ROMICAT II

Rule Out Myocardial Ischemia/Infarction Using Computer Assisted Tomography

A Randomized, Controlled, Multicenter, Diagnostic Trial

Study Protocol Version: 6.0
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Investigator Protocol Signature Page

I have read and understand the protocol and agree that it contains all the ethical, legal and scientific information necessary to conduct this study. I will personally conduct the study as described. I will provide copies of the protocol to all physicians, nurses and other professional personnel responsible to me who will participate in the study. I am aware that this protocol must be approved by the Institutional Review Board or Ethics Committee. I agree to provide all patients with informed consent forms, as required by government regulations and International Conference on Harmonization guidelines.

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Principal Investigator (print name)

_____ _____

Principal Investigator (signature) **Date**

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Amendment 1 Summary of Changes

1. Changes to Inclusion/Exclusion Criteria (page 19).
    - In order to ensure targeted population is enrolled, the following inclusion criteria was added: Participant must have 2 or more cardiac risk factors (diabetes, hypertension, hyperlipidemia, current smoker and family history of coronary artery disease)

2. Clarification of consent and randomization procedures (pages 21-22).
    - Patients can be consented but not randomized before the first troponin test result is available. Patients whose initial troponin level is markedly elevated will not be randomized and will not be included in the intent-to-treat population. Patients whose subsequent troponin testing is markedly elevated will be included in the intent to treat population.

    - Removed the phrase, 'based upon blocked assignment in groups of 30' from the end of the sentence: 'Study subjects will be randomized into the standard care arm or the intervention arm by means randomization stratified by institution and gender using a central computerized randomization system.'

3. Clarification of the Statistical Considerations section (pages 5, 18, 24, 27-28).
    - Removed sentence, 'Length of hospital stay between study arms will be compared in subgroups of patients directly discharged from the ED and patients admitted to the hospital.' from primary endpoint analysis.

    - Minor clarification to emergency department triage accuracy assumption discussion.

    - Minor clarification to secondary aim of health care utilization.

    - Removed sentence, 'We will use an uncorrected chi-squared statistic to evaluate this null hypothesis.' from discussion of secondary aim for comparison between two groups of rate of MACE at I and 2 years.

Amendment 2 Summary of Changes

1. Changes to Inclusion/Exclusion Criteria (page 20):

    - Page 20: The baseline population of ROMICAT I (age >40) had an ACS rate of 9.3%. For subjects with >= 1 risk factor, the ACS rate rose to 10.0% at the cost of losing 17% of the population, while for subjects with >=2 risk factors, the ACS rate rose to 13.9% with a loss of 46% eligible subjects. As the role of risk factors in determination of ACS is controversial, and based on DSMB recommendations, this criterion will be removed from the inclusion criteria.
    - Page 21: The exclusion criteria of subjects who present to the ED more than 4 hours ago will now be extended to more than 6 hours ago. This is based on DSMB recommendations as a useful technique to capture subjects who present with chest pain early in the morning.

2. Clarification of Study Protocol

    - Pages 31, 43: Currently the CT protocol only covers retrospective gating. This will be amended to extend to allow prospective triggering also, as this is a pragmatic trial which should reflect current clinical practice. This also has the potential benefit of reduced radiation exposure (<5mSv).

    - Page 24: Subjects discharged within 24 hours of presentation to the hospital will be followed up at the 48-72 hour period. This was mentioned as 48 hours in the protocol, and was a typographical error.

    - Page 25: We will remove all language suggestive of facilitated handling of patients in the CT arm (including scheduling the CT scan immediately after randomization, and notification of the ED caregivers about the results of the CT scan in a given time frame). The sentences “To facilitate timely CT imaging, the cardiac CT exam will be scheduled immediately after randomization”, ” The results of cardiac CT including the presence and extent of coronary atherosclerotic plaque, coronary artery stenosis, and global and regional LV dysfunction will be provided to the ED caregivers immediately“ and ”In subjects randomized to receive a cardiac CT, patient management will be additionally informed and guided by the cardiac CT findings on coronary plaque and stenosis and LV function. CT will be discussed with the ED physicians caring for the subject. “ have been removed from page 23. “The CT reader will contact the Emergency Department (ED) treating physician and report the results of the cardiac CT” has been removed from page 49 of Appendix B.

    - Page 24: Gender stratification will not be used in the randomization schema for the simplicity, and to use it as a covariate in further statistical analysis.

- Page 33: MD over read will be performed for internal quality control assessment of findings related to CAD and significant cardiac findings such as pulmonary embolism and aortic dissection, to increase awareness to sites of non-coronary findings.

3. Clarification of Aims

    - Page 18: The language of the aims and related hypotheses has been expressed in a more clarified manner.

Amendment 3 Summary of Changes

1. Changes to Inclusion/Exclusion Criteria (page 25):

    - Page 25: Participant must have at least five minutes of chest pain or equivalent (chest tightness; pain radiating to left, right, or both arms or shoulders, back, neck, epigastrium, jaw/throat; or unexplained shortness of breath, syncope/presyncope, generalized weakness, nausea, or vomiting thought to be of cardiac origin) at rest or during exercise within 24 hours of ED presentation, warranting further ~~inpatient~~ risk stratification, as determined by an ED attending.
    - Page 26:
      ~~9.~~ Currently symptomatic asthma ~~(or taking daily medication for asthma)~~
      10. Contraindication to beta blockers **(taking daily antiasthmatic medication)**: This exclusion only applies to patients with a heart rate > 65 bpm at sites using a non-dual source CT scanner

2. Clarification of Study Protocol:

    - Page 28: *Interventional Arm:* In subjects randomized to the intervention arm, a contrast enhanced cardiac CT will be performed (after initial troponin level is available) in addition to the ~~standard evaluation~~ **initial ED evaluation**.

3. Extension of follow-up time windows:

    - Page 28: The 48-72 hour follow-up phone call has been extended to accommodate calls that fall either during the weekend or during a holiday.
    - Page 29: The 12 month and 24 month follow-up phone call windows have been extended from +/- 2 weeks to +/- 4 weeks.

Amendment 4 Summary of Changes

1. Study Synopsis (page 13):
   Duration of Study Participation: Participants will be followed during index ED visit/hospitalization. There will be a phone call at 48-72 hours for those discharged within 24 hours. All participants will receive a follow up phone call at 28 days, ~~1 year and 2 year~~ post emergency room discharge.

2. Changes to Inclusion Criteria (page 27):
   - Participant must be in ~~normal~~ sinus rhythm.

3. Elimination of the 1 and 2 year follow-up interviews:
   - Page 16: All participants will receive a 28-day~~, a one year and two year~~ follow-up phone interview. The efficiency of each strategy will be determined by comparing 1) the length of hospital stay (primary endpoint), 2) the time to diagnosis (secondary endpoint), 3) the rates of ED discharge (secondary endpoint), 4) utilization of other diagnostic testing, i.e. invasive coronary angiograms, and resulting interventions, i.e. coronary revascularization procedures during index hospitalization **and** 28 days~~, one year and two year~~ (secondary endpoint). The safety of the two strategies will be compared by determining the occurrence of adverse events within 48-72 hours in directly discharged patients as well as determination of major adverse cardiovascular events (MACE) within 28 days~~,~~ ~~one year and two years~~ after discharge from the index hospitalization.
   - Page 26: ~~To compare the two study arms in terms of rates of MACE (major adverse cardiac events – cardiac death, AMI, revascularization, unstable angina, and rehospitalization) within one and two years.~~

     ~~**One/two Years:** Defined as one/two years post the day of discharge from index hospitalization.~~

     ~~Hypothesis: *The rates of MACE in both arms during the follow up period will be lower in the CT arm.*~~
   - Page 30: A reminder letter will be sent or phone call will be made to participants, two weeks prior to the 28-day follow up phone call. **If unable to contact the participant by phone, mortality will be assessed online using the SSDI website.**
   - Page 30: ~~***5.4 12 Month Follow up***~~
     ~~*Follow up one year phone call:* All subjects will be interviewed via a telephone call at one year post ED discharge (12 months +/- 4 weeks) to determine the occurrence of MACE and readmissions to the hospital using a standardized questionnaire. All cases of recurrent chest pain, hospital admissions, and diagnostic testing will be verified by review of medical records.~~

~~A reminder letter will be sent or phone call will be made to participants, two weeks prior to the 12-month follow-up phone call.~~

~~*5.5 24 Month Follow up*~~

~~*Follow up two year phone call:* All subjects will be interviewed via a telephone call at two years post ED discharge (24 months +/- 4 weeks) to determine the occurrence of MACE using a standardized questionnaire. All cases of hospital admissions and diagnostic testing will be verified by review of medical records.~~

~~Note: A reminder letter will be sent or phone call will be made to participants two weeks prior to the two year follow up phone call. A minimum of five (5) phone attempts will be to contact each participant. If unable to contact the participant by phone, mortality will be assessed online using the SSDI website.~~

- Page 34: ~~*To compare the two study arms in terms of rates of MACE (cardiac death, AMI, revascularization, unstable angina, and rehospitalization) within one and two years.*~~
  ~~This analysis will be performed from the intent to treat perspective. The occurrence of MACE will be assessed via patient follow-up and medical chart review. The primary analysis for this aim will be performed at the patient level by determining whether any MACE occurred or not. Event rates will be estimated and compared between study groups using exact procedures. Prior data estimate a MACE rate of 5% over two years. We anticipate a MACE rate between and 2% and 5% in both groups and have 80% power to detect a difference between 2 and 5% between the two groups. The Type I error probability associated with this test of this null hypothesis is 0.05.~~
  ~~In a secondary analysis, the rates of each type of MACE will be examined separately.~~

4. Extension of 28-Day follow-up time window:
   - Page 30: The 28 day follow-up phone call window has been extended from +2 weeks to +4 weeks.

Amendment 5 Summary of Changes

1. Study Synopsis (page 15):
   Number of sites: 9 ~~7~~

2. Part I: Study Overview (page 17):
   The study is designed as a randomized, controlled, diagnostic, multicenter trial and will enroll 1,000 participants at nine ~~seven~~ sites over a 15 month period.

3. Study Design (page 18):
   The study is designed as a randomized, controlled, diagnostic, multicenter trial and will enroll 1,000 participants at nine ~~seven~~ sites over a 15 month period.

