Translational Development of Photon counting CT-Imaging

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CLINICAL RESEARCH PROTOCOL

NATIONAL INSTITUTES OF HEALTH CLINICAL CENTER

PROTOCOL NUMBER: 19-CC-0070 **PROTOCOL VERSION:** 4.23.2019

TITLE: Translational Development of Photon-counting CT imaging

SHORT TITLE: Photon-counting CT

IDENTIFYING WORDS: photon counting CT, photon counting detectors, computed tomography

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ESTIMATED DURATION OF STUDY: 5 Years

START DATE: 05/06/2019 END DATE: 10/21/2023

NUMBER AND TYPE OF PATIENTS:

ACCRUAL CEILING: 750

	Number	Sex	Age Range
Patients	750	Males or Females	18 and above

PROJECT USES IONIZING RADIATION:

_____None
__X__Medically indicated:
__X__Research indicated:
RSC Approval Number:_____2701_Expiration Date: 10/30/21 _____

PROJECT USES DURABLE POWER OF ATTORNEY: No

OFF-SITE PROJECT: No

MULTI-SITE PROJECT: No

DATA SAFETY MONITORING BOARD (DSMB) INVOLVEMENT: No

TECHNOLOGY TRANSFER: Yes (CRADA, MTA/SLA)

ABBREVIATIONS:

CD	Clinical Director
CFR:	Code of Federal Regulations
Cr	Creatinine
CRADA;	Cooperative Research and Development Agreement
CRIS:	Clinical Research Information System
CT:	Computed Tomography
DM	Diabetes Mellitus
eGFR	Estimated glomerular filtration rate
HRPP	Human Research Protection Program
IRB	Institutional Review Board
IV:	Intravenous
rem:	Unit of radiation dosage
MTA:	Materials Transfer Agreement
PACS:	Picture Archiving and Communication System
PCCT:	Photon Counting Computed Tomography
PI	Principal Investigator
PII	Personally identifiable information
RAD&IS:	Radiology and Imaging Sciences
SLA:	Simple Letter of Agreement
SOP	Standard operating procedure
UP	Unanticipated Problems (
UADE	Unanticipated Adverse Device Effect

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Precis

NIH develops new imaging techniques as one of its priorities for accelerating science, including methods for non-invasive patient assessments. Computed tomographic (CT) imaging is a mainstay of diagnostic imaging. The latest major technological advance is photon counting CT (PCCT) which uses a new x-ray detector that measures x-ray penetration of the body and the energy of each x-ray photon. NIH has one of three prototype Siemens PCCT CounT systems in the world for investigational use. The scanner can perform standard CT and PCCT imaging. In this protocol, NIH patients already enrolled in a clinical research protocol and who are referred to Radiology for diagnostic CT as part of that research may be enrolled in this study of PCCT. The diagnostic CT scan requested by their medical care team will be performed on the CounT scanner, providing the clinically indicated imaging, along with a single, brief PCCT exam to support PCCT development. The data will be used to characterize quality of the PCCT images and to develop testable hypotheses and new diagnostic applications using PCCT capabilities.

Current CT systems, such as the Siemens SOMATOM Flash, have two x-ray tubes, each paired with an x-ray detector that measures total x-ray penetration of the patient and uses that information to create the images. The CounT scanner is a modified version of the Flash in which one of the two standard detectors has been replaced with a PCCT detector. The two imaging modes for the CounT scanner are (i) standard detector study as in a Flash scanner and (ii) PCCT scan. The patient scan will thus include clinically indicated radiation exposure with the standard detector and research radiation with the PCCT detector. The CounT system is sited at the Clinical Center under a CRADA with Siemens Medical Solutions.

Compared to current scanners, PCCT offers four major advantages:

- lower radiation dose
- greater spatial resolution
- reduced imaging noise
- x-ray energy discrimination

The primary objectives are to:

- develop and characterize new medical imaging methods
- facilitate translation of PCCT advantages into clinically useful applications.

As a translational development protocol, all imaging studies are open-label and data may be analyzed as they are collected. Bias is minimized using objective measurements. Observational data may be characterized using descriptive statistics. Simple comparisons between the standard CT and PCCT may use paired and unpaired parametric and non-parametric techniques. These studies will form the foundation to develop advanced clinical imaging capabilities and applications.

1. Introduction, Background and Rationale

The NIH intramural program specifically includes developing novel imaging techniques as one of its priorities for accelerating science, including generating new methodologies for non-invasive patient assessments (https://irp.nih.gov/our-research/accelerating-science/developing-novel-imaging-techniques). Computed tomography (CT) is a core imaging modality in medicine. In CT imaging, an X-ray tube and an X-ray detector are rotated around the patient with the detector recording X-ray penetration continuously during exposure. That data is then used to reconstruct cross-sectional images of the patient for diagnostic purposes. There are myriad ways to structure the examination of a body area, e.g. the system settings for the X-ray exposure, data collection and reconstruction and display of the images. Typical, optimized exam protocols have been developed for CT imaging for each area of the body and each organ as well as unique aspects of physiology, allowing for visualizing differences between normal and abnormal tissues and function.

