Official Study Title: Comprehensive Characterization of Coronary Atherosclerotic Disease Using Photon Counting-Detector Dual-source CT and Its Impact on Patient Management

NCT Number: NCT05240807

Document Name: Protocol and Statistical Analysis Plan

Approval Date: 1 February, 2023

MAYO CLINIC

General Study Information

Principal Investigator: Cynthia H McCollough, PhD

Study Title: Comprehensive characterization of coronary atherosclerotic disease using photon counting-detector dual-source CT and its impact on patient management

Protocol version number or date: Version 5; 02.01.23

Abstract

Background

Photon counting computed tomography (PCD-CT), which use photon counting detectors (PCD), offers higher spatial resolution, increased spectral sensitivity and lower radiation dose requirements compared to conventional CT systems, which use energy integrating detectors (EID). Different than conventional EID-CT, PCD-CT quantifies the energy of individual X-ray photons. This ability facilitates innovative approaches to improving soft tissue differentiation and decomposing materials into their basis elements. We have extensively demonstrated numerous benefits in phantoms, animals, and almost 500 human subjects. These human subjects were imaged on the whole-body research PCD-CT scanner in the Opus building under IRB protocol 16-001988.

In April 2021, a new PCD-CT is being installed on Mayo 3 in a clinical CT imaging work area. This system is updated from the prior system to allow state-of-the-art cardiac imaging, which is the focus of our NIH grant (1R01EB028590-01A1) on cardiac PCD-CT. Comprehensive evaluation of the system's performance has demonstrated that the image quality exceeds that of the clinically used Somatom Force and X.Cite commercial systems, on which this scanner is based.

Purpose:

Coronary artery disease (CAD) remains the main cause of morbidity and mortality in the United States. Cardiac CT provides fast non-invasive assessment of CAD with a high sensitivity and negative predictive value – provided that the lumen can be visualized. However, heavily calcified or stented coronary segments may be non-assessable, precluding non-invasive diagnosis of flow-limiting coronary plaques in an estimated 2 million U.S. adults. In addition, the spatial resolution of state-of-the-art CT systems is insufficient for robust visualization of features associated with high-risk plaques. Further, while CT can quantitatively evaluate the impact of obstructive CAD on myocardial perfusion using dynamic perfusion imaging, this requires relatively high patient radiation doses, which has limited widespread adoption. Considering the high personal and societal cost of CAD, robust, accurate, non-invasive imaging of calcified and stented coronary arteries, high-risk plaque features, and myocardial perfusion defects in a single, low-radiation-dose exam is critically needed.

Built by Siemens Healthcare, a first-of-its-kind, whole-body, photon-counting-detector PCD-CT system was installed in 2014 at the Mayo Clinic. With support from NIH award EB016966, we showed that the increased iodine contrast-to-noise ratio, decreased electronic noise, spectral imaging capabilities, and improved spatial resolution of PCD-CT relative to commercial CT enabled us to accurately measure increased vasa vasorum density in injured swine carotid arterial walls, demonstrating the exceptional potential of PCD-CT in vascular imaging. Because this system lacks cardiac imaging capabilities, our grant's purpose is to develop and validate a PCD dual-source CT system and novel imaging algorithms to accurately assess CAD in humans, especially in

patients with heavily calcified, stented, or high-risk plaques, and to identify patients with myocardial perfusion defects. Our premise is that the established benefits of PCD-CT, used with a dual-source geometry and advanced noise reduction and material decomposition algorithms, can meet these objectives.

Our proposal is significant in many ways: the technology developments will benefit all of CT imaging; robust, accurate, non-invasive imaging of calcified and stented coronary arteries, high-risk plaque features, and myocardial perfusion defects in a single, low-radiation-dose exam will obviate the need for additional imaging, reducing the overall time and cost to comprehensively evaluate CAD and its clinical significance. To extend the demonstrated benefits of PCDs to cardiac CT will require numerous physics, engineering, and algorithm innovations, including novel noise reduction and material decomposition algorithms using energy, spatial *and* temporal domain redundancies, as well as deep learning. Many of these advances are now complete and incorporated into the new PCD-CT on Mayo 3. The purpose of this protocol is to demonstrate in a large clinical study that the images are not only "better," as is so often done, but that PCD-CT provides clinically-significant improvements in the diagnosis and management of patients with suspected CAD.

Study Design:

Overview: This study will focus on demonstrating the benefits of PCD-CT for clinical indications and findings where the improved spatial and temporal resolution, decreased quantum and electronic noise, improved spectral imaging capabilities, and increased iodine signal are expected to benefit the diagnosis and characterization of CAD and myocardial perfusion defects.