Study Synopsis

Sponsor(s)	National Heart Lung and Blood Institute (NHLBI)
Protocol Title	**R**ule **O**ut **M**yocardial **I**schemia/Infarction **U**sing **C**omputer **A**ssisted **T**omography - A Diagnostic Randomized Multicenter Trial
Diagnosis and Main Criterion for Inclusion	Adults (≥40-75 yrs) without known/documented history of coronary artery disease, who have come to the emergency department (ED) presenting with a lead symptom of acute chest pain suggestive of acute cardiac ischemia, defined as chest pain lasting for at least 5 minutes, and occurring within the last 24 hours but without diagnostic ECG changes of acute myocardial ischemia are eligible for participation. Only patients in whom the ED attending feels that further inpatient risk stratification is required will be included.
Primary Study Objective	To determine whether length of hospital stay is significantly shortened in the interventional arm vs. standard of care
Secondary Study Objectives	• To determine whether time to diagnosis (for ACS and no ACS) is significantly shortened and rates of direct discharge from the emergency department are increased in the interventional arm vs. standard of care • To determine a) the additional number of invasive coronary angiograms in both arms and b) to determine the number of coronary revascularization procedures. • To determine the safety of immediate ED discharge after a normal cardiac CT defined as the occurrence of ACS within 48-72 hours after discharge. • To determine whether subsequent testing and follow-up, including invasive coronary angiograms, diagnostic (imaging) tests, interventions, repeat ED visits for cardiac related problems and repeat hospitalizations for chest pain or equivalent during 28 days after hospital discharge is decreased in the interventional arm, compared to SOC. • To determine the two study arms in terms of rates of MACE within 28 days. • To compare the two study arms in terms of rates of MACE within one and two years. • To estimate and compare the sensitivity, specificity, NPV and PPV of contrast-enhanced CT and non-contrast CT, with clinical diagnosis of ACS as the reference standard. • To determine whether the cost of care (per TSI) for index hospitalization and after 28 days is decreased by implementing cardiac CT into the early ED evaluation of patients with acute chest pain. • To determine the cost-effectiveness of incorporating cardiac CT into

	the standard ED evaluation of patients with acute chest pain over a 28-day and lifetime horizon as compared to SOC.
Tertiary Study Objectives	• To determine whether CT leads to increased test burden after the initial tests during index hospitalization. • To compare the consistency of physician decisions management depending on the results of diagnostic testing (i.e. normal CT – what fraction is immediately discharged) • To determine whether hospital setting, availability of observation unit, CT experience of hospital and readers, and reader performance are associated with primary or secondary outcomes.
Primary Endpoint	The primary endpoint is time from ED presentation to hospital discharge. The length of hospital stay is defined as the time from ED presentation to the time of discharge note or order. This includes time in the ED, time in any institution-specific specialized chest pain unit, and time as an inpatient on the floor
Secondary Endpoints	• The time to diagnosis: For ACS, defined as the time from ED presentation until the first test during index hospitalization that leads to the diagnosis of ACS (tests may be biomarkers, CTA, ETT, nuclear imaging, stress ECHO or cardiac catheterization); for no ACS, defined as the time from ED presentation to the final test during index hospitalization. • Admission to hospital: Participants are considered to be admitted if the ED attending admitted the subject to a hospital floor (medical floor, step down unit, telemetry hospital floor or intensive care unit). • Direct ED discharge: will include all subjects who are not admitted to the hospital. • Health care utilization: number of invasive coronary angiograms, diagnostic (imaging) tests, interventions, repeat ED visits. • Rates of MACE: major adverse cardiac events – cardiac death, acute myocardial infarction, revascularization, unstable angina and rehospitalization. • Cost of care derived from the cost-accounting database (i.e., TSI).
Tertiary Endpoints	Increased test burden: Further imaging tests performed after index hospitalization
Primary Hypothesis	Adding cardiac CT to the initial ED evaluation of subjects with acute chest pain significantly decreases length of hospital stay.

Secondary Hypothesis	Addition of cardiac CT to the initial ED evaluation of subjects with acute chest pain will significantly increase the ED discharge rate, and shorten the time to diagnosis and it will be a cost-saving and cost-effective modality. There will not be an increase in the number of invasive angiograms or coronary revascularization procedures as compared to the SOC arm. With a high negative predictive value, patient safety will not be compromised. There will not be an increase in subsequent further testing and the rate of MACE in both arms in the follow-up period will be similar. The test characteristics of contrast enhanced CT will be significantly better than that of a non-contrast CT.
Study Design	The study is designed as a randomized diagnostic multicenter trial and will enroll 1,000 participants at seven sites over a 15 month period. Participants presenting with acute chest pain in the ED will be randomized to standard of care (SOC) or to an interventional arm. Patients in the interventional arm will receive standard evaluation supplemented by contrast-enhanced cardiac CT imaging
Duration of Study Participation	Participants will be followed during index ED visit/hospitalization. There will be a phone call at 48-72 hours for those discharged within 24 hours. All participants will receive a follow up phone call at 28 days post emergency room discharge.
Number of Subjects	1,000 subjects will be enrolled, with 500 each in the standard of care and interventional arms.
Number of Sites	9
Statistical Considerations	The primary aim of the study is to compare the two study arms in terms of a difference in mean length of hospital stay (LOS) between the two arms. We have conducted a power evaluation using the estimated mean and standard deviation based on observed data from ROMICAT I and simulated data based on health outcomes. We will have 95% power to detect a difference in 10 hours of LOS at a Type-1 error rate of 5% for an independent samples t-test using 500 patients in each arm.

Part I: Study Overview

The study is designed as a randomized, controlled, diagnostic, multicenter trial and will enroll 1,000 participants at nine sites over a 15 month period. Participants presenting with acute chest pain in the ED will be randomized to a standard of care arm (SOC) or interventional arm; patients in the interventional arm will receive standard evaluation supplemented by contrast-enhanced cardiac computed tomography (CT) imaging (Figure 1).

In both arms, the initial Emergency Department (ED) evaluation (electrocardiogram [ECG], physical examination, clinical presentation, renal function lab, and medical history) will determine eligibility of patients. After randomization, standard of care will be performed in both arms. However, for patients randomized to the interventional arm, a CT will be performed. The following decisions made by the caregiver team will be tracked: admission or discharge after initial ED evaluation plus CT/other initial diagnostic test, in admitted participants, the length of hospital stay, the extent of further testing including serial cardiac markers and ECG, and other diagnostic tests or interventions. For safety reasons, participants discharged in less than 24 hours of ED arrival will receive a phone call 48-72 hours after discharge. All participants will receive a 28-day follow-up phone interview. The efficiency of each strategy will be determined by comparing 1) the length of hospital stay (primary endpoint), 2) the time to diagnosis (secondary endpoint), 3) the rates of ED discharge (secondary endpoint), 4) utilization of other diagnostic testing, i.e. invasive coronary angiograms, and resulting interventions, i.e. coronary revascularization procedures during index hospitalization and28 days (secondary endpoint). The safety of the two strategies will be compared by determining the occurrence of adverse events within 48-72 hours in directly discharged patients as well as determination of major adverse cardiovascular events (MACE) within 28 days after discharge from the index hospitalization. We will also perform a cost and cost effectiveness analysis. In subsequent analyses, we will determine the patient, physician, and institutional factors that affect the primary endpoint or secondary endpoints.

Primary Objective:

To determine whether length of hospital stay is significantly shortened in the interventional arm vs. SOC.

Hypothesis:

Adding cardiac CT to the initial ED evaluation of subjects with acute chest pain decreases length of hospital stay.

Part II: Study Description

1. Background and Significance

1.1 Standard Evaluation of Participants with Acute Chest Pain

Accurate triage of participants presenting with acute chest pain to the ED remains difficult because neither the chest pain history,[1,2] a single set of established biochemical markers for myocardial necrosis (troponin I, troponin T, creatine kinase MB-type [CK-MB]),[3,4] nor initial 12-lead ECG alone or in combination (acute cardiac ischemia time-insensitive predictive instrument) identifies a group of participants that can be safely discharged home without further diagnostic testing.[5–7] As a result, the threshold to admit chest pain participants remains low and over six million are admitted annually to U.S. hospitals.[2,8–10]

The standard "rule out" myocardial infarction (MI) protocol consists of serial ECG and cardiac biomarker measurements, and usually requires a noninvasive stress test to rule out MI. These tests (exercise treadmill ECG testing [ETT], stress echocardiography [Echo], and rest or stress myocardial perfusion imaging with Tc-99m [SPECT]) require the exclusion of myocardial necrosis with negative serial biomarkers and are performed to rule out the presence of a hemodynamically significant coronary stenosis. While they have good sensitivities (ETT: 76%, SPECT: 83% and Echo: 85%) for detecting the presence of significant coronary artery stenosis when compared to coronary angiography[11–13] their specificities are only moderate (ETT: 60%, SPECT: 64%, and Echo: 77%). Moreover, these tests are time consuming (i.e. SPECT 2–3 hours) and usually not available 24/7. Thus, the standard evaluation of patients with chest pain to rule out myocardial ischemia requires hospital admission for 24 to 36 hours in over 90% of U.S. hospitals.[14] Because of the moderate specificities of standard diagnostic testing, 33% to 44% of patients with suspected acute coronary syndrome (ACS) who undergo cardiac catheterization have no significant coronary artery disease (CAD).[15,16] The remarkable inefficiency of current evaluation strategies is also documented by the fact that only <10% of the six million admitted each year in the U.S. ultimately receive a diagnosis of ACS at discharge.[17,18] The inpatient care for the negative evaluations imparts a significant economic burden in excess of $8 billion annually[19–21] for the U.S. health care system.

Thus, an improvement of the ED triage of participants with acute chest pain, particularly the increase in ED discharge rates in participants who ultimately do not have ACS, would have enormous clinical and economic implications. This research will determine if noninvasive cardiac CT, that accurately visualizes the coronary arteries for plaques and/or stenosis, can be an effective strategy to facilitate early ED discharge in this patient population.

1.2 Accuracy of Cardiac CT for Detection of Coronary Artery Disease and LV Function

Advances in CT technology with an improvement of volume coverage (≥64 parallel detectors) and temporal (<210 ms) and spatial (<0.6 mm) resolution enables a nearly motion free contrast-enhanced imaging of the coronary artery tree and the heart chambers during a single short breath

hold (8–13 second scan).[22] The data acquired during an ECG-gated, contrast-enhanced, multi-detector CT scan allows for 1) accurate assessment of the coronary arteries for plaque and stenosis and 2) the assessment of global and regional LV function in a cine mode.

CAD: Over the last several years, we and others have demonstrated that cardiac CT has excellent diagnostic test characteristics for the detection of significant coronary artery stenosis as compared to invasive coronary angiography.[23–28] There is strong consensus that the strength of cardiac CT is its ability to reliably rule out the presence of stenosis and relevant coronary plaque (negative predictive value [NPV]: 95% to 98%, positive predictive value [PPV]: 92% to 97%).[22] In addition, cardiac CT also accurately detects the presence and extent of calcified and non-calcified coronary atherosclerotic plaque in good agreement with intravascular ultrasound (IVUS), especially in proximal coronary segments (sensitivity 84% to 92%).[29, 30]

Global and Regional LV Function: Cardiac CT also permits the assessment of global regional LV function in a cine mode. Studies have shown excellent reproducibility (κ=0.86) and agreement to cine magnetic resonance imaging (CMRI) for the detection of global and regional LV dysfunction (r=0.91).[31–36]

1.3 Accuracy of Cardiac CT to Detect ACS in Participants with Acute Chest Pain

Preliminary data generated by the investigators suggest that cardiac CT, using at least 64-slice technology, can be performed safely and with excellent image quality in the acute care setting.[37] In addition, our observational data in 368 patients demonstrated that the presence of significant coronary artery stenosis as assessed by cardiac CT can be definitively ruled out in 70% of participants presenting with acute chest pain to the ED (see Sections 3.1 and 3.2). This finding has a 100% NPV for ACS during index hospitalization and major adverse cardiac event (MACE) during follow-up (see Section 3.1).[38] There are now several studies that support these results and suggest that cardiac CT has the potential to improve the management of participants with acute chest pain in the ED. Rubinshtein et al., in a study of 58 participants with acute chest pain but negative initial cardiac troponin levels and non-diagnostic ECG, demonstrated a NPV of 100% and specificity of 92% (n=35/38) for a diagnosis of ACS in the ED by cardiac CT.[39] Participants were discharged (n=35/58) without stress testing if obstructive CAD was excluded by cardiac CT and if serial troponin measurements were negative. There were no deaths or myocardial infarctions during a 15-month follow-up. Earlier, Goldstein et al.[40] randomized 200 participants at very low risk for ACS into a cardiac CT based triage system or a stress SPECT based triage system. They found no or minimal CAD in 68% of patients, which was a safe predictor for the absence of ACS and MACE over 6 months. The study further shows the potential of cardiac CT to shorten length of hospital stay and decrease costs of evaluation of patients with acute chest pain. However, a potential drawback of CT was noted, as the CT arm had more invasive angiograms and revascularization procedures (n=11 vs. 3 and 4 vs. 1, respectively). However, this most likely represents that at this time the association between CT findings and clinical outcomes was unknown.