The current clinical CT scanners at the NIH/RAD&IS have dual source capability with two X-ray tube/detector pairs that rotate around the patient simultaneously. Dual-source CT can be used to double the speed of acquisition or to perform dual energy scanning that may aid in determining tissue composition. These traditional CT systems detect X-rays using scintillator crystals and a photodiode array in an energy-integrating detector (EID) system that measures the total X-rays that pass through the patient and reach the detector. In these detectors, the individual imaging elements are separated by metal septae that limit the achievable spatial resolution.

In contrast, the photon-counting CT (PCCT) system utilizes very efficient semiconductor detectors that directly convert the X-ray energy of each individual photon into electric signal pulses. This not only allows detection of individual X-ray photons but also the energy associated with each photon. There are no metal septations between imaging elements in the detector, therefore much higher spatial resolution is possible. Altogether, the efficiency of the detector, the ability to discriminate between X-ray photon energies and the lack of septations in the detector permit higher spatial resolution, improved contrast to noise ratios and imaging with lower radiation dose.[1,2] This may be of particular value in low-signal scans (i.e. obese patients or lung exams).[3,4,5] Recent phantom studies and preliminary testing on humans demonstrate comparable image quality for both radiation dose-matched PCCT vs. current CT technology, notably in abdominal, cardiovascular, brain and lung scans, and improved contrast-to-noise ratio in renal tissue enhancement via iodine mapping in PCCT.[6,7,8,9,10]

Among its potential applications, PCCT provides spectral information for material decomposition analysis, which can help determine types of renal calculi[11] and generate contrast material density maps (including that of water). The capability for material decomposition allows subtraction of calcium from extremity CT studies that may enhance detection or assessment of metastatic disease in cancer patients, particularly with clinical suspicion for metastases or new onset of pain, or new evaluation techniques in patients with metabolic musculoskeletal disease. High resolution imaging may generate a spatial map of radiopaque drug-eluting embolic beads used to treat liver cancer, leading to dose maps for therapy. Pre-clinical studies have evaluated multiple-contrast imaging in delineation of infarcted myocardial tissue, and biodistribution of gold nanoparticles, while postmortem

studies demonstrate ability to characterize atherosclerotic plaque.[12,13,14,15,16] Low dose imaging with PCCT may reduce cumulative radiation dose in the follow-up of patients who undergo repeated clinical CT.

Superior spatial resolution compared to standard CT provides greater detail in anatomic imaging.[17] A major implication is the potential to advance radiogenomics, the correlation between imaging features and treatment outcomes or the genomics of a particular tumor.[18,19] The NIH patient population is ideal for this component of the research, as there are significant populations with specific diseases, including uncommon and rare diseases. Furthermore, substantial longitudinal follow-up of patients is common, often with correlative information on treatment outcomes as well as genetics of specific tumors or other disorders.

High spatial resolution image acquisition at lower radiation exposure with added spectral capabilities has promising potential for more dose-efficient imaging, new applications and more widespread utility compared to conventional CT. One might think of PCCT is analogous to high resolution color film, whilst conventional CT is black and white film.

2. Study Objectives

Developmental studies in normal volunteers have been conducted at the NIH.[2,6,7,8,10] This protocol serves to more conclusively evaluate and confirm the clinical performance of PCCT, optimize clinical protocols and develop clinical applications of this latest advance in CT technology. The primary objectives of this study include, but are not limited to:

- Objective 1: To develop and characterize novel methods of evaluating patients using PCCT; and,
- Objective 2: To facilitate the translation of PCCT technology and imaging methods into clinically useful applications for patients.

The applications being developed will take advantage of the potential for dose reduction, improved spatial resolution, noise reduction and x-ray energy discrimination. X-ray energy discrimination may be used for material decomposition wherein various materials such as iodine, gadolinium and calcium that all appear similar on conventional CT can be differentiated by PCCT imaging.

Because this is a translational development protocol for new technology, all imaging procedures are open-label and data may be analyzed as they are collected. Bias is minimized by defining and using objective measurements and recording them for review. Observational data may be characterized using descriptive statistics. Simple comparisons between the standard and PCCT images may use paired and unpaired parametric and non-parametric techniques as appropriate. New methods may be compared to the standard CT or computational models of the imaging studies. Objective quantitative measurements used in CT performance include, but are not limited to noise level and standard deviation, signal to noise ratio and variance, radiation dose and qualitative measures such as radiologist ratings of image quality, lesion conspicuity, image noise, beam hardening artifact, motion artifact.

