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FOCUS-CCTA:

FOcused field of view CalciUm Scoring prior to Coronary CT Angiography

Table of Contents

MEMORANDUM FOR CHIEF, DEPARTMENT OF RESEARCH PROGRAMS, AT WALTER REED NATIONAL MILITARY MEDICAL CENTER (WRNMMC) AT BETHESDA, MD

SUBJECT: Application and Request for Approval of Clinical Investigation Study Proposal

STUDY SITE(s): (X) WRNMMC only

1. GENERAL INFORMATION

1.1. PROTOCOL TITLE: FOCUS-CCTA: FOcused field of view CalciUm Scoring prior to Coronary CT Angiography

1.2. PRINCIPAL INVESTIGATOR:

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RESPONSIBILITIES: Patient Enrollment, Data analysis and Manuscript preparation (Dates: from IRB approval to study completion and publication)

1.3. ASSOCIATE INVESTIGATORS:

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RESPONSIBILITIES: Data analysis (Dates: from IRB approval to study completion and publication)

Rank, Name, Corps: CPT David Reynolds, MD, MC USA
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Current Duty Station: Walter Reed National Military Medical Center
RESPONSIBILITIES: Enrollment, data entry, data analysis (Dates: from IRB approval to study completion and publication)

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RESPONSIBILITIES: Enrollment, data entry, data analysis (Dates: from IRB approval to study completion and publication)

1.7. MEDICAL MONITOR:
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2. ABSTRACT:

2.1 Purpose

Coronary computed tomography angiography (CCTA) is a frequently performed test for the diagnosis and/or exclusion of coronary artery disease (CAD) in appropriately selected patients[1]. The performance of non-contrast computed tomography for the detection and quantification of coronary calcification is typically performed prior to CCTA in an effort to identify significant calcification which may influence subsequent data acquisition during the CCTA. However, performance of calcium scoring adds significant radiation and most coronary calcification is proximal in its location, potentially visualized using a focused non-contrast scan.

The purpose of this study is to prospectively compare the usefulness of a modified non-contrast CT, using a significantly shorter scan length and lower radiation parameters, as compared to standard coronary artery calcium scanning for the detection of coronary calcification that may influence subsequent CCTA performance.

2.2 Research Design:

This is a prospective, randomized single center cohort study to evaluate the diagnostic and clinical impact of a modified versus standard calcium scoring in patients obtaining a coronary CT angiography (CCTA) for the evaluation of symptomatic coronary artery disease.

2.3 Methodology /Technical Approach:

INCLUSION CRITERIA

1) Consenting adult patients $\geq$ 50 years of age;
2) Suspected but without known prior history of CAD. Prior CAD is defined as a history of myocardial infarction, coronary revascularization or $\geq$ 50% coronary lumen stenosis on prior coronary angiography
3) Scheduled for non-emergent clinically indicated coronary CT angiography

EXCLUSION CRITERIA

1) Prior coronary bypass graft (CABG) surgery
2) Suspicion of acute coronary syndrome (MI or unstable angina)
3) Known complex congenital heart disease
4) Evidence of ongoing or active clinical instability, including chest pain (sudden onset); cardiogenic shock; unstable blood pressure with systolic blood pressure < 90 mmHg; and severe congestive heart failure (NYHA class III or IV); or acute pulmonary embolism
5) Atrial fibrillation
6) Abnormal renal function (GFR < 60 ml/min; Creatinine > 1.5 mg/dL)

7) Concomitant participation in another clinical trial in which patient is subject to investigation drug or device
8) Pregnancy or unknown pregnancy status
9) Allergy to iodinated contrast agent
10) Contraindications to nitroglycerin
11) Unwilling or unable to give consent
12) Inability to comply with study procedures
13) Prior coronary artery calcium score and/or coronary CT angiogram

DURATION OF STUDY ENROLLMENT: 12 months

SAMPLE SIZE (total enrollment): 175 subjects

3. OBJECTIVES AND SPECIFIC AIMS:

Prior to undergoing CCTA, non-contrast CT scanning of the entire heart is usually performed in adults over 50-years of age in order to assess for the presence and severity of coronary artery calcium. By providing a modified CT scan with a reduced length the same data can be obtained by the imager to ensure a high quality scan while decreasing the patient's overall radiation exposure. Our objectives and specific aims to validate our hypothesis include:

- To assess the impact on CCTA image quality using modified calcium score approach
- To determine the rate of changes in the coronary CT angiography acquisition parameters after evaluation of the modified versus standard calcium scoring scout series. Significant changes in CCTA acquisition include any of the following as compared to recommended CCTA parameters prior to scout CT performance: a change (increase or decrease) in tube current (mA) by 50, any change in tube potential (kV), change to/from retrospectively-gated CCTA, any change in padding (acquisition window), or changing to/from a high definition CT scan acquisition.
- To assess the difference in patient estimated effective radiation exposure (mSv) between the modified versus standard calcium scoring techniques.
- To assess the difference in patient estimated effective radiation exposure (mSv) of the entire CCTA study (plus calcium scoring) between groups.
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4. BACKGROUND AND SIGNIFICANCE:

4.1 Literature Review.

Cardiovascular disease is the leading cause of mortality and morbidity in the United States. The impact of coronary disease on our society has prompted increased emphasis on primary prevention. To identify the patients who would benefit the most from primary prevention, such as

the use of HMG-CoA reductase inhibitors, multiple risk factors have been identified that independently correlate with atherosclerotic disease. Of these risk factors, the coronary artery calcium (CAC) score has emerged as a non-invasive independent risk factor for atherosclerotic disease and a tool for the prediction of future cardiac events in asymptomatic patients.[2] The CAC score has also been identified as having the ability to restratify[3] and extend to multiple ethnic groups[4] the predicted risk obtained from the Framingham risk score.

Although the role of the CAC score in the asymptomatic population has been well established its role in a symptomatic patient with suspected coronary artery disease is less clear.

Role of Calcium Scoring Prior to CCTA in the Symptomatic Patient

The most commonly utilized role of the CAC score prior to CCTA is as a gatekeeper to angiography because the specificity and accuracy of the CCTA may vary depending on the amount and location of the coronary calcium[6]. The decrease in sensitivity and specificity is often thought to be due to blooming artifact which can lead to an overestimation in the degree of stenosis or can make the segments un-interpretable on contrast CT angiography. Of note, the data from the Coronary Artery Evaluation Using 64-Row Multidetector Computed Tomography Angiography (CORE-64) study showed that the accuracy and negative predictive value of CCTA to detect a coronary stenosis $\geq$ 50% in patients referred for ICA is reduced when the CAC score is ≥ 600[7]. In a meta-analysis by Abdulla, it suggests that careful pre-angiographic planning needs to occur in patients with CAC score ≥ 400[8] to ensure appropriate study quality and diagnostic accuracy. Furthermore, multiple studies have revealed that high levels of coronary artery calcification is also one of the most important factors associated with a non-diagnostic coronary CTA[9,10] leading an imager to decide to not proceed with angiography in cases of very high coronary calcification.

Based on the above information, non-contrast CT scanning of the entire heart is usually performed in adults over 50-years of age in order to assess for the presence and severity of coronary artery calcium. This is performed so to identify patients with high degrees of coronary calcium such that the imagers may modify the scan parameters of the subsequent coronary CTA scan in order to optimize image quality and diagnostic accuracy of CCTA. Specific variables that may be adjusted on the subsequent CCTA scan based on the absence or presence and severity of CAC include: tube current (mA), tube potential (kV), use of high-definition scanning, and type of ECG gating/triggering. Of note, the performance of non-contrast CT scan prior to CCTA is typically done using the well-established Agatston method. In this method, the entire heart is scanned using a relatively high tube potential of 120 kV. While this higher tube potential may not be needed to identify calcium, it is a prerequisite in order to calculate an Agatston coronary artery calcium score and is therefore the standard method to perform non-contrast scanning prior to CCTA in our lab and most labs worldwide. Given that the prognostic value of CCTA is superior to calcium scoring, many wonder if the type of non-contrast scan should be modified in order to reduce patient radiation

exposure.