Patient recruitment: Individuals scheduled for a clinically indicated coronary CTA, stress cardiac MRI, or nuclear cardiovascular stress scan in our outpatient practice will be invited to participate in this study. The study coordinator will either contact the patient via phone or in person. After their clinical exam, patients approached by a study coordinator to discuss the research study. After providing written informed consent, the patient will be escorted to the PCD-CT suite on Mayo 3 and scanned on the same day. If the patient's schedule does not allow same day scanning, scanning will be performed within 3 days of the clinical exam. Our enrollment target is 250 undergoing clinical coronary CTA. An additional 200 patients undergoing clinical cardiac nuclear medicine or cardiac MRI stress test will be recruited to receive a research cardiac perfused blood volume (PBV) with coronary CTA. The PBV study will include rest and stress CTA scans.

Consecutive patients receiving 1) a clinical contrast-enhanced coronary CTA exam, with an accrual target of 170 with CT findings of CAD (to include both obstructive and nonobstructive disease) and 80 without, or 2) a clinical cardiac nuclear medicine or MRI perfusion exam, with an accrual target of 100 with a myocardial perfusion defect and 100 without, will be recruited to receive a PCD-CT contrast-enhanced cardiac CT exam. When accrual of subjects in a group is reached, the recruitment efforts will shift towards the under-recruited group. A total of 450 patients will be enrolled over a 2.5-year period. Based on the volume of cardiac imaging exams performed in our practice and our rate of successful recruitment in previous and ongoing prospective studies, we are confident that the enrollment of 450 patients in 2.5 years is very feasible. All cost associated with the clinical exams will be paid for by the patient or his/her insurer. All PCD-CT (research) scans, including staffing and medications, will be covered by the CT Clinical Innovation Center, which is directed by Dr. McCollough and is where the scanner will be located.

Patient scanning: All research scans will be performed on the PCD-CT within 10 days after the patient's clinical exam is performed on an FDA-cleared commercial CT, nuclear medicine, or MRI scanner. For lumen and plaque evaluation, a contrast-enhanced scan will be performed on PCD-CT. For myocardial defect imaging, 2 contrast-enhanced scans will be performed on PCD-CT, the first during pharmacologically induced stress and the second at rest. Two peripheral IV's will be placed. One for the administration of Regadenoson and in case we need to reverse Regadenoson with Theophylline or Aminophylline. The second IV will be used to administer the IV contrast. Stress imaging will be performed with the injection of 0.4 mg/5 mL of Regadenoson (Lexiscan®) over 15 seconds followed by 0.9% NaCL 5 mL IV flush over 15 seconds immediately after medication injection. Regadenoson is a selective A2A adenosine receptor agonist and vasodilator that will increase coronary blood flow up to 3.4-fold. Patient will be monitored during the examination per protocol attached and if needed the reversal agent Aminophylline will be administered to relieve any symptoms. Myocardial regions supplied by physiologically significant stenotic coronary arteries will have an attenuated hyperemic response. Depending upon the severity of coronary stenosis and coronary flow reserve limitation, a relative heterogeneity is induced in myocardial blood flow, causing the iodine concentration to be reduced in regions of the myocardium with decreased PBV, thereby highlighting a perfusion defect.

We will require that average patient HR prior to PCD-CT scan initiation be within 20 BPM of that for the clinical scan, except for the scan during the Regadenoson infusion. We anticipate no image quality or motion artifact concerns at the elevated HRs during stress as we currently successfully perform DSCT cardiac exams at HRs of 100 to >120 BPM, even in patients with irregular heart rates.

All cardiac PCD-CT exams will be performed using the same acquisition protocol. This is possible with PCD-CT due to the count weighting of detected photons rather than energy weighting, which results in bright iodine signal independent of tube potential settings, and the capability to generate virtual mono-energetic images at lower keV. The use of 140 kV also improves the separation of the energy spectra measured by different energy thresholds, which in turn improves the material decomposition that will be used to remove calcium and quantify myocardial PBV. The use of a single fixed protocol greatly simplifies scanning workflow and eliminates the opportunity for changes in image quality or patient dose due to protocol changes.