3. Study Design and Methods

NIH patients referred to RAD&IS for diagnostic CT may be approached for participation in the study of PCCT-The study team has shared information about the PCCT study with NIH researchers that frequently schedule their patients for diagnostic CT scans as part of their studies. Those researchers or other NIH research teams may refer patients for study participation in this PCCT study. Enrolled patients will undergo the requested clinical diagnostic CT study on the PCCT system using the standard detector, with or without IV and/or oral contrast as indicated for the diagnostic CT scan. If contrast is not indicated for the diagnostic scan, it will not be administered for the research PCCT study. They will also undergo a brief PCCT scan as part of the examination. The standard detector and PCCT scans may be performed in any order. The scan will thus include both clinically indicated radiation exposure with the standard detector and research radiation with the PCCT detector.

From the patient perspective, the experience is the same as with a standard CT study. The CT scans are accomplished by having the subject lie down on a patient table which slides into the gantry of the scanner, a hollow cylinder 78 cm in diameter. The scan is performed by a qualified person in an adjacent room; audible communication is by intercom. In addition, the patient can be observed directly through the window between the two rooms. The patient can be removed from the scanner immediately upon request or in case of emergency.

The study team may use standard monitoring equipment during the CT scan. This may include electrocardiogram, or pulse oximeter, adhesive beads or fiducial markers and x-ray dosimeters (to determine exposure to radiation). Densitometry phantoms or iodine reference standards may be included in the scan to serve as references for x-ray attenuation and material decomposition. During the scan, individuals may be asked to perform tasks such as breath holding to enhance CT scan quality. Iodinated contrast may be injected intravenously using a standard clinical CT injector system. Oral CT contrast may be administered.

The duration of the entire examination in the CT room including positioning, setting up the CT injector, scan planning and the scans including the PCCT component, will be approximately 20 minutes, comparable to a clinical CT scan duration. The PCCT component adds approximately 5 minutes beyond the standard study duration

3.1. Study Implementation

1. Potential subjects will be referred by research teams to the PCCT team. Patients will be given a copy of the informed consent form which describes the study protocol. Protocol staff (PI or AI) will review the consent form and answer any questions the subject may have. The PCCT research team may review the patient's prior medical records and imaging to determine suitability for the PCCT scan. Patients will be registered on the protocol and the informed consent process will be documented in CRIS. CT scanning will occur on the PCCT scanner after confirmation that all standard of care CT scanning requirements are met by the study participant as required for any CT scan.

   Since the study involves research radiation, women of child-bearing age who may be pregnant will undergo blood or urine pregnancy testing.

2. After the informed consent form is signed and suitability determined, volunteers will receive the clinically indicated CT study using the standard CT detector. Oral iodinated contrast will be administered as clinically indicated. Intravenous (IV) contrast will be administered as clinically indicated. This may require establishment of an IV access line. The PCCT scan may be performed before, during, or after the administration of IV contrast. The standard detector and PCCT scans may be performed in any order. The PCCT scan may or may not add additional diagnostic information related to the patient's care. The patient's active involvement in the study ends at the conclusion of the PCCT examination. However, future imaging studies may be reviewed (see #5 below). Repeat consent will be obtained in the event a patient is scanned on more than one occasion (see #4 below).

3. The CT scan acquired with the standard detector will be stored in the NIH Clinical Center Radiology PACS and CRIS systems. Those exams will be submitted for interpretation by a board certified and NIH CC credentialed RAD&IS physician. Reports of findings will be managed according to standard practices for diagnostic imaging studies within the Department.

4. If the subject is later referred to RAD&IS for another CT examination, they are eligible to participate in this study again, provided at least one year has passed since the prior PCCT scan. These subjects will be re-consented and "re-enrolled" in this study with the updated active Consent Form. However, patients may not undergo more than one PCCT examination within a one-year period.

5. Information within the patient's medical record that was collected under other protocols may be collected as part of this study, including history and physical results, disease state and related diagnoses, treatment history and responses. Prior imaging data may be reviewed, analyzed and compared to the PCCT scan, as well as imaging data and information in the medical record generated after performance of the PCCT scan.

3.2. End of participation
Once a subject completes the clinical and PCCT scan their participation in the study is complete.

3.3. Alternatives to participation
Individuals will be allowed to withdraw from this protocol at any time and can also elect to not participate in this study. If they choose not to participate they will receive the standard CT study as ordered by their research team.

3.4. Privacy
All research activities will be conducted in as private a setting as possible.

4. Subject Recruitment
4.1. Recruitment plan
NIH patients currently on another NIH research protocol referred to RAD&IS for diagnostic CT may be approached for participation in the study of PCCT, subject to this study's enrollment and exclusion criteria.