Importantly, it has been demonstrated that the majority of coronary artery calcification occurs in the proximal to mid portions of the coronary arteries[13]. This important fact suggests that a more focused field of view during scout non-contrast CT imaging prior to CCTA may be effective as scanning the entire heart while limiting radiation exposure.

Radiation Exposure

The Society of Cardiovascular Computed Tomography (SCCT) guidelines on radiation dose and dose-optimization strategies in cardiovascular CT states that the imager should attempt to limit the radiation dose to the lowest reasonable level while acquiring as much information as possible in the diagnosis and characterization of a patient's coronary artery disease.

During a cardiac CT examination there are typically three phases: acquisition of a scout view for planning the scan length of the examination, obtaining a low dose non-contrast calcium score, and a contrast-enhanced CT coronary angiography for the evaluation of significant coronary artery stenoses. Typically the scan length of the calcium score is based off of the initial scout. The scan length is defined with the use of anatomic landmarks on an anterior-posterior projection image similar to a chest radiograph. For coronary imaging the scan should typically be started at the mid to lower level of the main pulmonary artery, although a location just below the carina is frequently used and should extend through the apex of the heart.

When performed prior to CCTA, calcium scoring can add anywhere from 1-3 mSv to the total radiation dose[4]. Considering that the mean patient effective radiation dose of a CCTA typically ranges from 2-8 mSv, the performance of a typical calcium score that covers the entire heart and proximal aorta adds proportionally considerable radiation to patients undergoing CCTA. This is of particular importance when the imager is implementing strategies for radiation dose reduction and the calcium score may even double the radiation delivered to the patient. During a CCTA the imaging cardiologist or radiologist may modify scan acquisition modes, x-ray tube potential, x-ray tube current, pitch, scan length and scan field of view dependent upon the method of scanning and the system used to reduce the radiation dose of the angiogram. During calcium scoring, image acquisition parameters are typically not dynamically manipulated but are performed in accordance with standard Agatston scoring parameters.[10] Given the additional radiation of the CAC score to the overall radiation dose of the CCTA there has been some uncertainty of whether CAC scoring should be performed in conjunction with CCTA. However, with this approach the imager would lose the potentially useful information regarding the amount and location of the coronary calcium that could impact decision-making in the acquisition parameters in patients that coronary calcium is likely. The imager may also lose the potentially

important information needed to abort a possibly non-diagnostic exam which would ultimately prevent the patient from receiving unnecessary radiation exposure.

4.2 Scientific Justification. See sections 4.1

4.3 Human Subjects Justification. The use of human subjects is necessary to meet desired endpoints outlined in section 3 to demonstrate the influence of the modified calcium scoring versus the standard calcium scoring for individuals undergoing CCTA.

5. PLAN:

5.1 Study Design

Prospective, randomized single-center cohort study.

5.2 Anticipated Requirements

a. Facilities: Walter Reed National Military Medical Center
   1. Cardiology Clinic
   2. Cardiovascular Health and Interventional Radiology, Angiography and Recovery [CVHIR]
   3. Radiology Department (CT Section)

b. Duration of enrollment: 12 months

c. Budget: no additional budget is needed.

5.3 Subject Population

a. One hundred seventy-five (175) male and female adult subjects (military health beneficiaries age greater than 50 years) who are clinically referred for CCTA will be eligible for participation.

b. The Walter Reed National Military Medical Center Cardiology Department and Radiology Departments perform multiple clinically appropriate and indicated coronary CTA studies weekly (approximately 8-12), which will allow for ease of subject recruitment. Although there are other open studies using CCTA in our department there is not a lot of overlap in their requirements and should not prohibit enrollment in our study. This study will enroll both men and women of all ethnic origins aged $\geq$ 50 years. All subjects will consent for themselves. All patients' participation in this research and subsequent contribution to our medical knowledge notwithstanding, no intent to benefit patients from enrollment is implied or offered. Pregnant women will be excluded from enrollment based on:
(1) Verbal admission of pregnant status; OR

(2) Positive urine pregnancy test performed within 7 days of CCTA in subjects not previously known to be pregnant.

5.4 Inclusion and Exclusion Criteria

INCLUSION CRITERIA

1) Consenting adult patients ≥ 50 years of age;
2) Suspected but without known prior history of CAD. Prior CAD is defined as a history of myocardial infarction, coronary revascularization or ≥ 50% coronary lumen stenosis on prior coronary angiography
3) Scheduled for non-emergent clinically indicated coronary CT angiography

EXCLUSION CRITERIA

1) Prior coronary bypass graft (CABG) surgery
2) Suspicion of acute coronary syndrome (MI or unstable angina)
3) Known complex congenital heart disease
4) Evidence of ongoing or active clinical instability, including chest pain (sudden onset); cardiogenic shock; unstable blood pressure with systolic blood pressure < 90 mmHg; and severe congestive heart failure (NYHA class III or IV); or acute pulmonary embolism
5) Atrial fibrillation
6) Abnormal renal function (GFR < 60 ml/min; Creatinine > 1.5 mg/dL)
7) Concomitant participation in another clinical trial in which patient is subject to investigation drug or device
8) Pregnancy or unknown pregnancy status
9) Allergy to iodinated contrast agent
10) Contraindications to nitroglycerin
11) Unwilling or unable to give consent
12) Inability to comply with study procedures
13) Prior coronary artery calcium score and/or coronary CT angiogram

5.5 Study Methodology/Procedures

5.5 Methods:

The FOCUS-CCTA study will be a prospective, randomized single center single cohort study to evaluate the diagnostic and clinical implications of modified scan length calcium scoring versus the standard scan length calcium scoring in CCTAs using a MDCT scanner. Significant diagnostic and clinical implications include the quality of the study in the modified versus standard scan length; changes in the cardiac CT after evaluation of the modified or standard calcium scoring (These changes include: a change in mA by 50, any change in kV, any changes

in padding and changing to high definition.); cancellation of the study and a comparison of the radiation received by each patient.

CCTA Study Design:

Patients who are scheduled for CT coronary angiography for evaluation of clinically suspected coronary artery disease who are fifty years old or older without known coronary artery disease and without a previous calcium score will be prospectively included in this study. The indications for CT coronary angiography will be used in accordance with the ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR Appropriate Use Criteria for Cardiac Computed Tomography. Exclusion criteria will include patients who are not able to obtain angiography to include: previous anaphylactoid reaction to iodinated contrast material and renal insufficiency (verified by a renal panel within 30 days of the procedure).

In accordance with standard operating procedures for CCTA (joint Cardiology-Radiology program), patients will arrive to the cardiovascular preparation area ("Prep and Recovery", Building 9A) and will receive a clinical assessment with vital signs by a physician and nursing staff. Patients without a contraindication to B-adrenergic blocking agents and/or calcium channel blocking agents (will be given a beta-blocker either by oral intake or intravenously prior to the exam to obtain a goal heart rate between 50-65 bpm). Once the patients are within this window they will be escorted to radiology, in accordance with standard CCTA policies. During the preparation time eligible patients will be consented by Ms. Bindeman and will be randomized at that time. The patient's chart will have an envelope with it that describes which investigational arm the patient will be in. The radiologist and cardiologist will view the card in the envelope after making their initial decision on the parameters for the CCTA.