All research scans will be performed with ECG gating, where scan and reconstruction parameters will have been optimized for each task and patient size. The manufacturer's automatic exposure control system will be used to appropriately adapt the tube current to the patient's body habitus. The rotation time will be set to 0.25 s and the 6 cm collimation setting selected. Helical pitch will be automatically adapted according to patient heart rate to ensure adequate sampling of the entire cardiac cycle for all projections. Contrast will be injected using the same protocol as for the patient's clinical exam, as determined by our routine contrast protocol: Omnipaque 350 mg I/cc (GE Healthcare, WI), total volume based on patient weight and scan time. ***All PCD-CT scans will pass over the heart only once as the PBV information is obtained from a single, routine dose scan; dynamic perfusion imaging is not needed.***

With the ability of PCD-CT to acquire fully simultaneous MECT data with a 66 ms temporal resolution, the concentration of iodine within the myocardium at a given point in time (i.e., the PBV) can be measured for any contrast-enhanced exams. For the CTA exams, this will provide information not currently available with our clinical EID coronary CTA exams because we do not use the dual-energy cardiac scan mode for coronary imaging due to the factor of 2 in temporal resolution price that is paid with EID-DSCT systems. While the myocardial PBV information comes along for "free" on PCD-CT, scanning at rest may be less sensitive to mild

perfusion defects than when imaged under pharmacologic stress. For the cohort receiving imaging at stress and rest, a sub-analysis of the differences in perfusion defect detection and confidence between stress and rest scans will be performed to measure this effect under our scan conditions. Conversely, for patients receiving scans at stress and rest, contrast-enhanced images of the coronaries can be obtained from the same scan and contrast injection. This ability to quantify the lumen, plaque and myocardial PBV with a single scan will allow physicians to assess not only coronary disease, but also to measure the impact of identified disease.

Image reconstruction, image processing, and image interpretation: Images will be reconstructed and processed with 66 ms temporal resolution using parameters optimized in phantom and specimen studies of Aim 2 of our grant: reconstruction kernel, image thickness and overlap, noise reduction method and strength, material decomposition and calcium removal method and settings. Lumen patency will be quantitatively assessed as percent area stenosis for all coronary segments using validated commercial software. The percent area stenosis will be automatically displayed to the reader for each computer-identified luminal narrowing. A custom-developed workstation will be used for reader interpretation that allows readers to mark findings, select confidence levels, and answer task-specific questions as cases are presented according to a preset randomization scheme. All data are automatically recorded in a format optimized for export to the statistical package used for a given analysis. Prior to reader interpretation, standardized reader training will be conducted to ensure consistent use of workstation features and confidence scores between readers.

A cardiac radiologist and a cardiologist trained in the interpretation of cardiac CT and MRI will independently evaluate each case. For each task, the reader will assign a confidence level using a 0 to 100 scale. For each detected lesion, the reader will mark lesion location, and assign a lesion grade and composition. Plaque composition will be graded as predominantly calcified, mixed calcified and non-calcified, or predominantly non-calcified. For each patient, readers will assign a CADRAD score. A confidence rating of 0 will represent a non-assessable location due to the presence of a calcification or stent.

For assessing detection and characterization of non-calcified plaques and 4 high-risk features of such plaques, readers will mark the location of detected non-calcified plaque, rate their plaque detection confidence (0 to 100 scale), and rate detection confidence (0 to 100 scale) of the following features in the identified plaque: lipid-rich necrotic core, spotty calcifications, thin fibrotic cap, and positive remodeling. For assessing detection and characterization of myocardial defects, readers will mark the location of detected defects, rate their detection confidence (0 to 100 scale), and grade the severity (e.g., transmurality and size) of each identified defect (0 to 100 scale). A detection confidence of 0 is equivalent to complete confidence that the plaque feature or perfusion defect is absent.

For patients receiving a coronary CTA exam on both the EID- and PCD-CT systems (EID/PCD cohort), the following images will be available: EID-DSCT coronary, PCD-CT coronary, and PCD-CT PBV at rest. For patients receiving nuclear medicine or MRI perfusion exams, and PCD-CT stress and rest PBV exams (NM-MRI/PCD cohort), the following images will be available: nuclear medicine or MRI perfusion images at rest and stress, PCD-CT coronary and PBV images at rest, PCD-CT coronary and PBV images under stress. We will evaluate all images in all patients. This will enable assessment of the value of the “extra” information available using PCD-CT. For all reading sessions, readers will be blinded to all patient information and other imaging exams. All images presented to the readers will be randomized. No single patient will be presented to the readers twice in the same reading session and reading sessions for a given subject will be separated by > 6 weeks.