Potential subjects may be identified by study staff in RAD&IS who have routine access to the clinical CT scan schedule and patient orders. NIH clinicians and their staff may identify a patient on their study for this study of PCCT and may then contact personnel on the PCCT protocol. In either case, the potential enrollment would be discussed with the subject. This could be in RAD&IS or in the Outpatient Clinic/Inpatient wards, or by telephone depending on the circumstances.

4.2. Recruitment materials and advertisements

None

5. Eligibility Assessment and Enrollment

5.1. Inclusion Criteria

- NIH patients currently on an NIH research protocol who are referred to RAD&IS for CT examination as part of that research protocol
- 18 years old or greater
- Able to understand and sign informed consent

5.2. Exclusion Criteria

- Studies that specifically require dual source CT scan capability or where dual source CT scan is requested
- Studies ordered for an emergency indication
- Pregnant women. When uncertain of pregnancy status, subjects of child-bearing potential will undergo serum or urine pregnancy testing on the day of examination. Post-menopausal and surgically sterilized subjects are automatically exempt from this testing
- Lactating women who are unable to stop breast feeding for 24 hours following the administration of contrast
- Body weight >500 lbs (227 kg) or a body circumference that prevents the study subject from lying flat in the scanner
- Patients who have undergone PCCT examination within the past year.
- Any contraindications that the research team identifies from the subject, RAD&IS CT questionnaires, and/or History and Assessment
- Employees or staff supervised by the Principal Investigator or an Associate Investigator will not be recruited to participate

6. Collection and Storage of Human Specimens or Data

6.1. Collection practices

Data from the clinical history and from laboratory tests will be maintained in the NIH medical record. No tissue or body fluid samples are collected and stored under this protocol. Blood may be collected for assessment of renal function. A pregnancy test may be ordered, as part of the screening process for the protocol. Clinical CT data acquired with the standard detector is transferred to the Diagnostic Radiology Department (DRD) for clinical interpretation. This CT data is archived per NIH Clinical Center and RAD&IS policy, on the radiology picture archiving and communication system (PACS). Access to the PACS is password protected and only provided through the Diagnostic Radiology Department. Patient name and medical record number are associated with the images stored in the

PACS and provide the means to retrieve this data. This is essential for continuity of the medical record, as these images provide clinically diagnostic information. The protocol number is retained in both Radiology Information System (RIS) and Clinical Research Information System (CRIS). Subjects may receive copies of the clinical portion of their CT examination from the film library in the DRD.

CT data (standard detector and PCCT detector) including personally identifiable information (PII) will be stored in Research PACS. Access will be limited to the Principal Investigator and Associate Investigators. CT data including PII may be transferred to individual investigator's NIH computers for analysis. In addition to imaging data, data from the clinical history and laboratory tests retained by Investigators will include personally identifiable information. Reports, analyses and data with PII will be stored on secure computer systems and/or secured paper files according to NIH policy.

The PCCT detector data will be stored redundantly on hard drives within the scan room.

Photon-counting CT is being developed in collaboration with Siemens Medical Solutions, the scanner manufacturer. Siemens will provide proprietary software for the image reconstruction and data analysis techniques used in the study. In order to provide quality assurance, to "debug" problems with the system and to aid in Siemens' development of new imaging capability for PCCT, de-identified image data may be provided to the manufacturer, Siemens Medical Solutions. All patients will be informed of the possibility of such data sharing

6.2. Image and data storage

While there are no plans to store and share de-identified imaging data by placing it into widely accessible scientific databases, the Informed Consent document provides for such sharing without further contact with the study subjects. In order to maximize the use of the data to advance PCCT imaging, de-identified data will be entered into an NIH-authorized and controlled research database with access restricted to scientists working to advance PCCT imaging. Any requests to use images in the database would be directed to the Principal Investigator of this study for approval. Data and images in this database will be identified only by a code number. The Principal Investigator or designated Associate Investigators will retain a list linking the code to specific patients.

The Informed Consent document stipulates that if a study subject does not wish for his or her stored data to be used for future research, he or she should inform the investigators. Any data that have not already been used or shared will be deleted and that data will not be used for future research. However, it may not be possible to withdraw or delete data once they have been shared with other researchers. Furthermore, the standard CT study obtained at the request of the health care team is a part of the patient's medical record and cannot be deleted.

6.3. Tracking

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system.

6.4. End of study procedures

The study will remain open so long as data analysis continues. Images from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time study staff will destroy them. Standard CT study images and reports cannot be destroyed. The standard/clinical CT study results will be shared with the requesting provider/research team. PCCT image data will not be shared with the subject.

6.5. Loss or destructions of data

As all CT imaging data is digital in nature, data loss can occur due to scanner or computer failure. Since the imaging data is archived on a redundant system, it is unusual for data to be lost irrevocably. Any loss of data from the archive will be reported to the IRB.