CT Protocol

All CT examinations will be performed on standard multi-detector CT machines typically utilized for CCTA, in accordance with SCCT guidelines. Prior to any imaging, both the radiologist and cardiologist (non-study personnel) clinically performing the CCTA will fill out a form choosing their initial proposed CCTA acquisition parameters (type of gating, mA, kV, padding, use of high-definition scanning) based on the patient's age, sex, BMI and achieved pre-scan heart rate, as is typical of all CCTA examinations. Then antero-posterior and lateral topograms of the chest will be obtained to plan subsequent data acquisition, as required for all CCTA examinations. Based on randomization, either a modified or standard calcium scoring series will be performed: Subjects will be randomized in a 1:1 ratio to either modified or standard calcium scoring using a computer program based on random number generation. Assignments will be concealed in sequentially numbered opaque sealed envelopes (SNOSE). The randomization assignment and envelopes will be prepared by a person who is not involved

in the recruitment process or clinical conduct or interpretation of the non-contrast studies or CCTA.

In patients randomized to standard coronary artery calcium scoring, this scan will be performed in usual axial fashion obtained at 70% of the R-R interval using the following parameters: rotation time 0.35 sec; collimation of 64 x 0.625mm; detector coverage of 20.0 mm; axial thickness 2.5; tube voltage, 120 kV and tube current 250mA. The scan length, in accordance with current protocol, will be from 1 cm below the carina through the diaphragms.

In patients randomized to undergo the modified non-contrast CT scan to assess coronary calcification burden, this study will be performed by a radiologist and cardiologist as follows: axial acquisition obtained at 70% of the R-R interval using the following parameters: rotation time 0.35 sec; collimation of 64 x 0.625mm; detector coverage of 20.0 mm; axial thickness 2.5; tube voltage 80kV and tube current 250mA. The scan length will be from 1 cm below the carina to the level beneath the proximal coronary vessels defined as the greatest diameter of the apex of the right atrium. This location has been chosen based off of the experience of the senior cardiologist and radiologist that by choosing this location you will be able to obtain the proximal portion of all the vessels to include the right coronary artery which can be the most difficult to image.

Following completion of the non-contrast CT, the clinically assigned radiologist and cardiologist will determine, based on the information from the non-contrast CT, whether to modify their initial CCTA acquisition parameters or if it is appropriate to continue with CT coronary angiography portion of the exam.

As per standard protocol, prior to initiating the coronary CT angiography, a clinical assessment with vital signs will be performed by a physician and sublingual nitroglycerin spray will be given to all patients for vasodilatation. A timing bolus technique (using 10 cc of iodinated contrast) will be used to determine appropriate timing of the contrast for CCTA, in typical fashion. Following the performance of the timing bolus, CCTA will be performed in accordance with the clinical cardiologist and radiologist parameters, in standard fashion using the injection of iodinated contrast material. The injection protocol will be in accordance with current CCTA lab protocols. Specifically, this will be performed by injecting a bolus of approximately 60 mL of iodinated contrast material (Isovue 370 or Visapaque 320 based on physicians discretion), followed by approximately 50 ml of a 50/50 contrast/saline mixture, then approximately 30 mL of saline solution injected into an antecubital vein via an 18-20 gauge intravenous catheter with an injection rate of 5mL/s by using a power injector.

All CCTA scans will be interpreted using 50% ASIR iterative reconstruction, as per standard CCTA lab protocol.

At the conclusion of the CCTA, the patient, in accordance with standard lab procedures, will be clinically assessed and then transported to the cardiology preparation and recovery area (or inpatient ward, as appropriate. Further care will be in accordance with CCTA standard policies.

CCTA Interpretation and Review:

Non-contrast Computed Tomography (calcium scanning)

Calcium scores performed will be scored in typical fashion using the Agatston scoring method[11]. The total number of lesions, location (coronary artery), and segment (18-segment model) will be recorded.

Scans performed using the modified calcium scan parameters will be assessed in the following manner:

1. No evidence of coronary calcification
2. Number of segments with visible calcification
3. Severity of calcification: small (<5 mm diameter), moderate (5-10 mm), large (>10 mm or circumferential)
4. Location (segment involved)

In all studies, mean image noise will be assessed as the standard deviation of HU within a 1 cm radius region of interest placed in the middle of the proximal ascending aorta, away from aortic valve and aortic tissue. All calcium scores will be interpreted in a random fashion by two trained readers (TCV and NG). Discrepancies will be resolved by consensus.

CCTA

CCTA studies for both the modified and standard calcium scoring reconstructions will be clinically interpreted by the assigned cardiologist and radiologist, in accordance with standard practice. These results will be provided to the patient and referring provider and reported in the health record in standard fashion. The clinical interpretation team will provide an overall assessment of image quality in the following manner: 1-4 (same scale).

In addition to clinical interpretation, all CCTA studies will be read by two experienced CCTA providers (TCV and NG) while blinded to group allocation. All data sets will be assigned a study ID and will be randomly assigned for interpretation. CCTA interpretations will be performed using all available phases. Coronary arterial segements will be graded for quality (see below), stenosis severity (none; <25%, 25-49%, 50-69% and greater than or equal to 70% or 100%), plaque presence, plaque type (non-calcified, partially calcified, mixed). Differences will be adjudicated by consensus. Interpretation of CCTAs will allow for use of any and/or all image reconstruction methods, including axial slices, multiplanar reformats, and maximum intensity

projections. CCTA image quality will be assessed on a per-segment basis using the 18-segment SCCT model . Image quality will be assessed on a per-segment basis using the following 4-point scale:

Score 1: Non-diagnostic: Impaired image quality that precluded appropriate evaluation of the coronary arteries due to severe motion artifacts, extensive coronary calcifications, severe image noise, or insufficient contrast.

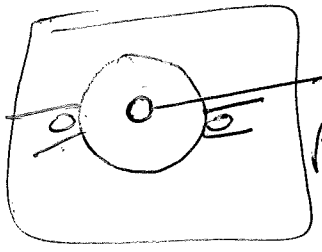
Score 2: Adequate: Reduced image quality because of artifacts due to motion, image noise or low contrast attenuation, but sufficient to rule out significant stenosis.

Score 3: Good: Presence of artifacts caused by motion, image noise, coronary calcifications or low contrast, but fully preserved ability to assess the presence of luminal stenosis as well as the presence of calcified and non-calcified coronary atherosclerotic plaque.

Score 4: Excellent: Complete absence of motion artifacts, strong attenuation of vessel lumen and clear delineation of vessel walls, with the ability to assess luminal stenosis as well as plaque characteristics.

The overall patient study quality will be determined by the mean of these scores after reaching consensus. In addition, CCTA signal (mean CT number, Hounsfield unit [HU]), noise (standard deviation in HU) and contrast/noise

The two readers will measure the signal and noise in the aortic root and each of the proximal coronary arteries with the mean of the readers used for comparisons. The contrast to noise will also be evaluated (difference of the mean arterial/aorta signal divided by the mean noise). √ this



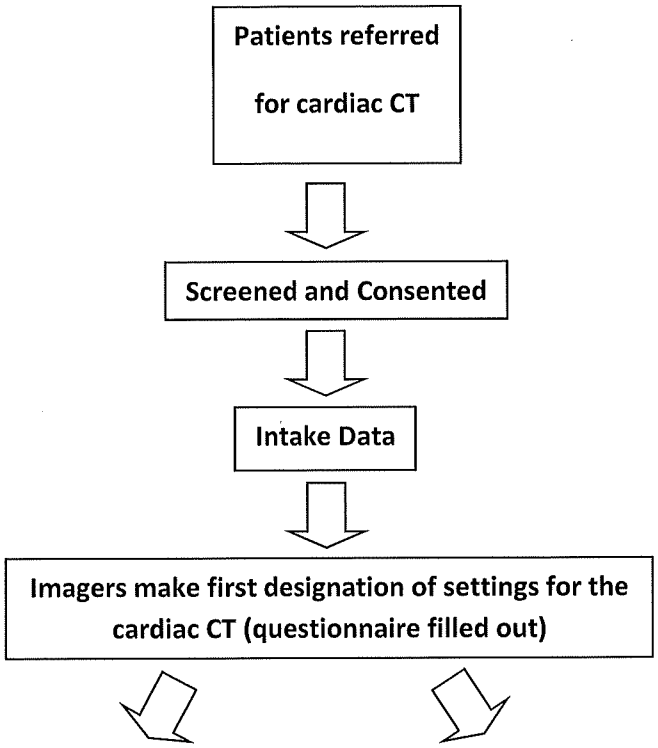
1cm ROI
Prox Asc. Aorta
@ level Coronaries
& ostium of LMCA & RCA