In addition, studies have suggested that the absence of coronary artery calcification (CAC) as detected in a non-contrast low radiation CT scan also has a high negative predictive value for

ACS in these participants.[41,42] However, the clinical utility of CAC alone for the assessment of ACS is inadequate because it cannot exclude the presence of high-grade non-calcified plaque/stenosis.

1.4 Cost Effectiveness of Diagnostic Testing in Subjects with Acute Chest Pain

Current management of subjects with suspected ACS is managed by a sequential strategy (decision rule) involving quality and duration of chest pain, risk factors, biomarkers, ECG's and diagnostic tests such as SPECT, echo, or ETT. However, cost-effective utilization of these tests remains poor[43, 44] and hospitalization rates for ACS have increased while length of hospitalization has been constant over the last 10 years[9, 45]. The introduction of chest pain observation units may have further decreased the threshold to admit patients. Acute appendicitis and pulmonary embolism are excellent examples of the effects of the implementation of advanced imaging technology on patient management in the ED. Because of the costs associated with unnecessary appendectomy and one day of in patient observation, the implementation of the CT scan resulted in significant cost savings[46]. A similar approach is warranted to determine whether cardiac CT reduces cost and is cost effective in subjects with acute chest pain. Moreover, a formal, model-based cost-effectiveness analysis is essential to project possible costs and benefits from a broader perspective (including the assessment of potential risks associated with CT) and longer time horizon. Modeling can also help to answer questions and perform comparisons not possible within the confines of the clinical trial. The current proposal critically investigates these issues.

1.5 Significance of the Proposed Clinical Trial

Evaluation of the appropriate clinical use of novel diagnostic imaging modalities is now more important than ever as the cost of these examinations steeply rises, and now exceeds, the cost spent on prescribed drugs. All major professional medical societies, have publicly demanded that clinical use of diagnostic imaging should be dictated by evidence-based medicine to not only control costs but also to minimize additional extraneous testing, as it is currently unclear whether their usage will result in improvement in the current standard of care.

Advanced cardiac CT is one of these novel diagnostic imaging technologies that may potentially enhance standard of care in patients presenting to the ED with acute chest pain but non-diagnostic ECG and negative initial biomarkers, a population that remains diagnostically challenging and currently causes a significant clinical burden on each hospital every day. Preliminary studies demonstrate that cardiac CT accurately detects absence of coronary atherosclerotic plaque. Levels of atherosclerotic plaque as detected by cardiac CT is a powerful predictor of the absence of ACS, and can be detected in a significant fraction of participants with acute chest pain. Thus, we anticipate the implementation of cardiac CT in the early ED triage process will (1) enable earlier and safe discharge of significant fraction of patients directly from the ED, who currently would have been unnecessarily admitted, as well as (2) allow for earlier detection and better treatment of CAD compared to the current standard of care.

The proposed research will constitute the largest randomized multicenter clinical trial using cardiac CT to date and will provide an unbiased assessment of the above stated hypotheses. It

will be conducted by a group of experienced clinical researchers consisting of CT imagers, ED physicians, and cardiologist with clinical expertise in the management of chest pain syndromes. The results from this trial will determine the clinical utility of cardiac CT in patients with acute chest pain and may lead to a change in the management of these patients.

2. Preliminary Data

In support of the aim of the proposed research, we provide data from a double blinded observational cohort study ("Cardiac CT for triage of participants with intermediate likelihood of ACS" R01 HL080053-03), demonstrating the association between cardiac CT findings on plaque, stenosis, and LV function with clinical outcomes in patients with acute chest pain. These data demonstrate: 1) the absence of any CAD in up to 50% of patients with acute chest pain, 2) the high NPV of absence of plaque and stenosis for ACS and thus the safety to discharge patients from the ED and the incremental diagnostic value of LV function assessment for risk stratification.

2.1 Final Results of ROMICAT I

2.1.1 Cardiac CT Based Detection of Coronary Stenosis and Plaque in the Assessment of Participants with Acute Chest Pain

Objective

To determine the usefulness of cardiac CT angiography in patients with acute chest pain**.**

Methods

Observational cohort study in chest pain patients with normal initial troponin and non-ischemic ECG. 64-slice coronary CT was performed prior to admission to detect coronary plaque and stenosis (> 50% luminal narrowing). Results were not disclosed. Endpoints were ACS during index hospitalization and MACE during 6- month follow up.

Results

Among 368 participants (mean age 53 ± 12 years, 61% male) 31 had ACS (8%). By cardiac CT, 50% of these participants were free of CAD, 31% had nonobstructive disease, and 19% had inconclusive or positive CT for significant stenosis. Sensitivity and NPV for ACS were 100% (n=183/368; 95% confidence interval [CI]: 98%–100%) and 100% (95% CI: 0.89–1.00) with the absence of CAD; and 77% (95% CI: 59%–90%) and 98% (n=300/368, 95% CI: 95%–99%) with significant stenosis by cardiac CT. Specificity of presence of plaque and stenosis for ACS were 54% (95% CI: 0.49–0.60) and 87% (95% CI: 0.83–0.90); respectively. Only one ACS occurred in the absence of calcified plaque. Both, the extent of coronary plaque and presence of stenosis predicted ACS independently and incrementally to TIMI risk score (AUC: 0.88, 0.82 vs. 0.63; respectively, all $p<0.0001$).

Conclusion

Fifty percent of participants with acute chest pain and low to intermediate likelihood of ACS are free of CAD by CT and have no ACS. Given the large number of such patients early cardiac CT may significantly improve patient management in the ED.

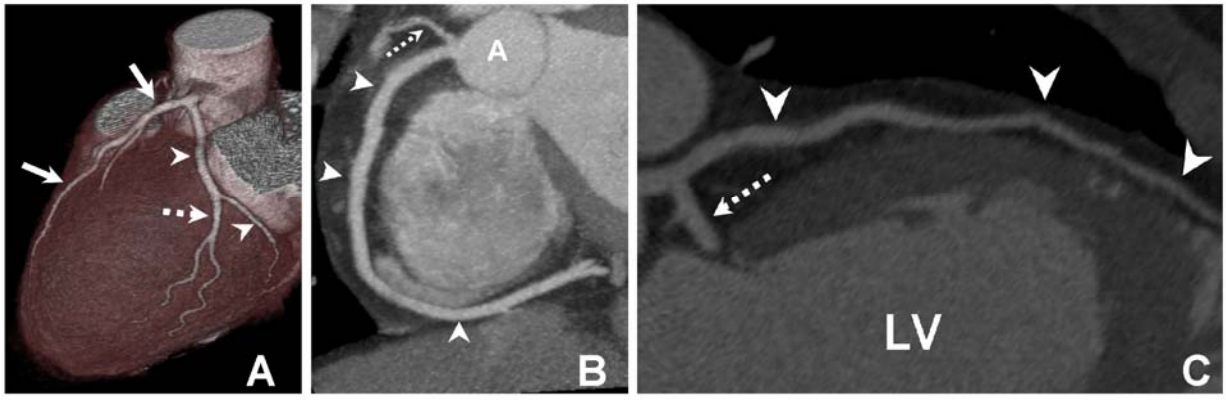

Figure 1, A-C: 67 year old female, 3 hours of substernal chest pain radiating to the back, negative initial troponin and CK-MB, ECG: sinus bradycardia, admitted to rule out MI. All coronary arteries are widely patent with no evidence of coronary atherosclerosis. **A:** Volume rendered 3-dimensional CT image (surface weighted volume rendering technique) of the heart depicting the left circumflex coronary artery (LCX, arrowhead), obtuse marginal branch (dashed arrow) and left anterior descending (LAD, arrow) two hours after presentation to the ED. **B:** CT based evaluation of segments 1 to 3 of the right coronary artery (RCA, arrowheads) and conus branch (dashed arrow), using a 5mm thick maximum intensity projection (MIP). **C:** Curved multiplaner reformatted (MPR) image of the LAD (arrowheads) and proximal LCX (dashed arrow).

Figure 2, A-C: 40-year old male with hypercholesterolemia and a family history of diabetes woke with chest pressure and noticed intermittent chest pressure during his 1 mile walk to work. He had similar symptoms a week prior to admission. Initial troponin and CK-MB were negative and ECG showed a normal sinus rhythm without ST-segment or T-wave abnormalities. Coronary CT was performed two hours after presentation to the ED and revealed a significant mid LAD stenosis. Eight hours after ED presentation, cardiac biomarkers became positive. The mid LAD stenosis was confirmed on coronary angiography the next day and the participant was treated with a stent placement. **A:** Volume rendered 3-dimensional CT image of the heart depicting the right coronary artery (RCA, arrow) and the left anterior descending coronary artery (LAD, arrowhead). Discontinuation of the contrast-enhanced coronary lumen in the mid section of the LAD (dashed arrow) was detected. **B:** CT based evaluation of the right coronary artery (RCA, arrowheads) demonstrates calcified and non-calcified plaque in segments 1 to 3, no significant coronary stenosis was detected. **C:** Curved MPR image of the LAD reveals good luminal contrast enhancement without any plaque in the distal LAD and calcified plaque in the proximal

segment (arrowheads). A significant luminal narrowing (arrow) was detected in the mid portion of the LAD.

2.1.2 Incremental Diagnostic Value of Regional LV Function Over Coronary Assessment of Cardiac CT for the Detection of ACS in Participants with Acute Chest Pain

Objective

To determine incremental value of regional left ventricular function (LVF) over coronary assessment for the diagnosis and prediction of acute coronary (ACS) in patients with acute chest pain but inconclusive initial emergency department (ED) evaluation.

Methods

We enrolled 356 consecutive patients (mean age 53±12 years, 62% male) with acute chest pain and inconclusive initial ED evaluation. These patients underwent 64-slice contrast-enhanced cardiac CT prior to hospital admission. Regional LVF and presence of coronary atherosclerotic plaque and significant stenosis (>50%) were separately assessed by two experienced readers, blinded to the clinical course and other CT findings. Caregivers and patients remained blinded to the CT results. Incremental diagnostic accuracy and predictive value of regional LVF to predict ACS was determined in the entire cohort and in subgroups of patients with inconclusive or positive coronary assessment.