6.6. Publication policy

A description of this clinical trial will be available on http://www.Clinicaltrials.gov, as required by U.S. Law. A summary of the study results will be posted incompliance with the requirements. No PII will be released.

Results of the research will be shared through public presentations and publication in scientific journals. No PII will be included in such presentations or publications.

7. Statistical Analysis

7.1. Sample Size

Due to the early stage of development of this technology and its significant clinical potential, a sample size up to 750 subjects is requested for the protocol. PCCT is a new technology that offers advantages and new imaging capabilities compared to current CT scanner technology. However, the clinical utility and clinical applications related to these features (dose reduction, improved spatial resolution, noise reduction and x-ray energy discrimination) are as yet undefined. While preliminary development of scan parameters in normal volunteers has been conducted at NIH as well as at the Mayo Clinic where the other Siemens PCCT scanner is sited in the U.S., applications in patient populations remain to be defined and characterized. The manufacturer continues to develop and refine the system as well as the software used to reconstruct the imaging data, introducing new areas for study. It is anticipated that technical developments will continue and the need for subjects will continue over the next 5 years. The protocol is of an exploratory, observational nature, and will serve to generate hypotheses thus a statistical sample size cannot be reliably gauged at the onset due to insufficient pre-existing data. Consultation with one of the Clinical Center statisticians has been obtained concurring with our initial approach. We will plan frequent meetings with the statistician and adjust statistical sample size as we accrue data and can better predict the type of analysis that will be performed. Based on workflow using the PCCT prototype during prior studies of volunteers at the Clinical Center and subject accrual at Mayo Clinic, annual accrual is likely to be no more than 150 patients. Studies under this protocol will be used to develop data for the formulation of future hypotheses for investigation, which may be the subjects of future protocols or protocol amendments. At this time, subjects will not be divided into cohorts until a future time where a more informed delineation of cohorts may be determined.

7.2. Analysis of Study

Each patient will undergo a CT scan using the standard detector that will be submitted to the Radiology & Imaging Sciences Department for interpretation.

The PCCT scan will cover either identical volumes or, in many cases, a smaller volume. Often the smaller volume will be selected for study rather than the full clinically indicated body part(s) included in the standard detector scan. This allows direct comparison between the scans for image assessment. Objective quantitative measurements will include but are not limited to image noise level and standard deviation, signal to noise ratio and variance, radiation dose and qualitative measures such as radiologist's ratings of image quality, lesion conspicuity, image noise, beam hardening artifact, motion artifact. Comparisons of these quantitative and qualitative measures in different PCCT protocols among similar patients may also be made. As observational experience is gained with PCCT capabilities, the data will be used to generate hypotheses that may be investigated by future amendments, future cohorts, or future protocols. Because this is a translational development protocol for new technology, all imaging procedures are open-label and data may be analyzed as they are collected.

This protocol provides data for technical development purposes. The results may be used to iteratively improve the PCCT software and hardware for application to patient care. The relationship with the industry partner (Siemens Medical Solutions) is governed by an approved and active NIH CRADA. The CRADA document is available for IRB Chair review, upon request.

8. Data Safety and Monitoring Plan

8.1. Data and Safety Monitoring

Accrual and safety data will be monitored by the principal investigator, who will provide oversight to the conduct of this study. The PI will continuously evaluate implementation of the protocol for any unusual or unpredicted complications that occur and will review the data for accuracy and completeness.

The NIH Clinical Center's Quality Assurance Program will conduct study monitoring at least annually or more frequently as required for open studies unless studies are monitored by an outside organization or sponsor. Monitoring visits will include a review of patient consent documents, primary outcome and safety laboratory results and diagnostic test results will be monitored for accuracy, correct dating, and agreement between case report forms and source documents. All regulatory reports, reviews and amendments, adverse events and problem reports related to study, along with investigator credentials, training records, and the delegation of responsibility log will also be reviewed during monitoring visits. Any major findings will be summarized in writing and reported to the study PI who will be responsible for submitting the monitoring report to the IRB.

Monitoring will not apply to imaging data measurement, analysis and interpretation. An independent audit of these data is not planned.

8.2. Reporting of Unanticipated Problems and Adverse Events

Adverse events, protocol deviations, unanticipated problems (UP), Unanticipated Adverse Device Effects (UADEs), serious adverse events, sponsor and serious, are defined as described in NIH HRPP SOP 16 ("Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations."). All adverse events occurring during the study, including those observed by or reported to the research team, will be recorded. Serious unanticipated problems, Unanticipated Adverse Device Effects and serious protocol deviations, will be reported to the IRB and Clinical Director (CD) as soon as possible but not more than 7 days after the PI first learns of the event. Not serious unanticipated problems will be reported to the IRB and CD as soon as possible but not more than 14 days after the PI first learns of the event.
Deaths will be reported to the Clinical Director and IRB within 7 days after the PI first learns of the event.

