chest as breathholding permits) for the purpose of calcium scoring, and to evaluate lung abnormalities. This will be followed by an intravenous injection of 80 to 120 mL of non-ionic iodinated contrast with bolus tracking in the descending aorta, and a saline flush. A dual-phase or three-phase injection may be utilized depending upon local practice. Nitroglycerin, either sublingual tablet or spray, may be used to improve coronary artery visualization according to local practice. Patients with known sensitivity to nitroglycerin, hypotension (generally systolic blood pressure < 100 mm Hg), and those with a recent history of phosphodiesterase inhibitor use should not receive nitroglycerine.

After the appropriate scan delay, an ECG-gated acquisition from the carina to the base of the heart will be performed. The use of radiation dose reduction techniques, including ECG-gated tube current modulation and low kVp scanning in smaller patients, is strongly encouraged. Sites with hardware and software allowing prospectively ECG-triggered acquisitions, as well as appropriate clinical experience with this technique, may choose to use it in selected cases for dose reduction according to their clinical routine. Image data will be reconstructed at multiple phases of the cardiac cycle and will be post-processed on a 3-D workstation using a variety of tools and applications depending upon local practice and availability. The imaging test will be considered positive if the participant has an equal to or greater than 50% stenosis of the right coronary, left main, left anterior descending, or circumflex arteries or of their first-order branches. Results will be communicated to the responsible Emergency Department staff

immediately upon interpretation. Reporting of studies will be according to the AHA coronary segment model and will also include an assessment of global and regional cardiac function (when available), calcium score, mass, and volume, and additional cardiac and non-cardiac findings.

Additional References

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APPENDIX V

ACRIN PA 4005

BLOOD PROCESSING/BANKING PROTOCOL

University of Pennsylvania Health System

Laboratory Testing:
Initial cardiac marker testing will be performed in accordance with institutional protocols. At HUP, this will be on the Biosite point-of-care testing machine. Reference ranges will be those that are set by the manufacturer and institutional norms. For all participants who consent to the blood collection, the quantitative results will be immediately presented to the attending physician responsible for patient care. The initial serum sample (0 minutes), as well as samples taken at approximately 90 to 180 minutes, and 6 hours, will be banked for future use.

Processing:
Study specimens will be collected at HUP and PPMC sites and will be sent to the designated storage facility for storage for future testing.

- Blood is to be collected in a 5.0 ml heparin tube with no separation gel.
- The tube must be filled at least three quarters full.
- All specimens must be centrifuged and frozen within **1 hour** of collection.
- Centrifuge the specimens at 3000 x g for 15 minutes.
- Transfer all the plasma in 0.5 ml aliquots into the appropriate cryovials.

ALL PLASMA COLLECTED FROM THE BLOOD DRAW FROM THE ENROLLED PARTICIPANT MUST BE TRANSFERRED TO THESE TUBES.

Use a vortex to mix the plasma thoroughly. If no vortex is available, mix the plasma as completely as possible by hand inversion.

Label the cryovials with the provided bar codes. Bar codes are provided for each participant and each blood draw. Be careful to use the participant specific and time specific bar code. Discard all unused bar codes after each sample is processed.

It is preferable that the specimens be frozen at -70 degrees Celsius (-70º C) however, if this is not available at your site, the plasma may be frozen at -20 degrees Celsius (-20º C). If freezing and storing the specimens at -20º C please use a non-defrosting freezer and do not store the specimens on the door shelf of the freezer.

Locally stored samples will be picked up monthly and delivered to the storage facility. Samples will be transported by trained study personnel in insulated containers with dry ice. They will be stored at -70 degrees Celsius (-70º C) until analysis.

Blood specimens collected during this study will be stored and investigated later for cardiac markers, neurohormonal markers, and markers of inflammation.

APPENDIX VI

ACRIN PA 4005

STANDARDIZED CARDIAC DIAGNOSIS DEFINITIONS

NOTE: These definitions may differ from standard practice at your site and are to be used for reporting of data to ACRIN for this trial.

AMI (Acute Myocardial Infarction)
Elevated cardiac troponin above lab threshold for normal (0.4) in setting of symptoms with or without ECG changes.

- **STEMI (ST segment elevation MI)**
  AMI subcategory where the patient has new ST segment *elevation* on the ECG at the time of presentation to the ED (ECG impression of c/w AMI or ST elevation greater than 1mm on ECG form).
- **NSTEMI (non-ST segment elevation MI)**
  AMI subcategory where the patient does NOT have ST segment elevation on the ECG at the time of presentation to the ED (ECG impression of c/w AMI or ST elevation greater than 1mm on ECG form).

Unstable Angina (UA)

- Stress test with reversible ischemia:
  - Reversible perfusion defect on nuclear imaging;
  - Reversible wall motion abnormality on stress echocardiography; or
  - Transient ECG changes alone, if no imaging performed;
- Cardiac catheterization with a lesion $\geq$ 70%;
- CT Angiography with a lesion $\geq$ 70%.

Acute Coronary Syndrome (ACS)
Anyone with AMI (STEMI or NSTEMI) or UA.

Stable Angina

- Patients with known AMI, UA, ACS who have symptoms less severe than their typical regular symptoms.

Coronary Disease without ACS

- Known disease from prior CABG (bypass), catheterization, coronary CTA, PCI without an evaluation for ischemia (no stress, etc.) during this visit
- Known disease from prior CABG (bypass), catheterization, coronary CTA, PCI with a negative evaluation for ischemia during this visit
- Had coronary CTA or catheterization with disease 50% to 69% during this visit without a positive stress test (can be negative or not done)

Non-ischemic Chest Pain/Symptoms

- Stress test without reversible ischemia or transient ECG changes;
- Cardiac catheterization with the maximal lesion $\leq$ 50%;
- CT Angiography with the maximal lesion $\leq$ 50%.

Chest Pain/Symptoms NOS (also, CPNOS; not otherwise studied)
Received no testing for coronary disease, regardless of other diagnosis given by the hospital team.