Results

Regional LVF was impaired in 46 patients (12.9%) and 31 patients developed ACS (8.7%). Adding regional LVF resulted in a 10% increase in sensitivity to detect ACS (87%, 95%CI: 70-96%) when compared to detection of significant stenosis. In the subgroup of 33 patients with significant stenosis, impaired regional LVF correctly predicted ACS in 17/19 patients (PPV: 89.5%, 95%CI: 67-99%). In the subgroup of patients with inconclusive coronary CTA (n=33), normal regional LVF correctly predicted the absence of ACS in 24/26 patients (NPV: 92.3%, 95%CI: 75-99%). Impaired regional LVF, independent of the extent of plaque and the presence of stenosis, was associated with a 25 and 20 fold increased risk for ACS (RR: 20.23, 95%CI: 7.47 to 54.82, and RR: 25.34, 95%CI: 9.36 to 68.57; respectively). Moreover, c-statistics improved significantly after the addition of regional LVF to both the extent of plaque and the presence of stenosis (c-statistic: 0.88 vs. 0.94 and 0.82 vs. 0.90, respectively; both $p<0.03$).

Conclusions

Regional LVF assessment at rest improves overall sensitivity of coronary CTA for ACS in patients with acute chest pain. Combined assessment of coronary morphology and regional LVF is especially helpful to guide further testing and interventions if coronary assessment is inconclusive or positive.

2.1.3 Initial Decision Model to Assess the Cost Effectiveness of Coronary CT in Triage of Subjects with Acute Chest Pain

Objective

To develop a preliminary decision-analytic Markov model to predict the long-term consequences of four competing strategies 47 in the ED evaluation of subjects with acute chest pain.

Methods: The model consists of the six health states: chest pain, healthy, early heart disease, undiagnosed CAD, diagnosed CAD and death. Subjects start in the chest pain state. The probability that the chest pain is caused by CAD depends on the underlying risk of CAD as

determined by age, gender, and cardiovascular risk factors. As simulated subjects progress through the model, CAD (if present) can remain stable or progress. Subjects may die from cardiovascular disease or other causes, at rates determined by disease stage and demographics. By simulating hypothetical cohorts of subjects, we determined quality-adjusted life expectancy (QALE), quality-adjusted life year (QALY), and cost-effectiveness ratios for competing strategies.

We considered four competing strategies for subjects presenting with chest pain to the ED:

1) *admission*, in which all subjects are admitted to the hospital for further evaluation; 2) *discharge*, in which all subjects are discharged directly home from the ED; 3) *cardiac CT with conservative treatment*, in which all subjects without any evidence of CAD are discharged and all other patients are admitted and undergo stress testing; and 4) *cardiac CT with aggressive treatment*, which is similar to strategy 3 but sends subjects with evidence of significant stenosis directly for invasive coronary angiography. It is important to note that the model permits an evaluation of each strategy using a similar cohort of subjects. The model also permits an evaluation of estimate life expectancy and lifetime costs.

Results

Strategies involving cardiac CT were associated with lower ED costs and incremental improvements in QALE when compared to a strategy of admission for all subjects. Relative to admitting all subjects, the use of cardiac CT yielded savings in ED and hospital costs ranging from $1,800-$2,200 in men and women ages 30-40, and from $500-$1,200 men and women ages 60-70 respectively. The incremental cost-effectiveness of strategies involving cardiac CT, compared with a strategy of discharging all subjects, ranged from $94,100-$267,200 per QALY in men and $74,800-$326,100 per QALY in women.

Conclusions

This preliminary decision model suggests that strategies involving cardiac CT are associated with lower ED costs and incremental improvements in QALE in both men and women across all ages. The precision of the model will be greatly enhanced by input of real clinical scenarios derived from this proposal.

3. Study Objective/Specific Aims

This primary objective of this protocol is to assess the efficiency of implementing cardiac CT into the diagnostic workup of patients with acute chest pain, normal initial biomarkers, and normal or non-diagnostic ECGs. Study participants will be patients with acute chest pain and low to intermediate likelihood of ACS and will be randomly assigned to the SOC arm or the interventional arm; patients in the interventional arm will receive the standard of care supplemented by cardiac CT.

3.1. Primary Aim

The primary aim is to determine whether length of hospital stay is significantly reduced in the interventional arm compared to standard of care. The primary endpoint is time from ED presentation to hospital discharge.

The length of hospital stay is defined as the time from ED presentation to the time of discharge note or order. This includes time in the ED, time in any institution-specific

specialized chest pain unit, and time as an inpatient on the floor. All time sequences must be documented and reported to comprise total length of hospital stay. Hypothesis: *Adding cardiac CT to the initial ED evaluation of subjects with acute chest pain significantly decreases length of hospital stay.*

3.2 Secondary Aims

1. To determine whether time to diagnosis is significantly shortened and rates of direct discharge from ED are increased in the interventional arm vs. SOC.

   A) Time to Diagnosis:

   For **ACS:** Defined as the time from ED presentation until the first test during index hospitalization that leads to the diagnosis of ACS (tests may be biomarkers, CTA, ETT, nuclear imaging, stress ECHO or cardiac catheterization), For no ACS: Defined as the time from ED presentation defined as the final test during index hospitalization.

   B) Admission to Hospital: Participants are considered to be admitted if the ED attending admitted the subject to a hospital floor (medical floor, step down unit, telemetry hospital floor, or intensive care unit)

   Direct ED Discharge will include all subjects who are not included in (B).

Hypothesis: *ED evaluation of subjects with acute chest pain supplemented by cardiac CT significantly increases direct ED discharge rates and shortens time to diagnosis for both ACS positive and negative patients.*

2. To determine a) the additional number of invasive coronary angiograms, both arms, and b) to determine the number of coronary revascularization procedures.

Hypothesis: *ED evaluation of subjects with acute chest pain supplemented by cardiac CT will not increase the number of invasive coronary angiograms without revascularization or revascularizations during index hospitalization.*

3. To determine the safety of immediate ED discharge after a normal cardiac CT defined as the occurrence of ACS within 48-72 hours after discharge.

Hypothesis: *CTA has a high negative predictive value based on which immediate ED discharge should not compromise patient safety.*

4. To determine whether subsequent testing and follow up, including invasive coronary angiograms, diagnostic (imaging) tests, interventions, repeat ED visits for cardiac related problems, and repeat hospitalizations for chest pain or equivalent during 28 days after hospital discharge is decreased in the interventional arm compared to SOC,.

Hypothesis: *Incorporation of CTA in the evaluation of acute chest pain patients in the ED will not lead to decreased further testing to manage chest pain when as compared to the SOC arm.*

5. To compare the two study arms in terms of rates of MACE (major adverse cardiac events—cardiac death, AMI, revascularization, unstable angina, and rehospitalization) within 28 days.

   28 Days: Defined as 28 days post the day of discharge from index hospitalization.

Hypothesis: *The rates of MACE in both arms during the 28 day follow up period will be similar.*

6. To estimate and compare the sensitivity, specificity, NPV and PPV of contrast-enhanced CT and non-contrast CT, with clinical diagnosis of ACS as the reference standard.

Hypothesis: *The test characteristics of contrast enhanced CT will be significantly better than those of a non-contrast CT for the diagnosis of ACS.*

7. Determine whether cost of care (per TSI) for index hospitalization and after 28 days is decreased by implementing cardiac CT into the early ED evaluation of patients with acute chest pain.

Hypothesis: *Incorporation of cardiac CT into standard ED evaluation of patients with acute chest pain will decrease the cost of care.*

8. Determine the cost-effectiveness of incorporating cardiac CT into the standard ED evaluation of patients with acute chest pain over a 28-day and lifetime horizon as compared to SOC.

Hypothesis: *Incorporating cardiac CT into the standard evaluation of patients with acute chest pain will be cost-saving and cost-effective over a 28-day and lifetime horizon.*

3.3 Tertiary Aims

1. To determine whether CT leads to increased test burden after the initial tests during index hospitalization.

Hypothesis: *Cardiac CT may diagnose coronary artery disease at a more incipient stage than determined by imaging tests in the SOC arm, which may increase test burden during the follow up period.*

2. Compare the consistency of physician decisions management depending on the results of diagnostic testing (i.e. normal CT - what fraction is immediately discharged)

Hypothesis: There will be comparable consistency between the two arms.

3. Determine whether hospital setting, availability of Observation Unit, CT experience of hospital and readers, and reader performance are associated with primary or secondary outcomes.

Hypothesis: *Enhanced CT experience of the hospital and readers, better reader performance during CT certification and hospital setting will be associated with improved primary or secondary outcomes.*

4. Participant Selection/Eligibility Criteria

Adult ED participants presenting with a lead symptom of acute chest pain suggestive of acute cardiac ischemia - defined as chest pain lasting for at least 5 minutes and occurring within the last 24 hours but without diagnostic ECG changes of acute myocardial ischemia - will be eligible for participation.

Only patients in whom the ED attending feels that further inpatient testing is required will be included. Patients with known/documented history of CAD will not be included since such patients most often have an abnormal or non-diagnostic cardiac CT. In addition, men and women younger than 40 years will be excluded due to the low pre-test likelihood for CAD and the increased radiation risk. Detailed inclusion and exclusion criteria are presented below.

4.1 Inclusion Criteria

1. Participant must have at least five minutes of chest pain or equivalent (chest tightness; pain radiating to left, right, or both arms or shoulders, back, neck, epigastrium, jaw/throat; or unexplained shortness of breath, syncope/presyncope, generalized weakness, nausea, or vomiting thought to be of cardiac origin) at rest or during exercise within 24 hours of ED presentation, warranting further risk stratification, as determined by an ED attending.
2. Participant must be able to provide a written informed consent.
3. Participants must be <75 years of age, but $\geq$40 years of age.
4. Participant must be able to hold breath for at least 10 seconds.
5. Participant must be in sinus rhythm.

4.2 Exclusion Criteria

1. New diagnostic ischemic ECG changes (ST-segment elevation or depression > 1 mm or T-wave inversion > 4 mm) in more than two anatomically adjacent leads or left bundle branch block
2. Documented or self-reported history of CAD (MI, percutaneous coronary interventions [PCIs], coronary artery bypass graft [CABG], known significant coronary stenosis [>50%])
3. Greater than 6 hours since presentation to ED to time of consent.
4. BMI >40 kg/m^2
5. Impaired renal function as defined by local standard of care - for example, measured serum creatinine >1.5 mg/dL
6. Markedly elevated troponin as defined by local standard of care
7. Hemodynamically or clinically unstable condition (BP systolic < 80 mm Hg, atrial or ventricular arrhythmias, persistent chest pain despite adequate therapy)
8. Known allergy to iodinated contrast agent
9. Currently symptomatic asthma
10. Documented or self-reported cocaine use within the past 48 hours (acute)
11. On Metformin therapy and unable or unwilling to discontinue for 48 hours after the CT scan

12. Contraindication to beta blockers (taking daily antiasthmatic medication): This exclusion only applies to patients with a heart rate > 65 bpm at sites using a non-dual source CT scanner
13. Participant with no telephone or cell phone numbers (preventing follow-up)
14. Participant with positive pregnancy test. Women of childbearing potential, defined as <2 years of menopause in the absence of hysterectomy or tube ligation, must have a pregnancy test performed within 24 hours before the CT scan.
15. Participant unwilling to provide a written informed consent.