Non-serious protocol deviations will only be reported to the IRB (within 14 days after the PI first learns of the event) if they represent a departure from NIH policies for the conduct of human subjects research, adversely affect the health care of the subject(s) or compromise the interpretation or integrity of the research. Non-serious protocol deviations that result from normal subject scheduling variations or technical issues associated with sampling that does not impact the health of the subject or the interpretation of the study data will not be reported.

The PI is responsible for summarizing all serious adverse events and adverse events at least possibly related to the research procedure and interventions at the time of Continuing Review. If (at any time during the course of the study) the severity or frequency of these events exceeds that anticipated, the events should be classified and reported expeditiously as Unanticipated Problems

All adverse events will be reported to Siemens Medical Solutions as part of our collaboration with the manufacturer to develop this technology.

Reports to the IRB, participating investigators, Clinical Center management, or FDA will also comply with the reporting requirements under 21 CFR 812.150 Reports, as appropriate. (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=812.150)

Expected Adverse Events
Expected adverse events can be divided into non-serious events not requiring treatment which will not be reported and serious events requiring treatment which will be reported to the IRB. No adverse events are expected from the performance of the PCCT scan.

Potential adverse events related to the placement of the intravenous (IV) line and the intravenous injection of contrast are a part of the performance of the standard CT scan and are not reportable.. Adverse events related to incidental imaging findings of no clinical significance will not be reported.

All serious events related to the PCCT scan will be recorded in CRIS and in the research records maintained by the study team. Serious adverse events will be reported to the IRB,

with a copy to the clinical director, as soon as possible, and no later than seven days in the case of death or life-threatening serious adverse events. Any additional unexpected serious adverse events will similarly be reported to the IRB as soon as possible and always within 14 days.

Unexpected Adverse Events

Unexpected adverse events are those that are not described in the published medical literature, in this protocol, or in the informed consent, as being associated with routine CT scanning. If they are coincident with research procedures and are possibly related to the protocol they will be reported to the IRB according to NIH guidelines.

9. Human Subjects Protection

9.1. Rationale for Subject Selection

Study of PCCT in normal volunteers has been conducted at the NIH. In a report of first human experience, Pourmorteza et al., (2016) compared radiation dose-matched, contrast enhanced CT of the abdomen performed with the standard detector and the PCCT detector and found no statistically significant difference in image quality although the PCCT scan included spectral information which may be used for material decomposition.[6] Pourmorteza et al., (2017) compared radiation dose-matched CT of the head performed with the standard detector and the PCCT detector and found greater gray-white matter contrast with PCCT, attributed to the higher soft-tissue contrast and lower image noise with the PCCT.[8] Symons et al., (2017) reported initial data comparing reduced dose chest CT with the two detectors and found that the PCCT images had lower image noise with better diagnostic quality and lung nodule contrast to noise ratios.[10] Symons et al., (2017), also reported first in vivo human results comparing vascular imaging of the head and neck with PCCT to the standard detector and found that image quality was greater with PCCT with lower image noise, less image artefact and improved iodine contrast to noise ratios.[7] Finally, Pourmorteza et al., (2018) reported first in human results with high resolution PCCT imaging compared to dose-matched standard resolution PCCT images that demonstrated improved image spatial resolution with reduced noise in the high resolution PCCT imaging.[2]

Advancing PCCT technology requires imaging of patients to develop optimal protocols and define utility and new applications in disease states. NIH patients referred to RAD&IS for diagnostic CT may be enrolled in this study of PCCT. Since the diagnostic imaging requested by the referring physician would be performed whether on a RAD&IS clinical scanner or as part of the photon-counting CT protocol, that component of the photon-counting CT protocol is not adding to the experimental radiation exposure to each patient.

Subjects from all racial/ethnic groups and genders are eligible for this study, subject to the inclusion and exclusion criteria.

9.2. Participation of Children

Children are excluded from participation on the study due to possible radiation exposure risks. The technical developments and refinements likely to result from this protocol are

anticipated to be generalizable to imaging techniques at younger.

9.3. Participation of NIH Employees and Staff

All employees/staff supervised by the Principal Investigator or an Associate Investigator are excluded from participation. Participation of employees/staff not supervised by a study investigator will follow the procedures outlined in SOP 14F (12).

Protection for employees and staff participating in this study include 1) assuring the participation or refusal to participate will have no effect, either beneficial or adverse, on the subject's employment or position at NIH, 2) giving employees and staff who are interested in participating the "NIH Information Sheet on Employee Research Participation" prior to obtaining consent, and 3) assuring that there will be no direct solicitation of employees or staff.