Because some information available in the PCD-CT images is not available on the clinical tests (e.g., CT PBV images for patients who had a clinical CTA exam and coronary CTA images for patients who had a nuclear medicine or MRI perfusion exam), and because the PCD coronary CTA may be diagnostic when the EID CTA is not, research interpretation of PCD exams will be performed within 7 days, with major discrepancies or any additional information provided to each patient's primary care provider, with the caveat that the information is from a research study on an initially non-FDA-cleared scanner; FDA clearance of the scanner is anticipated in fall 2021. The clinical EID or nuclear medicine/MR perfusion scan will have received a clinical interpretation and diagnosis at the time of the exam to guide the patient's care.

Impact on diagnosis and patient management: Impact on diagnosis based only on imaging findings will be assessed by evaluating agreement between the diagnoses made using the PCD research exam and the clinical exam, as well as changes in reader diagnostic confidence, first without and then with the "extra" information provided by PCD-CT. Agreement of the PCD exam results with those of the clinical exam will be performed on a per-patient basis, with agreement rules determined prior to analysis. A per-vessel agreement analysis will be performed separately for calcified and non-calcified stenosis. In cases of agreement in diagnosis, a confidence score difference of 30 points will be considered a discordant result. The total number of non-assessable segments, and mean number per patient, will be compared between EID and PCD exams.

Prior to recommending patient management, the physician co-investigators will review evidence-based guidelines to develop a reference decision tree to determine patient management recommendations, which we define to be the final recommendation to the ordering physician based on the imaging results and key clinical data abstracted from the patient's medical record (e.g., age, sex, BMI, smoking history, diabetic status, blood pressure, lipid profiles, medications, prior cardiac events or invasive procedures). The use of a standardized decision tree will provide a rigorous and reproducible decision-making strategy so that detection of changes in patient management recommendations is not influenced by personal preferences or unconscious biases.
The imaging findings, confidence levels, and key clinical data will be provided to each reader, who will independently evaluate the information and record a management recommendation based on the decision tree (e.g., no change in current care plan, alter current care plan, additional testing/information needed, recommend revascularization). For PCD studies, readers will assign management recommendations first using only PCD information also available on the clinical exam (e.g., percent stenosis for coronary CTA patients), and then again after the "extra" PCD data are shown (e.g., PBV images for coronary CTA patients).

After a case has been fully reviewed by both readers, the readers will compare their management recommendations and reconcile the results, by consensus, to yield a single management recommendation per patient for the clinical exam and separately (> 6 weeks apart) for the research exam. This approach will provide a single management recommendation for evaluation of the impact of PCD-CT relative to the clinical exam yet will also provide independent reader results up to this step for evaluation of inter-reader variability. For PCD studies, readers will reconcile management recommendations first using the management recommendations determined using only the PCD information also available for the clinical exam (e.g., percent area stenosis for coronary CTA patients), and then again after the "extra" PCD data are shown (e.g., PBV images for coronary CTA patients). Lack of consensus regarding the appropriate management recommendation will be resolved by Dr. Fleischmann, a consultant on the project.

To assess changes in management recommendations, the consensus recommendations (i.e., for the clinical exam and for the research exam, before and after consideration of the "extra" information) will be compared. Reclassification statistics will be calculated according to the number of categories moved, with and without weighting of the clinical significance of the reclassification (using predefined rules). The number of reclassifications made due to the ability to visualize the lumen in heavily calcified lesions, or the additional information provided by the PVB images, will be determined.

Statistical considerations

Sample size justification: Estimation of minimum sample size requirements is centered on the concept of paired measurements between EID and PCD, or nuclear medicine or MRI and PCD. This lends itself to measures of precision (e.g., confidence intervals on differences in diagnostic confidence) and tests for shifts in distributions (e.g., McNemar's test). We first estimate a sample size based on the latter concept using 80% power and a two-sided level of significance of 0.05. McNemar's test develops its power to detect differences in decisions between EID and PCD, or nuclear medicine or MRI and PCD, through discordant observations between the paired data. Based on our current knowledge and the results of Aim 2 of our grant, we hypothesize that PCD-CT, due to its increased temporal, resolution, noise, and spectral performance, will be more accurate relative to EID-CT for examinations of multiple coronary artery features (e.g., percent area stenosis, presence of non-calcified plaque). We set the minimum clinically relevant discordance to be 10% and have designed the study to be able to detect a 20% discordance between EID and PCD. The sample size required to achieve these design parameters is 155 subjects (with paired measurements). To increase the statistical power and accommodate situations where a higher percentage of paired assessments are concordant, we will target **250 patients** for this cohort.