4.3 Recruitment, Screening, and Consent

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. All clinical sites will perform screening Monday through Friday during daytime hours (9am-5pm). Potential subjects will be identified by research coordinator/study nurse staff shortly after admission to the ED usually after the initial ED evaluation consisting of ECG, physical examination, clinical symptoms and presentation, immediate and past medical history has been concluded and screened for eligibility based on a checklist providing inclusion and exclusion criteria.

Eligible subjects will be approached and, if the subject considers participation, the Clinical Research Coordinator (CRC) will describe the rationale of the study, the study procedures with associated risks and benefits. A study physician/study nurse/CRC will speak directly with an ED physician caring for the patient to obtain an assessment of pretest probability for ACS and will verify that the ED physician feels that further observation or diagnostic testing is warranted in this patient.

If the subject agrees and further testing or observation is planned as SOC, key study personnel, typically a study physician or the attending ED physician, will review the study procedures, as well as all potential risks and discomforts and the opportunity to decline or cease participation in the study at any time, answer any remaining questions, and consent the subject.

Patients can be consented but not randomized before the first troponin test result is available. Patients whose initial troponin level is markedly elevated will not be randomized and will not be included in the intent-to-treat population. Patients whose subsequent troponin testing is markedly elevated will be included in the intent to treat population.

Patients can be consented before a pregnancy test is available. However, patients with a positive pregnancy test will not be randomized.

Patients who are not randomized will not be considered part of the intent to treat population.

Informed Consent:

- A potential subject will then be afforded as much time as clinically feasible to review the consent form and decide upon their participation without adversely effecting their ED care, which is typically 1 hour.
- If the ED staff caring for the patient determines that the potential subject's previously determined plan of care must proceed before the potential subject has had adequate time to decide upon his/her participation without undue pressure, the potential subject will be excluded from enrollment.
- Subjects will be provided with a copy of the informed consent form.

4.4 Randomization

After the patient has been consented by the study physician, the study subject will be randomized into the standard care arm or the intervention arm (cardiac CT) by means randomization stratified by institution using a central computerized randomization system.

5. Study Procedures

5.1 Index Hospitalization

Standard of Care Arm: Subjects will be evaluated according to each hospital's specific protocol to evaluate and manage patients with acute chest pain. Typically, the standard evaluation in the ED will include the past and current medical history, a physical examination, an ECG and a cardiac biomarker (Troponin and CK-MB) as well as other routinely obtained blood testing. Patients may undergo cardiac CT as part of SOC but only as a secondary diagnostic test. Patients in the CT arm may undergo further diagnostic testing as well.

All admitted subjects will undergo each hospital's standard rule out myocardial ischemia protocol. This protocol typically consists of observation and monitoring including serial ECGs and repeated cardiac biomarker measurements as well as a noninvasive stress test (often imaging based) to evaluate for myocardial ischemia. The participating clinical sites perform routinely either nuclear perfusion imaging [SPECT] at rest and stress, and/or stress echocardiography, and/or exercise treadmill test [ETT]. Depending on the results, subjects may undergo additional noninvasive or invasive testing (coronary angiography), and/or coronary revascularization during their hospital stay.

Interventional Arm: In subjects randomized to the intervention arm, a contrast enhanced cardiac CT will be performed (after initial troponin level is available) in addition to the initial ED evaluation.

The ED physicians will resume care of the patient and make all clinical decisions for further care of the patient (e.g., need for further evaluation or admission) based upon their cumulative clinical assessment of the patient, including findings revealed on the CT scan.

In addition, in patients from both study arms who consented to a blood draw, we will obtain three fifteen (15) mL venous blood samples over a six-hour period, less than forty-five (45) mL in total. Blood samples will be centrifuged and frozen for future analysis for cardiac-related markers.

All diagnostic tests will be performed per Society Guidelines. Cardiac Computed Tomography is performed in accordance with best practice standards as delineated in the imaging guidelines of the Society of Cardiovascular Computed Tomography by competent[63] and appropriately credentialed physicians. This includes the optimization of the scan protocol to limit radiation exposure.

5.2 48-72 Hour Follow up after ED discharge

Follow-up phone call at 48-72 hours: Subjects who are discharged from the ED within 24 hours of presentation (for both randomization arms) will be contacted via telephone between 48 and 72 hours after discharge to avoid ascertainment bias. During this call, subjects will be interviewed to determine whether they have had any recurrent symptoms suggestive of myocardial ischemia and and/or whether they needed to seek further medical attention following their emergency department visit. If these phone attempts at 48 and 72 hours are not successful, a final attempt will be made at 96 hours to contact the subject

NOTE: If a subject is discharged on a Thursday, the 48-72 hour phone call may be extended to 96 hours. In the rare circumstance that a subject is discharged on a Thursday and the following Monday is a holiday, the follow-up call can be made during the next working business day.

5.3 28 Day Follow up

Follow up 28 day phone call: All subjects will be interviewed via a telephone call 28 days post ED discharge (+4 weeks) to determine the occurrence of MACE and healthcare utilization using a standardized questionnaire. All cases of recurrent chest pain, hospital admissions, and diagnostic testing will be verified by review of medical records.

A reminder letter will be sent or phone call will be made to participants, two weeks prior to the 28-day follow up phone call. If unable to contact the participant by phone, mortality will be assessed online using the SSDI website.

6. Data Collection

The following subject data will be collected during index ED visit/hospitalization and follow up phone interviews:

- Subject demographic information
- Medical history, including cardiac risk factors and medications
- Description of recent pain episodes
- Vitals signs, ECG, cardiac biomarker results
- Cardiac CT imaging and other cardiac-related diagnostic testing data
- Adverse events

7. Statistical Considerations

A total of 1000 participants will be enrolled in this study. Enrollment is planned to be completed in 15 months.

7.1 Primary Aim

To compare the two study arms in terms of the time from ED presentation to hospital discharge.
The primary aim of the study is to compare the two study arms in terms of a difference in mean length of hospital stay (LOS) between the two arms. Based on the results of ROMICAT I, we estimate the mean (± standard deviation) hospital LOS (including ED) of these patients in standard evaluation to be 40.5 ± 43.2 hours. The observed frequency distribution appeared to fit well to a log-normal distribution (Median was 77 hours and Range was 2.75 – 381.5 hours). We anticipate that the observed distributions of both Group A and Group B follow such a pattern. Because the independent samples t-test is robust to a departure from the data normality when applied to a large sample size, we will employ the t-test for this inference.

We have conducted a power evaluation using the estimated mean and standard deviation based on ROMICAT I for Group A and using the estimated the mean and standard deviation based on a simulated data for Group B. The simulated data consisted of 500 LOS values resulted as a mixture of three subsets randomly drawn from log-normal distributions of which the first subgroup was to represent the patients with normal LV function and without CAD (48.6%, Mean ± SD of 6 ± 1.2 hours), the second was to represent the patients with normal LV function and with non-obstructive CAD (28.8%, Mean ± SD of 10 ± 2.0 hours), and the third group was to represent all other possible conditions (22.6%, Mean ± SD of 57.9 ± 60.4 hours which was estimated from ROMICAT 1). We also incorporated in the possibility that some patients without CAD will not be correctly triaged.. The triage accuracy rate in the following table is the rate at which a patient without CAD would be correctly triaged. The following table summarizes, for each ED triage accuracy rate assumption, the estimated mean LOS and the power at a Type-1 error rate of 5% for an independent samples t-test using 500 patients in each arm. The proposed sample size will attain a sufficient power to detect a clinically meaningful difference in mean LOS between the two groups even in the presence some degree of ED triage inaccuracy.

Powers to Detect Estimated Differences in Mean LOS values at Assumed ED Triage Accuracy Rates (Type-1 error rate = 0.05)

Assumed ED Triage Accuracy Rate	Estimated Mean (± SD) LOS		Estimated Difference in Mean (hours)	Power
	Group A (Standard Eval.) N=500	Group B (CT Eval.) N=500		
65%	40.5 (± 43.2)	32.8 (± 46.7)	-8.3	83%
70%	40.5 (± 43.2)	30.5 (± 45.5)	-10.1	95%
80%	40.5 (± 43.2)	26.3 (± 41.7)	-14.2	99%
90%	40.5 (± 43.2)	22.4 (± 37.3)	-18.1	>99%
100%	40.5 (± 43.2)	18.8 (± 33.5)	-21.7	>99%

7.2 Secondary Aims

To compare the two study arms in terms of time to diagnosis and rates of direct discharge.
The time to discharge (defined as time from ED presentation until discharge to home) will be plotted using Kaplan-Meier curves because some patients will be in the hospital at 30 days post day of presentation/randomization. The curves for the two groups will be compared using a test based on the difference in the average length of stay in the two groups (truncated at 30 days) divided by the standard error of this difference.[60] We choose this test because the average length of stay is most closely associated with cost. It will be also instructive to compare the curves themselves as they will provide information on the effect of cardiac CT on different groups of patients. For instance one group of patients, those who are discharged due to cardiac CT, may have a shorter length of stay, while others may have a longer length of stay due to waiting for the results of the CT or other procedures that the CT indicates.

Sample Size: The planned sample size will also provide adequate power to detect the rates of direct discharge from ED. Screening data from a site survey of our clinical sites as well as published data indicate that the standard ED discharge rate is approximately 15% in the target population.
According to our preliminary data and data from other groups, we expect that 40% to 50% of participants have no detectable CAD by cardiac CT. The negative predictive value of this finding for ACS has been shown to be 100%. Our guidelines suggest that these participants will be discharged directly from the ED. However, realistically, we expect that because of administrative issues and remaining individual variation of the decision to discharge depending on the clinical presentation of participants actually only 60% to 80% of these participants will be discharged. Thus, anywhere from 24% to 40% participants could be discharged directly from the ED in the interventional arm. For the sample size analysis, we assume that 32% of participants will be discharged.

Based on the aforementioned key assumptions, for the *Standard Evaluation* we anticipate that 15% of all participants will be discharged and 85% will be admitted (discharge rate: 15%). For the *Cardiac CT Evaluation*, we assume a discharge rate of 32%. For the objective of superiority

of discharge rates we will have a 100% chance at a significance level of 0.05 to detect a 17% increase in discharge rates from 15% to 32%.

The comparison of time to discharge among patients who are admitted to the hospital is complicated by the fact that the two groups will not be the same group of patients. For instance, patients who would have been discharged in the cardiac CT group but admitted in the usual care group may have a relatively shorter time post admission than patients who would have been admitted in both groups. We have developed methods for analyzing these types of data using causal inference that will be applied to this analysis.[61] A similar analysis will be applied to other subgroups such as those with and without ACS.

To compare the two study arms in terms of cardiac health care utilization during the index visit. Health care utilization components will include invasive coronary angiograms and coronary revascularization..

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. Measures of key components of utilization will be compared across the two study groups using procedures appropriate for each measure (rate or count).