This study collects sensitive information regarding medical history, pregnancy status, and clinical interpretations of collected radiology images. The PI will train study staff regarding obtaining and handling potentially sensitive and private information about co-workers through staff discussions and written branch/section procedure. Information on medical history, pregnancy status, and clinical interpretations will be in the participant's NIH medical record.

9.4. Evaluation of Benefits and Risks/Discomforts

The risk related to participation in this study is limited to the radiation exposure from the single PCCT scan which is not required for their diagnostic scan. The diagnostic CT scan requested by the medical care team and related insertion of an IV line and the administration of oral and/or IV contrast would be performed, whether or not the subject is enrolled in this study of PCCT. The risks related to the diagnostic CT scan, including medical radiation from the diagnostic CT scan, IV insertion, and IV and/or oral contrast administration, would occur whether or not the patient in enrolled in this protocol. Contrast is only administered if required by the ordered diagnostic CT scan.

<u>Radiation exposure:</u>

CT scans use ionizing radiation (X-rays) to generate the images. The study is limited to NIH patients who are referred to RAD&IS for performance of a medically indicated diagnostic CT scan. Since the diagnostic imaging requested by the referring physician would be performed whether on a RAD&IS clinical scanner or with the standard detector on this device as part of the Photon-counting CT protocol, that medically indicated component of the procedure is not adding experimental radiation exposure to each patient. The CT study acquired with the standard detector will be stored in the NIH Clinical Center Radiology PACS and CRIS systems. Those exams will be submitted for interpretation by a board certified and NIH CC credentialed Radiology & Imaging Science Department physician and reports of findings will be managed according to standard practices for diagnostic imaging studies within the Department.

The expected research radiation total effective dose from the scan with the PCCT detector will be less than or equal to 2.2 rem for the average study subject. The dosimetry calculations were performed assuming the entire scan would be repeated at the abdomen dose or the highest dose that might be administered to a study subject. For the PCCT scan, we expect to scan a more limited volume than the complete diagnostic CT scan. Further the

chest exposure parameters will be less than what was used to estimate the dose. Even at this level, the research radiation dose from the PCCT scan will be below the maximum allowable research radiation dose guidelines established by the NIH Radiation Safety Committee for research participants. One possible effect that could occur as a result of using radiation is a slight increase in the risk of cancer. However, there has been no convincing epidemiological evidence that there is a risk of cancer development at these low levels. Unlike normal volunteers, there are no limits placed on medically indicated radiation exposures. Because patients will be selected from those already on clinical protocols at the Clinical Center and often receive many CT exams over the course of their treatment at NIH, the research radiation from the PCCT is likely to be only a small contribution to each patient's overall radiation dose.

In order to mitigate any risk, the volume scanned for the experimental PCCT exposure will be reduced compared to the standard detector CT, if possible, in order to reduce the exposure and radiation dose. Only one PCCT scan will be performed. Patients may not have more than one PCCT scan over a one-year period.

Since the study involves research radiation exposure, women of child-bearing age who may be pregnant will undergo blood or urine pregnancy testing. This may not always be the case for medically indicated CT scans, particularly if the body part is far from the pelvis.

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Possible Benefits:
The subject will undergo the clinically indicated CT scan as part of participation in this study. Those exams will be submitted for interpretation by a board certified and NIH CC credentialed RAD&IS physician and reports of findings will be managed according to standard practices for diagnostic imaging studies within RAD&IS.

The PCCT detector scan is unlikely to add additional diagnostic information with direct benefit to study subjects. The major expected benefit is to society, future patients, industry partners and the academic/scientific community as the result of the development and characterization of this new imaging technology. In particular, compared to current scanners, this new technology offers four major benefits to patients and medical imaging:

- lower radiation dose to patients;
- greater spatial resolution (the ability to distinguish between adjacent structures in the body);
- reduced imaging noise (image degradation due to variations in x-ray detection); and,
- advanced imaging applications based on the measured x-ray energies.

9.5. Risks/Benefits Analysis

The level of risk to the research participants is considered to be greater than minimal risk (45 CFR 46 102) without prospect of direct benefit. The primary expected benefit is to the public as a result of improved imaging techniques. There is no expectation of early detection of new or unknown disease process as an incidental finding with the use of PCCT.

9.6. Non-significant Risk Determination

According to 21 CFR 812.3 (m) and FDA “Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors: Significant Risk and Nonsignificant Risk and Nonsignificant Risk Medical Device Studies January 2006 (accessible at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf), the use of the Siemens CounT scanner is considered to be a Non-significant Risk medical device study which does not require an IDE application approved by the FDA. Specifically, 21 CFR 812.3(m) enumerates four criteria for a significant risk device; none of these apply to this device.