Conversely, we hypothesize that the presence and severity of any identified perfusion defects will be comparable between nuclear medicine or MRI and PCD-CT. To estimate this sample size requirement, we assume perfusion defects, as measured by the paired difference in confidence score of defect severity between modalities, will be distributed normally with a mean of 0. On a standardized scale, we set the limits of equivalence to be +/- 0.25 SD units. At alpha=0.05 (two-one sided tests at 0.025), 139 subjects are needed to establish equivalence with 80% power. To increase the statistical power and accommodate a binary interpretation as just presented, we will target **200 patients** for this cohort.

Analysis plan: The primary analysis for this grant is focused on estimating the differences in diagnoses and patient management recommendations between EID and PCD, or nuclear medicine or MRI and PCD. There will be a few statistical details that will warrant consideration, including paired measurements, multiple lesions within patients (clustered data), multiplicity considerations, and balancing between estimations and statistical testing ("p-values"). The analysis plan is written at a high level to provide a clear picture of our approach without unnecessary technical jargon.

Quantitative results (e.g., percent area stenosis) will be evaluated using established coefficient of variation protocols to provide estimates for each lesion. For binary interpretations (e.g., non-calcified plaque present or absent; perfusion defect present or absent), we will utilize a combination of kappa to estimate the agreement and McNemar's test (and the diagnostic odds ratio with 95% confidence intervals) to describe the discordance that is present. When more than 2 categories are evaluated, we will utilize Krippendorff's alpha, which is a flexible measurement of agreement that simplifies to kappa and ICC under certain scenarios. Furthermore, and

analogous to McNemar's test, we will utilize the Hodges-Lehmann estimator of the median difference in ratings to quantify the magnitude of differences that may be present.

These examinations will tend to have either interval or ratio measurement scales allowing for more flexibility in the analyses. Parametric approaches such as paired t-tests and mixed effects models (to further account for multiple lesions within a patient) are expected to be feasible. Agreement analysis of lesion classification will be conducted. Here, we will consider each feature individually (lipid-rich necrotic core, yes or no), as well as overall lesion grades and patient RADCAL scores, between the imaging strategies. Myocardial perfusion defects will be compared by looking at the change in perfusion severity between rest and stress. Differences between PCD-CT and the clinical exam will be tested using a linear mixed model to allow for the repeated measurements. Furthermore, we will test for equivalence in the PCD and clinical exams by interpreting the confidence interval for the difference in differences according to the pre-specified limits of equivalence of +/- 0.25 SD of the deltas. Contrasts and 95% CIs will be estimated from this model.

The ability of PCD-CT PBV images to identify myocardial perfusion defects will be evaluated on a per segment and per patient basis against the MRI reference in terms of area under the receiver-operating-characteristic curve (AUC) using both stress and rest images to make diagnosis. A second analysis will be performed using only rest images to determine the loss of performance without use of the stress exam.

Sex as a biological variable analysis: Stratified analyses by sex, with interaction terms, will be performed to quantify the differences, if any, in findings. Simplified tests such as chi-square tests of homogeneity will be used to test if differences in disease prevalence and PCD-CT findings are consistent across sexes. We hypothesize that PCD-CT will not perform differentially by sex when controlled for disease prevalence.

Specific Aim:

1. In patients, measure the clinical impact of cardiac PCD-CT on patient diagnosis and management

Subject Information

Subject population: 450 patients (18 – 99 years of age)

Inclusion Criteria:

- Adult male and adult female patients aged 18 to 99 years of age
- Patients referred for coronary artery cardiac CT imaging or nuclear medicine or MRI cardiac perfusion within the Department of Radiology or Cardiology.
- Patients who are able and willing to sign the informed consent will be enrolled
- Negative pregnancy test if subject is of child-bearing age (females of child-bearing potential will be screened for pregnancy using a urine pregnancy test, which will be administered by the unit study coordinator at no cost to the patient).