In particular the two arms will be compared in terms of the number of invasive coronary angiograms. This secondary endpoint will be analyzed in terms of a non-inferiority trial. In a non-inferiority trial the null hypothesis is that cardiac CT is worse than usual care in that the rate of coronary angiograms is increased and the alternative hypothesis is that it is not in worse and the rate of angiograms is the same. The reason for reversing the usual null and alternative hypothesis is that the purpose of this analysis is to prove that cardiac CT is not worse than usual care, this would not be accomplished by just showing that the difference between the two was not significant.

Screening data from a survey of clinical sites as well as published data indicate that the standard rate of invasive coronary angiograms in the target population is approximately 10%. According to our study guidelines we assume that most but not all participants with significant stenosis in CT (10% of participants) undergo invasive coronary angiography (notably those who also have a positive stress test and those who have high grade proximal stenosis or LAD stenosis). In addition, we assume that a minority of participants with indeterminate stenosis (<5%) and positive stress testing undergo invasive coronary angiography. Because of the moderate specificities of standard diagnostic testing up to 40% of participants who undergo cardiac catheterization have no significant CAD.[15,16] Because the diagnostic accuracy of cardiac CT for the detection of coronary stenosis is comparable or better than standard diagnostic testing, we believe that there will be no increase in the rates of invasive coronary angiograms. If we define a 5% difference as an “acceptable” difference in cardiac catheterization rates than we will have an 84% chance of showing that the CT arm is significantly less than 5% worse than the standard arm at a one sided p=0.05 significance level.

Another key measure of utilization is the number of coronary revascularization procedures: In ROMICAT I there were 18 revascularization procedures performed in 368 patients (5%). Thus, we expect 5% procedures in the standard evaluation. If we assume that not all participants with significant stenosis will undergo coronary revascularization (because if no MI it can be medically managed) and that cardiac CT may also avoid some angiograms by excluding disease, than we can realistically assume that there is not a difference between the two study arms. If we consider this in terms of a non-inferiority trial as above, we will have 80% power to rule a difference of 3.5%.

To compare the two study arms in terms of cardiac health care utilization within one year after index hospitalization. Health care utilization components will include invasive coronary angiograms, cardiac related diagnostic and lab testing, and ED visits.

This analysis will be performed from the intent to treat perspective. CP and CT related health care utilization will be assessed using medical record review. Measures of key components of utilization will be compared across the two study groups using procedures appropriate for each measure (rate or count).
We expect that the rate of additional cardiac work-up will be 29% in the SOC arm and will be 14% in the interventional arm. We will have >95% power to detect this difference.
We expect that the rate of hospital admissions with additional diagnostic cardiac testing will be 9.3% in the SOC arm and will be 4% in the interventional arm. We will have >95% power to detect this difference.
We expect that the rates of these measures will be associated with the CT findings at index hospitalization.

To evaluate the cost and cost-effectiveness of incorporating cardiac CT into the standard ED evaluation of patients with acute chest pain
These analyses will be performed by the Decision Analysis and Cost-Effectiveness Center (DACE). Therefore, the sites will collect and provide the necessary data to the DACE and the costs will be derived from the cost-accounting database (TSI). As a first step, incorporating cardiac CT into the standard evaluation of patients with acute chest pain will be tested for cost-saving over a 28-day and lifetime span as compared to standard care. Further on, cost-effectiveness of incorporating cardiac CT into the standard ED evaluation of patients with acute chest pain will be determined using first-order Monte Carlo microsimulations.

To compare the two study arms in terms of rates of MACE (cardiac death, AMI, revascularization, unstable angina, and rehospitalization) within 28 days.
The analysis for this secondary aim will be performed from the intent to treat perspective. The occurrence of MACE will be assessed via patient follow-up and medical chart review. The primary analysis for this aim will be performed at the patient level by determining whether any MACE 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 MACE will be examined separately.

Sample Size- Safety Considerations- Missed ACS: Mistaken discharges are the primary safety issue in this study. All available data indicate that the absence of any detectable CAD (absence

of any plaque and stenosis) has a very high NPV for ACS (100% or close to 100%).62 Thus, we anticipate that the occurrence of ACS in participants discharged home directly from the ED in the interventional arm will be also minimal or even zero and similar to the standard of care. If, as demonstrated in ROMICAT I, none of the participants without CAD will have MACE, defined as ACS within 30 days after direct ED discharge, this observation has 90% power to ensure that the true event rate is less than 1%. These assumptions are supported by the results of the ERASE trial, which reported similar and very minimal event rates in each group (only 2 pts with acute MI were mistakenly discharged, 1 in each randomization group, out of 1200 [event rate: 0.0008%]). In this trial, we would have an 80% chance of detecting at least one occurrence of an inappropriately discharged participant if the true rate where over 1%.

To estimate and compare the sensitivity, specificity, NPV, and PPV of contrast-enhanced CT and non-contrast CT, with clinical diagnosis of ACS as the reference standard.
The analysis for this aim will utilize data on participants randomized to Group B. In this arm, each participant will undergo non-contrast CT and contrast-enhanced CT, which will be interpreted as positive or negative for ACS. Clinical determination of presence or absence of ACS will be used as the reference standard. For each of the two types of CT, we will estimate the sensitivity, specificity, and positive and negative predictive value of the modality for ACS. Each measure of diagnostic or predictive performance will be compared between the two modalities, using statistical techniques that account for the correlation due to the paired test design. In addition to these measures, we will estimate the proportion of cases with a clinical diagnosis of ACS and a negative non-contrast CT in which contrasted enhanced CT was positive for ACS. This proportion provides a measure of the incremental value of contrast-enhanced CT for diagnosis ACS.

7.3 Tertiary Aims

To determine whether CT leads to increased test burden after the initial tests during index hospitalization

To compare the consistency of physician decision management depending on the results of the diagnostic testing (i.e. normal CT – what fraction is immediately discharged)

To determine whether hospital setting, availability of Observation Unit, CT experience of hospital and readers and reader performance are associated with primary or secondary outcomes.

Analysis of Data on Women and Minorities
We will analyze the effect of the intervention on women and minorities as outlined in the NIH guidelines. Thus, we include testing for gender-treatment and minority status-treatment interactions with the discharge rate and the angiogram rate.

8. Data Entry and Site Monitoring

8.1 Data Collection

Subject data will be collected by the research associates and paper records will be maintained at individual clinical sites. The Data Coordinating and Statistical Center (DCSC) will develop a web based electronic case report form. The de-identified study data will be entered into this electronic data capture system (EDC) and sent to the Data Coordinating and Statistical Center (DCSC) at Massachusetts General Hospital for further analysis.

8.2 Site Monitoring

Site visits will be performed on a regular basis by the Data Coordinating Center, to ensure that all regulatory requirements are being met and to monitor the quality of the data collected. Records of Institutional Review Board approvals and patients' charts will be examined on a spot check basis to evaluate the accuracy of the data entered into the database.

9. Risk and Benefit Assessment

9.1 Risks of Nonionic Contrast Agent

Rare risks of the nonionic contrast agent:

- Itchiness
- Rash
- Mild allergic reaction

Very rare risks of the nonionic contrast agent:

- Kidney disease/Contrast-induced nephropathy
- Death

Regarding the risks of contrast material, the rate of adverse reactions with nonionic contrast reagents is 0.2%.[50] More than 90% of such adverse reactions are allergic-like, very mild (itching, rush) and can be very effectively treated with available drugs (i.e., antihistaminic). Severe reactions occur in 0.02% and one death occurred in 57,739 injections of nonionic contrast material.[50]

Contrast-induced nephropathy (CIN): CIN is expected to be a very rare event among this patient population because patients with already impaired renal function (the strongest predictor of CIN) will not be enrolled). This assumption is strongly supported by our preliminary experience from ROMICAT I. In this study, none of the participants had such an event (0/368).

The very low risk associated with contrast administration has been documented in large scale trials previously. In a randomized trial in 1,196 participants, the incidence rate of CIN defined as an increase in serum creatinine ≥1mg/dL from baseline within 48 to 72 hours following the injection of contrast material was 0 in 359 participants (0%) who had no renal insufficiency and no diabetes melliltus.[51] The risk was 2 in 315 (0.6%) in participants with no renal insufficiency, but who had diabetes mellitus.[51] In this study, the mean volume of contrast-agent administered

was 140 ± 57 mL, which is much higher than the 80 mL of contrast that is administered for a coronary CTA. The risk of CIN may increase if participants in the cardiac interventional arm will be admitted and subsequently undergo further contrast-related diagnostic testing. However, among 209 participants who had both a pulmonary angiogram and a contrast-enhanced spiral CT in the Prospective Investigation of Pulmonary Embolism Diagnosis II, only one participant with diabetes mellitus had a transient episode of acute renal failure characterized by an increase in the serum creatinine level from 1.3 to 2.9 mg/dL.[52] In this study, the contrast-enhanced CT and pulmonary angiogram were performed within 22 hours. The elevated creatinine returned to normal after administration of intravenous fluids. Thus, overall we expect that the occurrence of CIN will be a rare event in this study.

9.2 Risks Associated With Radiation

While the radiation dosage for CT scanning varies with the part of the body being scanned, the exposure for this examination is approximately between 7 and 17 mSv. This exposure is comparable or less than stress nuclear myocardial perfusion imaging (14–22 mSv) (personal communication with Prof. Ronald Callahan, Chairman of the MGH Radiation Safety Committee). In comparison, the average yearly effective dose of natural background radiation is 2.5 mSv,[53] the allowed annual exposure of radiation workers is 50 mSv, the allowed exposure in five years is 100 mSv (Table 3).[54] Thus, even if an enrolled participant would undergo cardiac CT followed by a conventional stress test and selective coronary angiography, the participant would be well below the allowable annual effective dose for radiation workers. The radiation dose from cardiac CT has not been shown to have any adverse effects.

Radiation Exposure

Cardiac CT scanning results in a measurable radiation exposure.[55] In order to minimize risk for participants in this study we have implemented the following measures:

- Exclude women <40 years of age
- Exclude pregnant and breast feeding women
- Include only women who have a negative pregnancy test
- Application of cardiac CT protocols with the goal to minimize radiation exposure (i.e. use of tube modulation—decrease of radiation exposure by 30% to 50% and prospective triggering in appropriate conditions)
- Review and approval of these CT protocols by the CVCT Core Lab

General Risk Associated with Radiation Exposure

The risk of inducing a malignancy by exposure to radiation is estimated to be 5 cases of malignancy for each 100 individuals exposed to an effective dose of 1 Sv.[54] The risk is estimated to be higher in infants and children and lower in the elderly. The data, which these estimates are based on, are weak and apply to relatively high levels of radiation exposure[56] and it remains unclear whether there is a linear relation in lower levels of radiation. Assuming a linear proportion with a low level of radiation, exposure to 1 mSv would lead to 5 malignancies in 100,000 individuals exposed and a dose of 8 mSV would lead to 40 malignancies in 100,000 individuals.[56] Small amounts of radiation exposure, less than 100 mSv, have not been clearly

shown to have harmful effects. The amount of radiation to which patients will be exposed in this study is less than the amount that is known to cause a measurable harmful effect. Even so, it is generally assumed that a small amount of radiation will have a small chance of producing a harmful effect. These extrapolated risks of the effects of small amounts of radiation are probably overestimates because the estimates ignore the fact that the body can repair the damage done by radiation if the repair mechanisms are not overwhelmed. Radiation is a well-known teratogenic agent and the developing fetus is much more sensitive to radiation than the mother.