1. This device is not intended as an implant
2. This device is not purported or represented to be for use supporting or sustaining human life.
3. While it is for “a use of substantial importance in diagnosing … disease,” it does not “present a potential for serious risk to the health, safety, or welfare of a subject.” Specifically, as part of the imaging to be conducted under this proposal, the patient will receive a CT scan with the standard x-ray tube-detector pair similar to that which would be acquired on one of the Siemens SOMATOM Force CT scanners in clinical use in RAD&IS, thereby providing standard diagnostic imaging information. The use of the photon counting CT component has the potential to add additional and unique diagnostic information. The primary consideration would be the radiation dose for the patient. However, as we previously reported, the radiation dose from PCCT is comparable to or may be less than that for a standard scan. The radiation doses will be reviewed and approved by the NIH RSC prior to study commencement.
4. The device does not otherwise present a potential for serious risk to the health, safety, or welfare of a subject.

The protocol will comply with the abbreviated IDE requirements under 21 CFR 812.2(b), available at:
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=812.2

In accordance with Sec. 812.5 Labeling of investigational devices, the device is clearly labeled with the statement: "CAUTION--Investigational device. Limited by Federal (or United States) law to investigational use." and with the name and place of business of the manufacturer (Appendix C).

9.7. Informed Consent Process and Procedures

For outpatients:

- When feasible, patients will be approached in the clinic at an earlier visit. If the patient felt they had all questions answered they could provide informed consent at that time. This may be up to one month before the scheduled scan. In that case, when they come for the scan they will be verbally asked to confirm they are still willing to participate and answer any additional questions. The research team will confirm that a properly executed informed consent document is on file prior to performing the research scan.
- If we are not able to obtain consent in the clinic, we will contact patients by phone

and or email close to the scan date (within one month) and send them information about the scan along with the informed consent for their review in advance of their scan appointment. Along with the email we will provide a phone number for contact and schedule a phone call with a research team member to answer questions beforehand or meet with a research team member the day of the scan to answer any questions. If all questions are answered and they agree to participate, they will be permitted to sign the consent ahead of time and mail the consent to us or provide the informed consent when they arrive for the scan. If they consent ahead of the scan date, they would be interviewed before the scan to be sure they still want to participate. If the consent is mailed in ahead of time, the research team will confirm that a properly executed informed consent document is on file prior to performing the research scan.

For inpatients:

- They will be identified from the CT scanner schedule and the PI will be made aware of the study and asked if it is appropriate to enroll the participant. If the PI is agreeable, the patient will be approached the day before the scan and consent obtained in their room. They will be given time to consider the protocol and have questions answered. If they want to think about the protocol that day/evening and wait until the following day to ask additional questions and consent at that time, they will be provided the opportunity do so in Radiology when they come for their scan. The patients we would invite to participate will not be those who need urgent CT scans or are admitted for unexpected events/complications. Typically, these will only be patients who are here for routine evaluations such as cancer staging or natural history studies which include CT scans.

In Radiology, there is a private room just outside the CT scan waiting area that is used for consenting patients.

Each subject will receive an oral and written explanation of the purposes, procedures, and risks of this study in language appropriate for the individual's level of understanding. A copy of the signed consent form will be placed in the medical record.

We do not plan or anticipate the enrollment of non-English speaking subjects; however, they are not excluded from participation. Should we enroll a non-English speaking subject, we request IRB approval to use the short form consent processes as outlined in SOP 12 up to three times for each language before a full translation is required. The IRB will be notified at each continuing review the number of short form consents uses by language.

The following investigators are authorized to obtain informed consent from the study subjects and are marked with an asterisk (*) on page 1 of the protocol:

- Elizabeth Jones, M.D.
- Brad Wood, M.D.
- Marcus Chen, M.D.
- Mark Ahlman, M.D.
- Tracy L Cropper, R.N

- Charisse Garcia, RN, BSN, CCRP
- Caroline (Carole) Webb, RN, MSN, CCRP, CCRC

All employees/staff supervised by the Principal Investigator or an Associate Investigator are excluded from participation. If an NIH employee or staff member plans to enroll in the study and the individual obtaining consent is a nonsupervisory co-worker, the consent process will be independently monitored in accordance with the procedures outlined in SOP 14F.

10. Conflict of Interest

The PI assured that each AI listed on the protocol title page received a copy of the NIH's Guide to preventing conflict of interest. The National Institutes of Health reviews NIH staff researchers at least yearly for conflicts of interest. The following link contains details on this process https://ethics.od.nih.gov/forms/Protocol-Review-Guide.pdf. Neither the PI nor any AI has any potential conflict of interest to report.

11. Compensation

Patients will not receive monetary compensation. Upon enrollment, participants will already have clinical indications for conventional CT exam(s) as ordered by their NIH physicians. With informed consent, photon-counting CT scans of the same body regions of interest will immediately follow the regular CT scan on the same scanner.

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