Exclusion Criteria:

- Minors
- Patients unable to provide written informed consent

- Pregnancy
- eGFR ≤ 30 (1,2)
- History of prior moderate or severe contrast reaction includes unresponsiveness, severe respiratory distress, convulsions, arrhythmia, cardiopulmonary distress, progressive angioedema, laryngeal edema, dyspnea, bronchospasm, symptomatic tachycardia, symptomatic bradycardia, hypotension, hypertensive crisis.
- Any history of required premedication prior to iodinated contrast administration.
- Patients that consent to participation but do not undergo their clinically indicated, contrast-enhanced CT, or nuclear medicine or MR perfusion scanning for any reason (e.g., bad IV, infiltration, reaction, change in indication).
- Patients who have a pacemaker or an implantable cardioverter-defibrillator (ICD)
- Patients experiencing atrial fibrillation, premature ventricular contractions, or other heart rhythm abnormalities
- Hospitalized patients or patients under care in the Emergency Department

Specific exclusion criteria only for participation in the cardiac stress test arm of this study (requiring administration of Regadenoson):

- Anything by mouth within three hours of the examination
- Known hypersensitivity to Regadenoson, Adenosine, or Dipyridamole.
- Active ongoing wheezing or poorly controlled asthma or COPD (hospitalized within last month or receiving treatment for flair within last month).
- Second (type I or II) or third degree atrioventricular (AV) block or sinus node dysfunction unless patient has functioning artificial pacemaker.
- Ingested greater than 4 oz. of caffeine within the last 12 hours.
- Currently experiencing unstable coronary syndrome.
- Uncontrollable seizures within the last 3 months

1) McDonald, J. S., McDonald, R. J., Comin, J., Williamson, E. E., Katzberg, R. W., Murad, M. H., & Kallmes, D. F. (2013). Frequency of Acute Kidney Injury Following Intravenous Contrast Medium Administration: A Systematic Review and Meta-Analysis. Radiology, 267(1), 119-128. doi:10.1148/radiol.12121460

2) Davenport, M. S., Khalatbari, S., Cohan, R. H., Dillman, J. R., Myles, J. D., & Ellis, J. H. (2013). Contrast Material–induced Nephrotoxicity and Intravenous Low-Osmolality Iodinated Contrast Material: Risk Stratification by Using Estimated Glomerular Filtration Rate. Radiology, 268(3), 719-728. doi:10.1148/radiol.13122276

Subject Contact

In this prospective study, patients will be approached by the study coordinator prior to or after the CT/nuclear medicine/MRI exam. This includes mail or phone contact in advance of the patient's arrival to their appointment. If patients are interested in participating and meet inclusion but not exclusion criteria, the study coordinator will explain the study in greater detail. The study coordinator will observe the patient and determine if subject is alert, able to read and understand the consent, and is fluent in English. Study personnel

will also try to determine if subject is under any undue pressure from family members to participate in the study. The person obtaining consent will check for the subject's understanding through questions/answers to gauge if responses reflect adequate understanding. Study personnel will also make sure all questions are answered to participant's satisfaction and that they have expressed a clear decision to proceed with the study. The study coordinator will also remind potential participants that they can decide not to participate, or stop in the middle of the study, without affecting their care, rights, and benefits here at Mayo Clinic.

The subject will be given enough time to read the consent form and ask any questions. If the patient agrees to participate, they will be asked to sign the approved consent form. A copy of the signed consent form will be given to the subject, and a copy saved in the electronic patient file.

Prior to or after the consent process, a cardiac CTA scan will be performed on an FDA-cleared clinical CT system. For patients in the study arm undergoing a stress CTA scan, or a nuclear medicine or MRI stress scan will be performed on an FDA-cleared clinical nuclear medicine imaging or MRI system. The research cardiac exam will be performed on a PCD-CT scanner awaiting FDA 510k clearance, which is anticipated to be received in October 2021. The research cardiac CT exam will consist of one coronary CTA scan at rest (n=250 subjects) or two coronary CTA scans, one at rest and one after the administration of a pharmaceutical cardiac stress agent (n=200).

After the consent process, patients who will be having the research stress CTA scan will receive a 12 lead electrocardiogram (ECG) performed before and after the stress CTA scan. The pre-scan ECG will be done in the Preoperative Evaluation (POE)/Pre-anesthesia Medical Exam (PAME) clinic located in the Gonda Building subway-level. The post-scan ECG will be done in the CT CIC area located on the 3rd floor of the Mayo Building by ECG personnel. A "stat-ECG" request will be submitted by CT CIC personnel and the patient will be placed in a monitored recovery area, lying down, to wait for the ECG technician. Both the pre- and post-scan ECG exams will require interpretation and approval by a cardiologist, which will be documented in the study records. Co-investigator Dr. John Bois will be responsible for this step. In his absence, the cardiologist overseeing the Nuclear Cardiology practice that day will fill this role. The CT CIC staff will coordinate the process.

The study will not proceed if the pre-scan ECG displays any exclusion criteria, the patient's provider will be notified of the abnormal ECG, the ECG placed in the patient's clinical records, and a note added to the patient history from the interpreting cardiologist.