Table 3: Estimated radiation exposure for diagnostic tests, background radiation, and exposure limits.

Examination	Effective Dose (mSv)
Chest PA and lateral	0.07
Myocardial Perfusion Imaging (Rest and Stress)	14–22
Thorax CT for the Exclusion of Pulmonary Embolism	7-12
64-Slice CT coronary angiogram	7–17
2-view mammogram	3.0
Natural yearly background radiation	2.5
Max exposure in radiation workers	50

Lifetime Cancer Risk Attributable to Cardiac CT

The absolute cancer risk has been described recently and recommendations have been made[57.] The life time cancer risk from cardiac CT decreases with age and is higher in women than in men, in particular exposure of younger women should be avoided. In our study these recommendations have been incorporated. In comparison, the absolute cancer risk for women to develop breast cancer is 13% and for men to develop colon cancer is 7%, the risk attributed to a cardiac CT scan is 1:466 vs. 1:715 for a 60 year old women and 1:1241 vs. 1:1911 for 60 year old men (for CT without and with tube modulation (female: 21 and 14 mSv, male 15 and 9 mSv respectively).[57] Thus, the incremental risk induced by cardiac CT compared to the overall risk of the population to develop cancer seems moderate.

Effect of the Implementation of Cardiac CT in the ED Evaluation of Patients with Acute Chest Pain on a Population Basis

The number of CT scans performed in the US was 62 million in 2006[58]. Imaging of the abdomen (50%) and the head (33%) were major single contributors. Specific concern was given to the rise of pediatric CT imaging (from 6% to now 11%) and screening the adult asymptomatic population (i.e. lung, heart). Implementation of cardiac CT in the ED could lead to a small increase of the number of overall CT procedures. However, the effects of the implementation of cardiac CT in the ED would be minimal if 1) other procedures associated with radiation doses would be saved, 2) repeated testing, currently performed in 25% of patients, would be minimized, and 3) rates of unnecessary purely diagnostic cardiac catheterizations would

decrease. Furthermore, already cardiac CT scanning could be performed using single phase acquisition with prospective triggering which would decrease the dose to <5 mSv.
In addition, MD over-read will be performed for internal quality control assessment of findings related to CAD and significant cardiac findings such as pulmonary embolism and aortic dissection, to increase awareness to sites of non-coronary findings.

9.3 Other Risks/ Additional Risks of CT Scans

- Discomfort
- Claustrophobia

Risks of IV Needle Placement

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

9.4 Potential Benefits

- Subjects may benefit from randomization into the interventional arm of trial from detection of pathology that may not have been otherwise detected during SOC (e.g., a non-significant coronary stenosis or non-obstructive coronary artery disease that would likely not have been detected by a stress test).
- Data from prior studies indicate that patients in the interventional arm may be earlier discharged and may not have to spend the night in the hospital, there is also the chance that alternative diagnosis such as pneumonia or Pulmonary embolism may be detected - patients may avoid the dual radiation exposure of a CT protocol solely to evaluate for pulmonary embolus followed by a SPECT myocardial perfusion scan.
- Subjects may also benefit in their assessment for long term prognosis and risk for adverse cardiac events and may receive preventive medication as a result of CT.

10. Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (International Conference of Harmonization [ICH] guidelines), applicable government regulations, and NIH 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 the ROMICAT PI before implementation of the study.

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. 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.

10.1 Inclusion of Women and Minorities

The 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.

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

Table 1: Gender and Minority Accrual Estimates

Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	66	79	145
Not Hispanic or Latino	384	471	855
Ethnic Category: Total of all participants	450	550	1,000
Racial Category			
American Indian or Alaskan Native	2	2	4
Asian	35	42	77
Black or African American	125	153	278
Native Hawaiian or other Pacific Islander	2	2	4
White	254	312	566
Other/Unknown	32	39	71
Racial Category: Total of all participants	450	550	1,000

11. Adverse Event Reporting

Mistaken discharges are the primary safety issue in this study. All available data indicate that the absence of any detectable CAD (absence of any plaque and stenosis) has a very high NPV for ACS (100% or close to 100%).[62] Thus, we anticipate that the occurrence of ACS in participants discharged home directly from the ED in the cardiac interventional arm will be also minimal or even zero and similar to the standard of care. If, as demonstrated in ROMICAT I, none of the participants without CAD will have MACE, defined as ACS within 30 days after direct ED discharge, this observation has 90% power to ensure that the true event rate is less than 1%. These assumptions are supported by the results of the ERASE trial, which reported similar and very minimal event rates in each group (only 2 pts with acute MI were mistakenly discharged, 1 in each randomization group, out of 1200 [event rate: 0.0008%]). In this trial, we would have an 80% chance of detecting at least one occurrence of an inappropriately discharged participant if the true rate where over 1%.

At the time of ED discharge, investigators will determine at if any adverse events have occurred. An **Adverse Event (AE)** is any untoward medical occurrence in a study participant that may or may not 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

Serious Adverse Event (SAE):

An 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.

Reportable Adverse Events
Any untoward medical occurrence that occurs after randomization and prior to discharge from the ED should be reported to the CCC by completing the electronic adverse event case report form.

Immediately Reportable Adverse Events

Any adverse event that is judged by the investigator to be serious AND unexpected AND related to study procedures should be reported within 24 hours of discovery by phone or email to the Coordinating Center. The local Institutional Review Board must also be notified in a timely manner.

Investigators must also report Unanticipated Problems, regardless of severity, associated with the study procedures within 24 hours. An unanticipated problem is defined as follows:

Unanticipated Problem (UP): any incident, experience, or outcome that meets all of the following criteria:

- Unexpected, in terms of nature, severity, or frequency, given the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and the characteristics of the subject population being studied;
- Related or possibly related to participation in the research, in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research;
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

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Appendix A: Cardiac CT Imaging Protocol Guidelines†

Cardiac CT Imaging: Diagnostic Intervention to Be Tested

Equipment
Cardiac CT imaging will be performed using at least 64-slice CT scanner technology according to the vendor specific protocol for the evaluation of the coronary arteries and LV function (Table 2).

Table 2. Overview of vender-specific protocols as used in the proposed trial

CT Scanner	Spatial Resolution/ Slice Collimation	Gantry Rotation Time/ Temporal Resolution	Tube Voltage, Tube Current	Estimated Radiation Exposure (mSv)*
Siemens Definition Dual Source 64-row MDCT	2 x 64 x 0.6 mm	330 ms/83 ms	100-120 Kvp, 850 effective mAs	7-15 mSv
Toshiba Acquillion 64-row MDCT	64 x 0.45 mm	400 ms/200 ms	100-120 Kvp, 700 mAs	10-14 mSv
Siemens Somatom 64-row MDCT	64 x 0.6 mm	330 ms/165 ms	100-120 Kvp, 850 mAs	7-14 mSv
GE Lightspeed VCT 64-row MDCT	64 x 0.6 mm	350 ms/175 ms	100-120 Kvp, 750 mAs	11-17 mSv
Philips Brilliance iCT 256-row MDCT	64 x 0.624mm	270 ms/135 ms	100-120 kVp, 850 mAs	7-13 mSv

* includes radiation exposure from CAC imaging, assumes the use of tube modulation. Actual radiation doses will depend on the subjects' body habitus, as well as the rate and regularity of the heart during acquisition.

Image Acquisition
Based on preliminary data from the clinical sites, the image acquisition takes approximately 20 minutes. The participant will be transported to the CT suite and returned by qualified study personnel. Continuous heart rate and rhythm will be monitored during the study exam with 4-lead ECG electrodes. Blood pressure and heart rate will be measured before and after the study exam.

General recommendations include:

- Minimal flow rate: 5ml/sec
- Retrospective ECG triggering with use of tube modulation techniques to permit assessment of LV function

† This appendix is intended as example of a cardiac CT imaging protocol. Please refer to the current version of the Massachusetts General Hospital Cardiovascular Imaging Core Laboratory (CVIC) Study Imaging Procedure for ROMICAT II study imaging procedures.

- Prospective triggering in subjects with appropriate conditions, to further minimize radiation exposure.
- 100 kvp if BMI <30 kg/m2
- 120 kvp if BMI > 30 kg/m2

In general the image acquisition protocol consists of the following 3 steps:

Step 1—Participant Preparation: Participants will be instructed and trained in breath holding. ECG electrodes will be mounted on the chest to enable co-registration of image acquisition and ECG signal. At sites WITHOUT a dual source computed tomography (DSCT) scanner, all participants with a heart rate >65 beats per minute will receive beta blocker (5 to 20 mg Metoprolol, I.V.) to optimize image quality and 600 mcg sublingual nitroglycerin to maximally dilate the coronary arteries unless their systolic blood pressure is <100 mm Hg or other contraindications are present.[43] At sites with a DSCT scanner, due to the improved temporal resolution, beta blockers are not required though may be given and participants will receive sublingual nitroglycerin if there are no contraindications.

Step 2—Image Acquisition: All image acquisitions will be performed during a breath hold on inspiration with the following acquisitions:

a. Topogram—The cardiac CT imaging protocol will start with a topogram of the chest permitting the localization of the position of the heart.

b. Noncontrast calcium score scan—A prospective gated low dose non-contrast CT scan (100 kVp for BMI<30, or 120 kVp for BMI >30, 320 mA), with scan initiation at 70% (Siemens scanners) or 75% (all other manufacturers) of the RR-interval, will be performed.[44] Contiguous 2.5 to 3 mm images will be acquired to quantify the presence and amount of coronary artery calcification.

c. Contrast-enhanced CT angiography—Image acquisition will conclude with a contrast-enhanced CT scan to evaluate the presence of coronary atherosclerotic plaque, significant coronary artery stenosis, and global and regional LV dysfunction. For this scan, on average 90 mL of contrast will be injected as a bolus at a rate of 5-6 mL/s to opacify the lumen of the coronary arteries, the aorta and the left ventricle. Appropriate timing of the contrast bolus will be ensured by either the determination of the transit time or the bolus trigger technique. Scanning will be performed continuously throughout the cardiac cycle. Using ECG gating, the tube current will be reduced during systole according to each manufacturer's specific protocol to minimize radiation exposure. Alternatively, in subjects where prospective triggering is appropriate, it may be performed, per the manufacturer's specific protocol to further reduce radiation exposure.

Step 3—Image Reconstruction: The following data sets will be reconstructed immediately after the scanning on a dedicated offline work station: 1) axial images from the non-contrast-enhanced scan for the quantification of CAC (pixel matrix: 512 x 512, field of view [FOV]: 25 cm); 2) two end-diastolic and one end-systolic data set (0.5-0.75 mm thick axial images, 50% overlap) from the contrast-enhanced CT scan for the

detection of coronary plaque and stenosis (pixel matrix: 512 x 512, FOV: 25 cm); 3) one multiphase reformatted dataset of 1.5 mm thick axial images at 10% increments (10 phases) for single source CT scanners or 5% increments (20 phases) for dual-source CT scanners throughout the cardiac cycle from the onset of the R-wave for the assessment of global and regional LV function in a cine mode and 4) a full field of view with 3 mm thick axial images, covering the portions of the thorax acquired during the cardiac CT scan, for the assessment of major incidental findings. All CT data sets will be transmitted to the CVIC Lab's picture archiving and communication system (PACS) via internet using a dedicated routing system (Code of Federal Regulatory compliant) and stored.