RCA = SIGNAL
vm NOISE
SNR

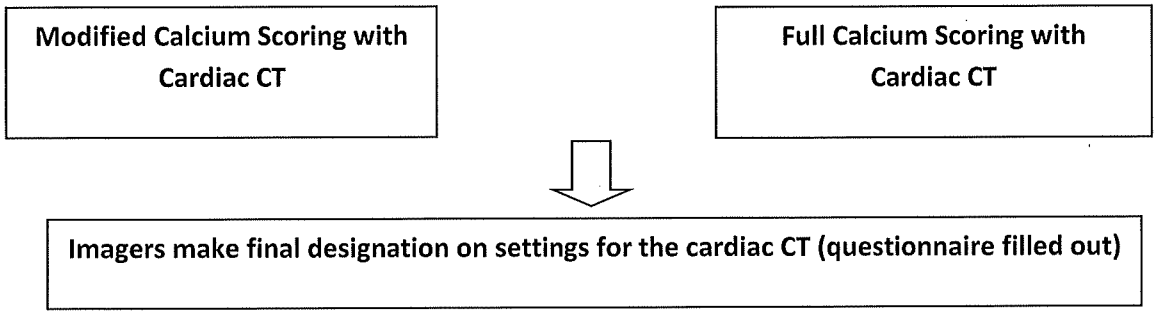
mean HU = SIGNAL
Stnd dev = Noise

CNR (study)

Flow sheet

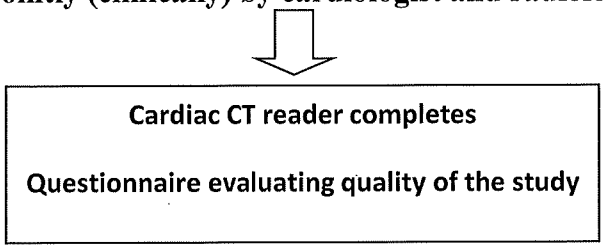


Patients receive calcium score



Coronary CTA is performed

Coronary CTA is read jointly (clinically) by cardiologist and radiologist



5.5.1 Describe when, where and how the study subjects will be identified and recruited.

Patients seen in Cardiology clinic who are deemed by their referring provider(s) as potential candidates for the FOCUS-CCTA trial will be referred to Ms. Bindeman (Research Nurse, Associate Investigator) to determine their eligibility, there will be no screening process prior to identification by their primary cardiologist to identify potential candidates. The patient can choose to meet with Ms. Bindeman in person or be contacted via a phone call to determine eligibility and enrollment based on inclusion/exclusion criteria. If the patient is not eligible for enrollment he/she will be thanked for his/her interest and willingness to participate and will be directed back to the referring provider for continued care. If the patient is deemed eligible he/she will be requested to obtain the appropriate labs if not already documented, complete informed consent and HIPAA Authorization for enrollment and a de-identified random subject number will be generated.

5.5.2 Consent Process

a. If eligible, the patient will fill out the 'Informed Consent Form and HIPAA authorization'. To prevent coercion the patient will be educated that enrollment is voluntary and his/her decision to participate will not impact our commitment to provide current standard of care. The patient must sign for himself/herself, no authorized legal representatives will be permitted to sign for the patient. The consent will take place in a clinic room in the cardiology clinic or in the prep and recovery area in the patient's personal bay to ensure privacy.

b. Potential subjects will have as much time as needed to review the consent, ask the study Principal Investigator, study doctor, and/or site study coordinator questions about the consent and study, and will be reminded that they can at any time, if they are uncomfortable about participation, call the site study coordinator and/or the study PI to ask questions or withdraw.

c. The investigators will request the subject voice an understanding of the consent form prior to signature and will prompt the subject for any questions prior to enrollment. A copy of the consent/HIPAA form with contact information for any questions will be provided to the patient at his/her request and the original copy will be kept in a secured location in the cardiology clinic to protect the patient's privacy.

5.5.3 Compensation for participation

N/A. No compensation will be given to patients for being in this study.

5.5.4 Research Interventions

No additional lab draws or nursing requirements are needed beyond current standard of care for the purposes of this research.

5.5.5 Data Collection

a. Method of Collection from Study Participants.

Data will be collected on data collection sheets prior to the patient's arrival, during the procedure and after the study has been performed.

Initial assessment will be collected according to the 'Patient Information' and 'CT Acquisition' Data Sheets to include the following information:

Patient Information Data Sheet:

- Age
- Height/Weight
- Gender
- Ethnicity
- Cardiac risk factors
- Symptom status
- Reason for referral for CT coronary angiography
- Lab values (BUN, Cr, Total Cholesterol, LDL-C, HDL-C)
- Medications
- Prior stress testing
- Adverse Clinical Events
- Protocol Violations

X Name

'CT Acquisition Data Sheet':

- Date of scan
- Coronary calcium score
- CT acquisition premedication status
- Contrast (type, iodine concentration, volume)
- Type of scan (data acquisition): prospective ECG-triggered or retrospectively gated(pre and post calcium scoring)
- Padding (pre and post calcium scoring)
- Tube current (pre and post calcium scoring)
- Tube voltage (pre and post calcium scoring)High definition (Y/N)- please mark whether this was decided before or after calcium scoring
- Heart rate (pre/post scan)
- Dose length product
- Estimated mSv
- Adverse Events
- Protocol Violations

This information will be uploaded and encoded per patient by a unique, random identifier according

consent form to stay + source documents until study closes with CRF and redact PII

to procedures outlined in the study.

b. Source and Type of Data Collected <u>from Existing Data Sources.</u> Answer the questions below after considering the minimum necessary data required for the research study.

i. Have you received a data consultation with a data expert to determine the data elements to be extracted or the data system to access? (Consulting with a data expert often saves time later in the compliance process because the data expert can advise on the data available in the numerous MHS data systems, the quality of that data and the methods for encrypting and collapsing data. You may contact a data expert at the following email address: TMADataDetermination@tma.osd.mil._____)

☐ Yes, then complete the questions in this subparagraph b according to the information received from the data consult

☒ No, then complete the questions in this subparagraph b according to the best of your knowledge (**NOTE:** It is highly recommended to get a data consult.)

ii. Indicate whether you will receive a data extract from the MHS or will access a data system to create a data set. A data extract is when the MHS or a contractor provides the data set directly to the researcher. When receiving a data set through data extract, the researcher may indicate whether the data elements should be provided as is, encrypted or collapsed. In contrast to a data extract, access to a data system means that the researcher may access a data system and create a data set for the research study.

☐ Data Extract ☒ Access

iii. Do you intend to use only a de-identified data set in your research study?

A de-identified data set is a data set that does not include any of the identifiers listed in the table in 5.5.5 (b)(vi). In addition, the researcher does not have actual

knowledge of another way the data can be used alone or in combination with other known information to identify an individual. De-identified data is also data that a person, with appropriate knowledge of and experience with generally accepted statistical and scientific principles and methods for rendering information not individually identifiable, determines is not individually identifiable in accordance with the conditions outlined in 45 CFR 164.514 (b)(1).