After the stress-CTA scan, the patient will be evaluated by the supervising physician, study coordinator, nurse, or CT technologist for dismissal using the same criteria used after contrast injections in the CT clinical practice. In addition, the post-scan ECG will be performed and interpreted. The patient's provider will be notified of any abnormalities of the ECG, the ECG placed in the patient's clinical records, and a note added to the patient history from the interpreting cardiologist. The interpreting cardiologist will determine if any abnormalities require urgent attention and take appropriate action to have the patient seen by the appropriate clinical service or the patient will be transported to the Emergency Department if the situation is critical. The likelihood of such an event is extremely low.

If the patient doesn't have time to have the PCD-CT scan immediately after his/her clinical scan, an appointment will be made for the patient to be scanned on the PCD-CT system when it is more convenient for the patient, provided that the PCD-CT scan is performed within three days of the clinically indicated scan.

Specimen and Data Collection Procedures

Describe the subject contact schedule (baseline, follow-up, additional blood draws, etc.): *NA.*

Describe the specimens that will be collected. For blood samples, describe the amount and frequency of the blood collection: *NA.*

Describe the procedures for specimen collection. i.e., where/how the specimens will be obtained, how the specimens will be transported to the repository, etc.: *NA.*

Describe the subject data that will be collected:
CT projection data and images.

Describe the procedures for subject data collection:
Data acquisition will be performed on the PCD-CT system in the CT CIC. Data will be archived after the CT exam.

Will permanent cell lines be established? If yes, describe. *NA*.

Will DNA be extracted from the specimens? If yes, describe: *NA*.

Specimen and Data Storage/Retention

Describe the physical location and design of the repository, including storage facilities for specimens:
Data are stored on an institutional LAN server in password protected server folders.

Describe how access to specimens is regulated and who will have access to specimens: *NA*.

Describe how specimens are labeled: *NA*.

Describe the type of database utilized: *CT projection data and images.*

Describe how the database is maintained and secured:
Access to study database is limited to specific study personnel and will required a security password.

Describe how data is transferred to the database:
Data is transferred to a designated server using Mayo's institutional intranet. All data will be treated in accordance with established policies of Mayo Clinic to protect identifying information, which will be kept electronically, and accessible only by study personnel as authorized by the investigator.

Describe how access to the database is regulated and who will have access to data, including subject identities and other personal identifying information:

The master list containing the participants' names, Mayo Clinic numbers and their corresponding study ID number will be saved on a password-protected LAN server. Access will only be granted to study personnel by the principal investigator or study coordinator.

If informed consent will be obtained, describe what will happen to a subject's specimen/data if the subject withdraws consent:

The subject's participation in the study concludes after the PCD-CT research scan. Their data will be retained for research purposes once they have completed the research scan.

Specimen and Data Distribution

Describe the approval process for use of repository specimens and data by both internal and external recipients, including how requests will be prioritized. Include a description of Data Use Agreements and Material Transfer Agreements:

The manufacturer of the PCD-CT system may require access to the data to assist in evaluating any unexpected technical findings or to perform further research on this device. Such data sharing is covered by the existing legal agreement between Mayo Clinic and Siemens Healthcare.

Describe how the repository will assure that current and future uses of specimens are consistent with the informed consent:

Any requests for access to data must be approved by the principal investigator of this protocol.

Risks to Subjects

Describe potential physical, emotional, or other risks to subjects:

Subjects will be exposed to a small amount of radiation during the CT scan(s) performed on the PCD-CT scanner. The radiation dose will be the same as or less than routine clinically indicated coronary artery CT angiographic examinations. The risk associated with diagnostic levels of radiation dose is negligible [The specific risk statement prescribed by the radiation safety office will be used in the informed consent document.].

As with all research, there is a chance that confidentiality could be compromised; however, we will take precautions to minimize this risk.

Additionally, there are small inherent risks associated with the use of intravenous contrast. Complications of iodinated intravenous contrast range from minor side effects, such as a sense of warmth, to serious reactions such as anaphylactoid reactions, contrast induced nephropathy, and contrast extravasation. The risk of these events occurring is low.

For patients participating in the stress CTA exam, the administration of Regadenoson is associated with the following risks: angina, arrythmias, nausea, headache, dizziness, dyspnea, flushing, and rarely acute coronary syndrome, myocardial infarct, anaphylaxis, stroke, and bronchospasm. We have established

exclusion criteria to minimize the potential for such event. The use of beta blockers to reduce the subject's heart rate and nitroglycerin to dilate the coronary arteria are routine standard of care for the performance of coronary CT angiography. The subject's heart rate will be monitored, and the drug Aminophylline will be available to reverse the effects of the Regadenoson, as is done in the clinical practice. Nurses providing support for this protocol will be familiar with these procedures as they are the same as used in the clinical stress MRI exams supported by the same team of nurses.