Image Evaluation

Reconstructed data sets will be evaluated for the presence of CAC, coronary atherosclerotic plaque and stenosis; and global and regional LV function by dedicated highly trained cardiac CT imagers using established criteria[22].

Step 1—Coronary Artery Calcification: All non-contrast enhanced CT scans will be assessed for the presence of CAC. If present, the amount of CAC will be *quantified* using a dedicated semiautomatic software and expressed as an Agatston Score (AS) as described elsewhere.[45]

Step 2—Assessment for Stenosis: Contrast-enhanced CT images will be *qualitatively* evaluated for the presence of coronary atherosclerotic plaque and significant coronary artery stenosis using axial data sets; thin slice (5 mm) reconstructions orthogonal and perpendicular to the vessel centerline, and short axis cross-sectional reconstructions. Assessment will include each of the major epicardial vessels (left main, left anterior descending, left circumflex, and right coronary artery) and their side branches.[46–48]

***Step 3—Global and Regional LV Function*:** Global and regional LV function will be assessed visually with the multiphase reformatted dataset in cine mode to correspond to those typically used in echocardiography, including LV horizontal long-axis (4-chamber view), vertical long-axis (2-chamber view), LV outflow tract long-axis (parasternal long axis), and short-axis view. Global LV function will be reported as normal or impaired (mild, moderate, or severe). Regional wall motion (RWM) of the myocardium will be assessed to be normal or abnormal (hypokinesia, akinesia, dyskinesia, aneurysm) in short-axis segments of the LV corresponding to the AHA/ACC/ASE 17-segment model. Hypokinesia will be defined as a segment with impaired thickening and motion, akinesia by absent thickening and motion, dyskinesia as a paradoxical outward motion of the segment during systole, and an aneurysm as a segment with wall thinning and diastolic deformation. The abnormality has to be present in at least two contiguous myocardial segments or in one segment visualized in two different views.

Step 4—Major Incidental Findings: The full field of view will be assessed by a CT reader for the presence of major cardiac and non-cardiac incidental findings such as aortic dissection, pericardial effusion, pulmonary embolism, pneumothorax, or mediastinal masses.

CT Reporting

Cardiac CT Findings

The Cardiac CT Report will be reported and included in the hospital's electronic medical record, which is accessible to all treating physicians and will be the basis for in-hospital patient management. The triage and management of the patient will be at the discretion of the ED physician.

Image Submissions

The protocol-required images must be in DICOM format and submitted to the Cardiovascular Imaging Core Laboratory (CVIC) via the internet using secure File Transfer Protocol (FTP), along with an Imaging Transmittal Worksheet. The submission procedure will be detailed in the CVIC site operations manual.

Appendix B: Adjudication of Events by Clinical Events Committee

Introduction

Because patient safety is one of the concerns in a trial assessing new technology, clinical events and serious adverse events will be independently adjudicated by the Clinical Events Committee, under the direction of Stephen Wiviott, MD. This committee will adjudicate events in all subjects who potentially could have a major adverse cardiovascular event (MACE), such as, death, unstable angina pectoris (UA), myocardial infarction (MI), or coronary revascularization that occur after symptom assessment at patient's initial emergency department (ED) presentation. There is a possibility that MACE will occur during index hospitalization. For example, a second episode of chest pain diagnosed as acute coronary syndrome (ACS) occurring after the chest pain the patient presented with has resolved and all diagnostic tests were negative or recurrence of symptoms with or without hospitalization and re-hospitalization with or without testing.

Definitions of Adverse Cardiovascular Events

Adverse cardiovascular events comprise cardiovascular death, MI, unstable angina pectoris (UAP), coronary revascularization and/or re-hospitalization that are distinct from the qualifying event (after patient's initial ED presentation).

Definitions of events are listed below:

Cardiovascular Death: Any sudden cardiac death, death due to acute myocardial infarction, death due to heart failure, death due to stroke, and death due to other cardiovascular causes. In addition, any death without a clear non-cardiovascular cause, or a death without known cause will be considered cardiovascular death.

MI: In Subjects with no recent revascularization in whom normal biomarkers were never elevated or have been documented to return to normal after a qualifying (or recent) MI who meet the following criteria:

1.) Typical cardiac biomarker rise and/or fall AND at least one of the following:
   a) Ischemic discomfort at rest lasing ≥10 minutes
   b) ECG changes indicative of ischemia (ST elevation ≥0.1 mV or ST depression ≥0.05 mV, or new T-wave inversions.

OR;

2.) Development of new, abnormal Q waves (≥30 msec in duration and ≥1 mm in depth) in >2 contiguous precordial leads or ≥2 adjacent limb leads; or increase R amplitude in V1-V3 consistent with posterior infarction.

OR;

3.) Pathologic findings of an acute MI

4) Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood

In subjects with percutaneous coronary intervention within 48 hours, an elevation of CK-MB >3x ULN distinct from a prior event will be considered to be a procedural MI.

In subjects with CABG within 48 hours, an elevation of CK-MB > 10x ULN distinct from a prior event will be considered to be a procedural MI.

UA: An event not meeting the definition of myocardial infarction and with the following characteristics. Chest pain or anginal equivalent at rest or in accelerating pattern AND at least one of the following objective signs:

a) New ST-segment changes

b) New TWI

c) Positive stress test with imaging showing ischemia

d) Positive stress test without imaging resulting in increased anginal medication

e) Cath ≥70% stenosis or thrombus

Urgent Coronary Revascularization: Ischemic discomfort or equivalent meeting the following criteria:

a) Lasting ≥10 minutes at rest, or repeated episodes at rest lasting ≥5 minutes, considered to be myocardial ischemia upon final diagnosis

AND;

b) Prompting coronary revascularization during an unscheduled visit to healthcare facility or during an unplanned (or prolonged) hospitalization for these symptoms.

Note: Attempted revascularization procedures, even if not successful will be counted. Potential ischemic events meeting the criteria for myocardial infarction will not be adjudicated as urgent coronary revascularization.

Re-hospitalization: Coronary ischemia requiring re-hospitalization is defined as an event not meeting the definitions of myocardial infarction or urgent coronary revascularization: ischemic discomfort or equivalent meeting the following criteria:

a) Lasting ≥10 minutes at rest, or repeated episodes at rest lasting ≥5 minutes, or an accelerating pattern of ischemic discomfort (episodes that

are more frequent, severe, longer in duration and precipitated by minimal exertion), considered to be myocardial ischemia upon final diagnosis

AND;

b) Prompting hospitalization (including overnight stay on an inpatient unit) within 48 hours of the most recent symptoms or prolonging hospitalization if occurring during existing hospitalization.

AND;

c) At least one of the following additional criteria for coronary artery disease and/or ischemia:

- New and/or dynamic ST-depression ≥0.05 mV, ST-elevation ≥0.1 mV, or symmetric T wave inversion ≥0.2 mV on a resting ECG.
- Definite evidence of ischemia on stress sechocardiography, myocardial scintigraphy (e.g., an area of clear reversible ischemia), or ECG-only stress test (e.g., significant dynamic ST shift, horizontal or downsloping).
- Angiographic evidence of epicardial coronary stenosis of ≥70% diameter reduction and/or evidence for intraluminal arterial thrombus.

Note: If subjects are admitted with suspected myocardial ischemia, and subsequent testing reveals non-cardiac or non-ischemic etiology, this will not be adjudicated as meeting this definition. Potential ischemic events meeting the criteria for myocardial infarction will not be adjudicated as ischemia requiring hospitalization.

Adjudication Process

Adverse cardiovascular events (both during index hospitalization and within 28 days) will be independently adjudicated by the Clinical Events Committee (CEC). Potential events will be identified by the sites during a follow-up phone interview at 48-72 hours and 28 days. The information collected during the call will be recorded on an "Assessment of MACE" Case Report Form, which will be submitted to the Data Coordinating Center (DCC). The DCC will request de-identified medical records and source documents, supporting the adjudication of the events., including but not limited to as discharge summary, cardiac consultation notes, ECG reports, cardiac catheterization reports, biomarker laboratory values, death certificates, autopsy reports etc. The DCC will provide copies of the medical record pertaining to the index hospitalization and the potential adverse event for adjudication to the CEC. Based on the medical record review and site reported information, the adjudicator will complete an "Assessment of MACE" Case Report Form, which in turn will be submitted to the DCC.

Adjudicators are independent board certified or board eligible cardiologists, who have received formal documented training based on a CEC Charter, and will perform a composite review of the medical records to ascertain the presence or absence of MACE as defined in the CEC charter. The adjudication is performed by the TIMI (Thrombolysis In Myocardial Infarction) Study

Group CEC, which provides adjudication services for cardiovascular trials performed worldwide. Cases will be adjudicated by two independent cardiologists with an experience in cardiovascular event adjudication. In case of disagreement the adjudicators will meet, discuss the case and attempt to come to consensus. If consensus cannot be reached, a third adjudicator will cast a tie breaking vote. This is a standard, accepted technique to assess the presence of clinical events in cardiovascular trials. [18, 55-58]

Discharge Diagnosis from Index Hospitalization

The CEC will adjudicate the accuracy of the discharge diagnosis during index hospitalization for the first eight patients for each site, followed by a random selection of 10% of the participants. Discharge diagnoses are: ACS as defined above and consistent with the ACC/AHA Guidelines[59–61], including MI and UA, chest pain of cardiac origin, and chest pain of non-cardiac origin with or without a clear differential diagnosis.

Clinical sites use different cut-off values and tests to determine MI diagnosis. The DCC will provide each site's biomarker cutoffs for each individual case. The CEC therefore will adjudicate events in a manner consistent application of site-specific criteria.

For each MI identified by the CEC, a Type of MI will be assigned using the following guidelines:

Type 1: Spontaneous myocardial infarction related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection

Type 2: Myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension

Type 3: Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood

Type 4a: Myocardial infarction associated with PCI

Type 4b: Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy

Type 5: Myocardial infarction associated with CABG

Appendix C: Data and Safety Monitoring Board

The DSMB is responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, and for monitoring the overall conduct of the study.

The DSMB is an independent group advisory to the Director, NHLBI, and is required to provide recommendations about starting, continuing, and stopping the study. In addition, the DSMB is asked to make recommendations, as appropriate, to the NHLBI about:

- Efficacy of the study intervention (DSMB only)
- Benefit/risk ratio of procedures and participant burden
- Selection, recruitment, and retention of participants
- Adherence to protocol requirements
- Completeness, quality, and analysis of measurements
- Amendments to the study protocol and consent forms
- Performance of individual centers and core labs
- Participant safety
- Notification of and referral for abnormal findings

Meetings are usually held approximately twice a year, with additional meetings or conference calls scheduled as needed.