☒ Yes ☐ No

iv. Will you need MHS data with health information?

Data with health information means any information that is created or received by the MHS that relates to the past, present or future physical or mental health or condition of an individual, the provision of health care to an individual or the past, present or future payment for the provision of health care to an individual. Examples of MHS data with health information includes data maintained on AHLTA, CHCS and ESSENTRIS.

☒ Yes ☐ No

v. Do you intend to access a data base to obtain personally identifiable information that is not health information (PII)?

☐ Yes, will access data base for (PII)

☒ No, will not access data base for PII

vi. Include the following table in your protocol and put an "x" in the MHS column next to the categories of data that you are requesting from the MHS. If you are planning to receive a data extract of MHS data that includes a data element that will be de-

identified by the MHS, then you do not need to put an "X" in the column corresponding to the category of data for that data element.

	Study Participant	MHS	Other
1. Names	X		
2. Postal address with only town, city, State and zip code			
3. All geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly available data from the Bureau of Census: 1) the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and2) the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.			
4. All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older			
5. Telephone numbers			
6. Fax numbers			
7. Electronic mail addresses			
8. Social security numbers (In accordance with the DoD Social Security Number Reduction Plan, please justify the reason for collecting the social security number of study participants in the space after xi.)	X		
9. Medical record numbers			
10. Health plan beneficiary numbers			
11. Account numbers			
12. Certificate/license numbers			
13. Vehicle identifiers and serial numbers, including license plate numbers			
14. Device identifiers and serial numbers			

15. Web Universal Resource Locators (URLS)			
16. Internet Protocol (IP) address numbers			
17. Biometric identifiers, including finger and voice prints			
18. Full face photographic images and any comparable images			
19. Any other unique identifying number, characteristic, or code (DEERs ID, EDIPN, Rank)			

vii. If you are requesting access to an MHS data system, put an "x" in the Request from MHS column next to the MHS system(s) from which you are requesting data. If you do not know what system contains the elements you intend to request, please refer to the *Guide for DoD Researchers on Using MHS Data* or seek guidance from a data expert.

PHI Systems

MHS Data Systems	Request from MHS
AHLTA	X
CDM (from the MDR)	
CHCS	
ESSENTRIS	X
PDTS	
TRAC2ES	
M2	
MDR	
PDHRA	
PDHA	
TMDS	
PEPR	
JTTR	

PII Systems Only

MHS Data Systems	Request from MHS

DMDC	
MHS Learn	
DMHRSi	

De-Identified Data System

MHS Data Systems	Request from MHS
EAS	

Other Systems

List Other system(s):

viii. Do you intend to merge or otherwise associate requested data with data from any other sources outside of MHS, including other DoD sources that are not part of the MHS?

☐ Yes, will merge data ☒ No, will not merge data

ix. Using the tables in 5.5.5 (b) (vi), put an "x" in the Other column next to the categories of data or data elements that include the data elements you intend to merge.

x. Is there any possibility that the data will become identifiable because of triangulation, a small cell size, or any unique data element(s)?

Triangulation means using different data elements that are not themselves identifiable but that in combination can be used to determine the identity of an individual. For example, triangulation would be using rank and race together to determine the identity of an individual with a particular health condition.

Small cell size means that the categories contain a small number of eligible individuals that satisfy the category description. Guidance for acceptable cell size is available from the Centers for Medicare and Medicaid Services. For example, the rank category of five star generals with a particular diagnosis may be less than 30 so the data category may need to include lower ranks too.

A unique data element includes any unique features that are not explicitly enumerated in the categories of data in Table vi above, but that could be used to identify an individual. Examples of unique data elements include 1) a unique number, such as a medical record number or EDIPN; 2) a unique code, such as a diagnosis code or a bar code on electronic health record; and 3) any unique characteristic, such as a high rank like general or admiral or a unique race or gender with another unique characteristic.

☐ Yes, there is a reasonable possibility the data will become identifiable.

☒ No, there is no reasonable possibility the data will become identifiable.

xi. Please justify the reason for collecting the social security number of study participants.

This data is obtained with all of our clinically indicated CCTAs to ensure that the correct study is performed on the correct patient. The social security number will not be included in the de-identified data associated with the patient.

5.5.6 Collection of Human Biological Specimens

N/A

5.5.7 Banking of Human Biological Specimens

N/A

5.5.8 Study Time Line

- Study start-up: 1 October 2014
- Enrollment: For 12 months
- Interpretation of coronary CTAs: Within a month after all CCTAs have been enrolled and

performed

5.6 Investigational Drugs / Investigational Devices

N/A

5.6.1 Approval Status of Study Drugs

N/A

5.6.2 Approval Status of Study Devices

N/A

5.7 Statistical Considerations

The statistical evaluation will be performed as seen in the Data Analysis table below in 5.7.1. Of note, all outcomes compare the full and reduced scan groups.

5.7.1 Data Analysis Table

Aim 1- ***To assess the impact on CCTA image quality using modified calcium score approach.***	- Image quality (4 point scale) - Signal/noise ratio	- Treatment group - Treatment group	- Two sample t-test or Mann-Whitney (dependent upon the distribution of the data). - Two sample t-test
Aim 2- ***To determine the rate of changes in the coronary CT angiography acquisition parameters of the modified versus standard calcium scoring***	- Change in (increase or decrease) in tube current (mA) by 50 - Any change in tube potential (kV) - Change to/from retrospectively-gated CCTA - Any change in padding (acquisition window) - Changing to/from a high definition CT acquisition	- Treatment group - Treatment group - Treatment group - Treatment group - Treatment group	- Fisher's exact test

	All answered as yes/no		
Aim 3- ***To assess the difference in patient estimated effective radiation exposure (mSv) between the modified versus standard calcium scoring techniques.***	- Average of radiation exposure (mSv)	- Treatment group	- Two sample t-test
Aim 4- ***To assess the difference in patient estimated effective radiation exposure (mSv) of the entire CCTA study (plus calcium scoring) between groups.***	- Average of radiation exposure (mSv)	- Treatment group	- Two sample t-test

5.7.2 Sample Size Estimation

The proposed sample size is 158 based on sample size calculations for aim 1, as described below.

Power and sample size for aim 1 is based on a standard deviation of radiation exposure of 3 to 3.5 mSv, based on clinical experience, and an anticipated 40% reduction in exposure from 4 to 2.4 mSv. A sample size of 154 (77 per group) will have 80% power to detect a difference in radiation exposure of 1.6 mSv if the standard deviation is 3.5, based on a t test for independent samples with a 5%, two-sided significance level.

Examining power analyses for a noninferiority studies, assuming that the full and reduced methods will produce similar outcomes for image quality and any change in CCTA parameters:

--For the comparison of image quality (aim 1), it is assumed that the image quality for the full method will be 3.2 (standard deviation = 1.1). This study will have power of 80% to show that the mean for the reduced method is at least as high as the mean for the full method. This assumes that the mean image quality scores for the full and reduced populations are 3.20 and 3.15 respectively, with a common within-group standard deviation of 1.10, that a difference of 0.49 points or less is unimportant, that the sample size in the two groups will be 79 and 79, and that

alpha (1 tailed) is set at .05. To accrue complete data 158 subjects, a total of sample size of up to 175 will be recruited to account for a 10% dropout rate for technical difficulties.

--This study will have 81% power to show that the event rate (event rate = any change in CCTA parameters) for the reduced method is at least as low as the event rate for the full method. This assumes that the event rates for the full and reduced method populations are precisely equal (at 50.0%), that a difference of 20% points or less is unimportant, that the sample size in the two groups will be 79 and 79, and that alpha (1 tailed) is set at .05.