For Patients participating in the CT perfusion stress exam the ECG is associated with the following risks: temporary discomfort and / or skin irritation when removing the electrodes from your skin at the end of the recording.

Describe the policies/procedures in place to manage risks to subjects:

The PCD-CT scanner will undergo the same quality assurance and safety testing as Mayo's clinical scanners. This work will be performed by the same personnel, ensuring that the PCD-CT scanner meets or exceeds all regulatory safety requirements. The scanner has been in use under an approved IRB protocol since March 2021 and almost 300 patients have been scanned since then without incident.

We will reduce the risks associated with IV contrast by assessing patients with the IV contrast safety screening and history questions prior to contrast administration of the patient's clinical exam. A note will already be documented in the patient's electronic medical record with the answer to these questions by radiology nursing staff. We will also adhere to Mayo Clinic Radiology Clinical Practice Policies to ensure patient safety in the case of an adverse event. There will also be onsite physician trained in Advanced Radiology Life Support to manage any adverse events.

Privacy and Confidentiality

Describe potential risks to privacy and confidentiality:

Although unlikely, there is the potential risk of lack of confidentiality.

Describe the policies/procedures in place to protect privacy and confidentiality, including security measures, confidentiality agreements, data use agreements, encryption techniques, etc. Information regarding Certificates of Confidentiality can be accessed at http://grants.nih.gov/grants/policy/coc/:

All patient identifying information will be stored on password protected institutional LAN servers. Only approved study personnel who have a need-to-know patient-identifying information will have access to such information. Any raw data or images shared externally will have all HIPPA identifiers removed.

If family members are to be studied, how will subjects be protected against disclosure of medical or other personal information about themselves to other family members, whether by direct disclosure or information derivable by inference? *NA.*

Identifying Information

Describe the identifying information that will be collected on subjects. Review the list of subject identifiers below and check the box next to the individual identifiers being maintained within the repository. "Internal"

refers to subject identifiers that will be included in the dataset maintained by the study team. "External" refers to subject identifiers that will be shared with persons outside of the immediate study team, including internal (Mayo) and external persons.

SUBJECT IDENTIFIERS **check all that apply**	Internal Identifier	External Identifier
Name	X	
All geographic subdivisions smaller than a state, i.e., street address, city, county, precinct, zip code (except for the initial three digits of the zip code)		
Dates: All elements of dates directly related to an individual including birth date, date of death, date of diagnosis, admission/discharge date, etc. **Note:** Recording a year only is not a unique identifier.	X	
Telephone numbers		
Facsimile numbers		
Electronic mail addresses		
Social security numbers		
Medical record numbers, Mayo Clinic number, lab accession number, specimen or radiologic image number, study identification number, subject ID, or any other unique identifying number or code that could link the subject to their data	X	
Health plan beneficiary numbers		
Account numbers		
Certificate/license numbers		
Vehicle identifiers and serial numbers, including license plates		
Web universal resource locators (URLs)		
Internet protocol (IP) address numbers		
Biometric identifiers, including finger and voice prints		
Full face photographic images and any comparable images		
Any other unique identifying number, characteristic, or code.		
If None of the above identifiers will be recorded or maintained in the dataset and/or sent outside of the study team, please check "None".	☐ None	☐ None

If applicable, provide justification for maintaining the identifiers indicated above:

Internal comparison to the clinically indicated CT/nuclear medicine/MRI exam, report, and patient record will be required to compare that information to the information obtained using the PCD-CT scanner. Thus, patient identifying information will be required. For external sharing of any image data, the CT scanner's anonymization feature will be used to remove all HIPPA identifiers

If specimens/data will be de-linked from subject identities, explain how this will be done:

For external sharing of data, the CT scanner's deidentification feature will be used to remove all HIPPA identifiers.

Return of Research Results

Describe the repository's policy regarding return of individual research results to subjects, including provisions for counseling and formal evaluation of risks and benefits: *NA*.

Will any information generated throughout the course of the research become part of the subject's medical record?

Yes, we will be placing the patient's Electrocardiogram (ECG) report in their medical record.

Repository Oversight

Describe the mechanisms in place for the oversight of repository activities, i.e., oversight/access committee(s), advisory board(s), etc. *NA*.