While a 20% difference is relatively large, to detect a smaller difference between groups (i.e. difference of 10-15%) using the same assumptions, would require hundreds of subjects.

5.7.3 Data Analysis Plan

1. A patient flow diagram as per CONSORT guidelines will be provided to present the number of subjects recruited, screened, refusals or subjects excluded (with reasons), randomized, lost to follow up, etc. Beginning and ending months of recruitment will be described.

2. A table of baseline demographic and clinical characteristics will be presented for the full and reduced scan groups to include means with standard deviations for continuous normally distributed variables, medians with interquartile ranges for ordinal data and counts with percentages for categorical data. Groups may be compared using two sample t-tests, Wilcoxon rank sum tests or Fisher's exact test as appropriate.

3. Interrater reliability for quality scores will be examined using the Kappa statistic.

4. Univariate comparison of the primary and secondary endpoints are described above in the Data Analysis table.

5. Multivariate analysis of the quality score will include ordinal regression, with the concensus quality score (on a scale from 1 to 4) as the dependent variable and the independent variables to include demographic and clinical factors known to affect CCTA quality, such as BMI, breath-holding, resting heart rate, use of nitroglycerin, etc.

5.8. Endpoints

Primary

The measurement of quality in comparison of the modified versus non-modified CCTA using a qualitative (four point scale and measure above) and quanitative (CCTA signal, noise, contrast to noise ratio) score.

Secondary

1. Any changes in the cardiac CT after evaluation of the modified or standard calcium scoring. These changes include: a change in mA by 50, any change in kV, any changes in padding and changing to high definition
2. The measurement of radiation exposure as DLP/milli-sieverts in comparison of the modified versus standard calcium scoring.
3. The measurement of radiation exposure difference measured as DLP/milli-sieverts of the entire CCTA study on the modified versus standard calcium scoring.
4. Whether the imager cancels the study based off of the modified or standard calcium scoring.

6. HUMAN SUBJECT CONSIDERATIONS

6.1 Anticipated Benefits

This study does not offer direct benefit to participants but is likely to yield important information about the optimal approach to diagnose and manage low-intermediate risk patients presenting with possible coronary artery disease.

6.2 Risks and Discomforts

The risks are expected to be the same as if patients underwent the procedure while not a part of a research study. The only investigational component of this trial involves the performance of a modified pre-CCTA non-contrast calcium scan in lieu of a standard coronary calcium study. The performance of the modified calcium scan may lead to diminished accuracy of CCTA and this possibility is being investigated by this study. If the quality of the study is to the degree that the clinic question cannot be answered this study can be associated with additional tests which could include: a myocardial perfusion scan, a stress echocardiogram or a repeat CCTA. An additional CCTA or a myocardial perfusion scan could increase a patient's radiation exposure but overall radiation exposure is expected to be lower. The possibility of additional studies are also possible in the standard CCTA protocol. Otherwise the risk and discomforts are those intrinsic to the clinically indicated CCTA.

The possible risks and discomforts in patients undergoing a clinically indicated CCTA include:

Radiation

During this research protocol patients will be exposed to radiation from a scheduled calcium and coronary CT scan. The total exposure resulting from these imaging studies is calculated to be approximately 2-8 mSv. This is more than they would receive from one year of natural exposure in the Washington D.C, Maryland, Virginia area which is approximately 1.6mSv. Cumulative

exposure from radiation may increase their risk for developing certain types of cancer in the future.

The primary investigator for the research protocol has determine and verified that all of the imaging prescribed for this study would typically be performed as part of the standard medical care required to adequately monitor your current illness in accordance with the ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR Appropriate Use Criteria for Cardiac Computed Tomography and is considered standard of care. Non-radiation producing risk stratification alternative include: exercise stress testing and echo dobutamine and exercise stress testing but these tests were not deemed appropriate by the prescribing physician based off of their clinical assessment.

Pregnant women will not undergo this study due to the risk of harm to the unborn child from the radiation used during this study. A urine or serum pregnancy test will be obtained within a week of the study for child-bearing women. Patients will also be encouraged to inform the physician, nurse or CT technician if there is any possibility of pregnancy.

Intravenous Contrast

Patients will receive intravenous iodine-based contrast for the coronary CT angiography. Most patients tolerate intravenous contrast well but may experience nausea, vomiting, headache, pruritis, flushing, urticaria, wheezing, changes in blood pressure, dyspnea, contrast induced nephropathy, angioedema and anaphylaxis. Patient with a history of severe reaction to contrast (anaphylaxis) have been excluded from this study. Patient with pruritis and urticaria in the past will be treated with prednisone and benadryl(prednisone 50mg given thirteen hours, seven hours and one hour prior to the CT with a concomitant 25-50mg dose of Benadryl given one hour prior to the CT) to prevent a reaction.. These patients will be monitored in the CVIR prep and recovery and will have an escort provided by the patient to take them home. Moreover, all patients will have a serum evaluation of their urea nitrogen and creatinine within thirty (30) days of the cardiac CT to decrease their likelihood of contrast induce nephropathy.

IVs are routinely placed by the nurses and technician and are usually well tolerated by the patient but risks include: induration, thrombophlebitis, pain, discomfort, bruising and infiltration of saline or contrast.

Medications

Patients will be given an AV nodal blocking agent to achieve their target heart rate. Typically these medications are well tolerated but are not without risk. These risks include: hypotension, bradycardia, dyspnea, wheezing, fatigue, diarrhea, GI disturbances and worsening of certain neurologic conditions. Patients will be evaluated by a board certified physician prior to

prescribing these medications and they will be monitored prior to and after the procedure by nursing staff in the CVIR prep and recovery location with vital signs.

Patient will also receive Nitrolingual PumpSpray (nitroglycerin lingual spray) to cause vasodilatation to increase blood flow through the arteries to allow for better imaging of the coronary vessels. This medication is typically well tolerated but is not without risk to include: hypotension, headache, dizziness, parasthesia, dyspnea, pharyngitis, rhinitis, peripheral edema, asthenia and abdominal pain. Patients will be evaluated by the cardiologist with vital signs prior to administration of this medication by the nurse and will be monitored after the procedure by nursing staff in the CVIR prep and recovery location with vital signs.

Diagnosis of Disease

Although the calcium scoring and coronary CT angiography will focus on the heart other structure in the chest will be visualized and evaluated with this study. These findings include: pulmonary nodules, hepatic cysts, lung cancer, pneumonia, atelectasis, bony structure abnormalities. Diagnosis of these findings may incur more imaging, follow-up, and invasive testing for the patient. Furthermore, they may also bring emotional and psychological distress to the patient. All non-cardiac findings will be evaluated by a credential radiologist and clinical information will be provided to the patients' primary care manager to ensure appropriate clinical disposition of this findings.

During this study patient's will also receive a diagnosis of their degree of coronary artery disease which may incur more imaging, follow-up and invasive testing for the patient. These finding may also bring emotional and psychological distress to the patient. All cardiac findings will be evaluated by a cardiologist and will be disposition appropriately based off of the clinical information available. There is also an extremely low risk of false diagnosis as with all studies and test but is unlikely due to the high sensitivity and specificity of coronary CT angiography (sensitivity of 96%, specificity of 86%, positive likelihood ratio of 6.38 and negative likelihood ratio of 0.06).

Phlebotomy

Having blood drawn may cause some pain. A bruise may form where the needle enters the vein. Drawing blood may cause some people to faint.

There may also be side effects, other than listed above that we cannot predict, some of which may be life-threatening. Other drugs will be given to make side effects that occur less serious and less uncomfortable. In some cases side effects can be serious, long lasting or permanent.

Should an adverse reaction requiring further treatment or an unforeseen complication arise, appropriate medical care and/or consultation will be provided.

6.3 Actions to Minimize Risks

a. Safety Monitoring Plan

Safety of participants is of primary concern to study investigators, and every effort to avoid adverse events (AE) will be made. An AE will be defined as any unfavorable and unintended sign, symptom, or disease temporally associated with the study procedures, whether or not considered related to the procedure. Only symptoms/signs that begin, increase in frequency or worsen in severity after the procedure start will be considered as AEs. Any asymptomatic change from baseline such as results from diagnostic procedures (renal function or vital signs that is clinically significant (e.g., requires diagnostic or therapeutic intervention beyond confirmation alone) will be considered an adverse event.

CCTAs performed for this study are clinically indicated as designated by their primary cardiologist, and while risk is minimal for CCTA performance, all potential safety efforts will be employed. CCTA examination will be prescribed, performed and under the direct supervision of a study physician. Adverse effects of any CCTA exam (not specific to the choice of tube voltage) may include contrast reaction, impairment of renal function (by contrast dye) and exposure to small amounts of ionizing radiation. Patients will be screened for a history of contrast reaction. If a patient develops a contrast reaction, a fully equipped crash cart and ACLS-trained nurses will be present to administer appropriate care. Impairment of renal function will be avoided by the use of an iso-osmolar contrast agent as well as preferred selection for performance of CCTA. CCTAs will be performed by prospective ECG triggering as a first-line mode, given its merits for lowering radiation dose. Estimated radiation dose for prospectively ECG triggered scans is between 2-8 mSV.

Study personnel will remain vigilant for the occurrence of AEs, particularly those that may be life threatening. Personnel who are trained in the acute management of contrast anaphylaxis and other emergencies and who have access to appropriate clinical supplies will be immediately available while the subject is confined to the CT suite. All study individuals will be closely observed and questioned for any kind of AE at the start and throughout the performance of any CCTA study procedure with non-leading questioning (e.g., "How do you feel?"). The subjects will be instructed to immediately report any symptoms and signs to the study staff (i.e., between formal observations).

All AEs will be evaluated using acceptable diagnoses, if possible. The intensity of all AEs will be graded as mild, moderate, or severe using the following definitions:

- Mild: Tolerable.
- Moderate: Interferes with normal activity.

- Severe: Incapacitating (causes inability to perform usual activity/work).

Study investigators will be instructed to closely monitor each subject who experiences an AE (whether directly ascribed to the cardiac CT procedure or not). Further, study investigators will be vigilant for unexpected AEs, which will be defined as:

- An AE that has not been previously reported for the investigational product (VCT scanner), any procedure medications, or any concurrent medications.
- An AE that is documented in the device or product labeling but is occurring with unexpected severity or frequency.

If an AE has already been reported it will not be necessary to report each individual sign and symptom of that AE as a separate AE. For example, if myocardial infarction is reported as an AE, there will be no need to report elevated creatinine phosphokinase and abnormal ECG, or other related signs, symptoms, or laboratory values as separate AEs. However, if both occur in isolation and myocardial infarction was not diagnosed, then each event would be reported as an AE.

Serious adverse events will also be described, and will be defined as any AE that:

- Result in death.
- Is immediately life threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is another important medical event.*

** Other important medical events are those that may not have resulted in death, been life threatening, or required hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical intervention to prevent one of the outcomes listed above.*

Unexpected AEs and SAEs will be recorded if they occurred as follows: After a subject starts his/her cardiac CT procedure and throughout the subject's post administration period, whether or not considered related to the procedure; and after the subject's post-administration, and for which a causal relationship to the procedure cannot be ruled out. The research monitor will also look for any difference in AE rates between the two arms to ensure no undue harm has occurred in the research or control arm. A summary of AEs and SAEs will be immediately forwarded the

Independent Ethics Committee/Institutional Review Board (IEC/IRB) and local health authorities, according to local regulations.

b. Safety Analysis Plan

The medical monitor will be responsible for approving the protocol prior to study initiation and for reviewing any adverse events during the study period. Should any adverse events occur, the medical monitor will provide a summary of contributing circumstances to the investigators and the IRB, with recommendations for continuing enrollment (with or without protocol modifications), or for the termination of the study, if needed.

c. Confidentiality Protection

Case report forms and study documents will be stored in a locked cabinet in a secure, locked room (Cardiology Service). When a patient enters the study, they will be assigned a unique patient identification number that is not any part of their social security number. The study identification number will be assigned consecutively as the patient is enrolled into the study. This study identification number will be attached to the patient's data file. The link between the subject number and subject identifying information (master code) will be kept in a locked file in the principal investigator's office in the Walter Reed Cardiology Clinic. The research team in the Cardiology Service will keep the research data for three years from the date the study is closed, and consent form and HIPAA authorizations will be retained for 6 years after the end of the study. At that time all the information will be destroyed. The master code will be destroyed as soon as all data collection is completed.

d. Certificate of Confidentiality

N/A

6.4 Reporting Adverse Events and Unanticipated Problems

Expected adverse events which are not serious are reported on the Continuing Review (CR) Progress Report CR is generally performed on a 12-month cycle. More frequent Progress Reports may be required at the discretion of the IRB.

For multi-center studies, a summary of adverse events study-wide or the report of the Data Safety Monitoring Board (DSMB) should be included with the CR.

Serious Adverse Events: The PI, within 24 hours, must report all related or possibly-related AND serious adverse events (SAE) occurring in subjects enrolled at WRNMMC . This is accomplished by submitting an adverse event report to the IRB via IRBNet. For protocols involving investigational drugs or devices, the investigator must also report a serious adverse event to the sponsor of the IND or IDE immediately (within 24 hours). Serious adverse events must be reported even if the PI believes that the adverse events are unrelated to the protocol.

Unexpected (but not serious) adverse events occurring in subjects enrolled at WRNMMC which, in the opinion of the PI, are possibly related to participation AND places subjects or others at a greater risk of harm that was previously known or recognized in the protocol must be reported by the PI within 24 hours of discovery by email or phone to the IRB and the Research Monitor. A follow-up written report within 5 business days to the IRB and the Research Monitor through IRBNet is required.

Unanticipated problems involving risks to subjects or others (UPIRTSOs) must be reported to the IRB and Research Monitor via email or telephone within 24 hours of discovery and a written follow up report within 5 business days.

When a deviation occurs, the investigator shall report the occurrence to the IRB. The investigator is required to make the determination whether the deviation meets the criteria for an unanticipated problem involving risks to subjects or others. The IRB Chair or IRB staff member shall also make the determination if the protocol deviation meets the definition of an unanticipated problem involving risks to participants or others. If the IRB Chair or IRB Staff member determines and documents that the deviation is an unanticipated problem involving risks to subjects or others or the deviation resulted from serious or continuing noncompliance, the IRB staff member shall place the deviation on the agenda of the next available IRB meeting for review. If the IRB Chair or IRB Staff member determines and documents that the deviation is not an unanticipated problem involving risks to subjects or others, the IRB Chair or staff member shall acknowledge the submission and complete the review through an administrative review procedure.

As a reminder, according to DoDI 3216.02 (November 8, 2011), the IRB shall approve an independent research monitor by name for all DoD-conducted research involving human subjects, determined by the IRB to involve more than minimal risk to human subjects. Additionally, the

research monitor may be identified by an investigator or appointed by an IRB or Institutional Official (IO) for research involving human subjects determined to involve minimal risk.

The research monitor may perform oversight functions and will report their observations to the IRB or a designated official. The research monitor may discuss the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research. The research monitor shall have the authority to stop a research protocol in progress, remove individual subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report. Research monitors shall have the responsibility to promptly report their observations and findings to the IRB or other designated official. The research monitors shall have expertise consonant with the nature of risk(s) identified within the research protocol, and they shall be independent of the team conducting the research involving human subjects.

7. HIPAA AUTHORIZATION

i. Are you intending to collect subject's Protected Health Information (PHI) and any of the following 18 personal identifiers?

___ No – HIPAA does not apply – go to question #**iv**

_X_ Yes – please check which ones:

_X_ 1. Names

___ 2. Street address, city, county, 5-digit zip code

___ 3. Months and dates of major life events (years are OK) and ages >89 (unless all persons over 89 years are aggregated into a single category)

___ 4. Telephone numbers

___ 5. Fax numbers

___ 6. E-mail addresses

_X7. Social security number

___ 8. Medical record number

___ 9. Health plan beneficiary number

___ 10. Account number

___ 11. Certificate/license number

___ 12. Vehicle identification number (VIN) and/or license plate number

___ 13. Device identifiers and serial numbers

___ 14. URLs (Uniform Resource Locators)

___ 15. Internet protocol address number

___ 16. Biometric identifiers, such as finger and voice prints

___ 17. Full face photographic images or any comparable images

_X_ 18. Any other unique identifying number, characteristic, or code such as patient initials

ii. Can you limit your collection of personal identifiers to just dates, city/state/zip, and/or "other unique identifier" (#18 of the above)?

___ Yes – then your dataset may qualify as a Limited Data Set – please complete a Data Use Agreement and submit with your protocol. Then go to question #**iv**.

_X_ No – Go to question #**iii.**

iii. Is obtaining patient Authorization "impracticable"?

___ Yes – Authorization may qualify to be waived by the IRB. Submit a Request for Waiver of Consent/HIPAA to the IRB.

_X_ No – Research subjects will need to sign a HIPAA Authorization. Complete the HIPAA Authorization template portion of the Consent Template.

iv. What precautions will you take to protect the confidentiality of research source documents (Case Report Forms, questionnaires, etc.), the research data file, and the master code (if any)?

Subject information in the data collection sheet will be identified by unique subject numbers to maintain confidentiality. The link between the subject number and subject identifying information will be kept in a locked file in the principal investigator's office.

v. When will you destroy the research source documents, data file, and the master code?

I agree to maintain a study file that must be kept for three years from the date the study is closed (32 CFR 219.115(b)) and that HIPAA authorizations will be retained for 6 years.

vi. Will research data including Identifiable Protected Health Information be sent outside of WRNMMC?

___ Yes – Please explain assurances you have received from the outside party that they will appropriately follow confidentiality protections, follow the HIPAA requirements, and abide by the provisions of your Authorization. NOTE: If yes, an impact statement from WRNMMC IT department is required to ensure data transmission meets applicable standards.

_X_ No

8. INVESTIGATOR AGREEMENT

By submitting this protocol and providing an electronic signature in IRBNet, or an ink signature below, I agree to the following statements:

General Assurance: I agree to conduct the study as outlined herein. I certify that all procedures involving human subjects have been described in full.

Starting the Study: I understand that I cannot begin the study until I have received an approval letter documenting approval by the WRNMMC IRB.

Consent: I am responsible for assuring the quality of each subject's consent in accordance with current federal regulations. This includes ensuring that any "designee" that obtains consent on my behalf is completely familiar with the protocol and is qualified to perform this responsibility.

Adverse Events: I understand that I must report research related or possibly research related serious adverse events within 24 hours to the IRB. If the IRB has required a research monitor, the research monitor will also review the relatedness and the serious nature of the adverse event. I will report unexpected (but not serious) adverse events that may possibly be related to participation in the protocol within 5 working days to the IRB using the same procedure.

Training: I verify that the personnel performing these procedures described in this protocol are technically competent, have been properly trained, and are appropriately qualified.

Compensation: I am aware that members of the research team are not authorized to accept any form of personal compensation for our efforts in conducting this research.

Modifications: I am aware that all changes to the protocol must be approved by the IRB before implementation. Examples of changes to protocols that require IRB approval include change of on-site PI, addition of personnel on study, increased sample size, addition of other data points, sources of outside funding, and addition of data collection sites.

Deviations to the Protocol: I am aware that any protocol deviations discovered by either the PI or auditing official will be immediately reported to the IRB. All corrective actions will be documented and become a part of the master study file, along with the report.

Duplication of Effort: I have made a reasonable good faith effort to ensure that this protocol is not an unnecessary duplication of previous experiments.

Reports: I agree to provide a Continuing Review Progress Report 30 days prior to the anniversary of the protocol's initial approval or as stipulated by the IRB. I agree to submit a final report within 30 days following closure, completion or termination of the study.

Maintain Study Files: I agree to maintain a Study File that must be kept for three years from the date the study is closed (32 CFR 219.115(b) and that HIPAA authorizations will be retained for 6 years. If IND medication or IDE appliances are used, the file must be kept for 2 years after Food and Drug Administration (FDA) approval and can then be destroyed; or if no application is filed or approved, until 2 years after the study is discontinued and FDA notified (21CFR 312.62(c). I acknowledge that research data is the property of the Command and will not be removed without prior approval. When I am scheduled to PCS or ETS, study records will be given to a new PI or the Department Chief, or turned over to the Department of Research Programs.

This file may be inspected at any time by Department of Research Programs, DoD oversight entities, the FDA, and/or other applicable regulatory agencies responsible for the oversight of research. This file will include:

A. The approved protocol and applicable amendments.

B. The IRB minutes granting approval to initiate the study.

C. IRB approval letter.

D. Each Consent Form/HIPAA Authorization signed by the subject or Legally Authorized Representative (LAR)

E. Continuing Review Progress Reports.

F. Reports of adverse effects.

G. Reports of any significant new findings found during the course of the study.

H. All study documents generated from study date.

I. Publications, abstracts, reprints resulting from study data.

J. All information pertaining to an investigational drug or device.

Publications: I am aware that advertisements, abstracts, presentations or publications resulting from research protocols must have their products cleared by the Public Affairs Office, undergo Operation Security (OPSEC) review, undergo review for release of actionable medical information, and Publication Clearance.

HIPAA Compliance: I will provide each research participant with a copy of their signed and dated HIPAA Authorization and will immediately notify the IRB Privacy Board when a research participant revokes his/her signed Authorization, and I will no longer seek to obtain PHI pertaining to that individual for this research project, or any other purpose absent a separate authorization or appropriate waiver.

Applicable Regulations: I am familiar with applicable regulations governing research, and will adhere to all of the requirements outlined in the DoD Assurance for the WRNMMC.

I understand that if I fail to comply with any of these responsibilities, all projects for which I am an investigator may be suspended.

(Electronic signature in IRBnet)_____

LT Cicely A. Dye, MC

9. LEADERSHIP ACKNOWLEDGEMENT

I concur with the submission of this proposal to the Department of Research Programs for review and approval.

(Electronic signature in IRBnet)_____

COL Randolph E. Modlin, MC

Chief, Cardiology Service

10. REFERENCES

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11. BUDGET

Will any outside organization provide funding or other resources? Yes ( ) No (X)

If yes,

- Submit a ***budget page*** or provide detailed information about the transfer of funds/other resources. Include a copy of the grant award notice.

DRP Budget Request for Intramural Protocols Only:

	FY14	FY15	TOTAL
Consumable Supplies (Itemize each supply)			
Other*			
Travel**			
TOTAL ***	$	$	$

For DRP budget request, itemize consumable supplies and provide a brief Budget Justification for each budget category.

* Funds may be applied to the purchase of small clinical or laboratory equipment necessary for conduct of the study. Funds may not be used, however, to purchase computers.

** Funding request may be approved for intramural protocols for WRNMMC billeted staff and those PIs participating in GME. The funding is contingent on availability of funds. The funds are intended for use by the Principal Investigator.

*** Not to exceed $7,500 per fiscal year (including equipment), up to two years.