1) Protocol Title

Title: EXPLORER PET/CT: A Pilot Evaluation in Healthy Volunteers

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2) Objectives

The objective of this pilot study is to collect preliminary data using total body scans on a new, first of its kind, FDA 510k-cleared positron emission tomography/computed tomography (PET/CT) scanner, called EXPLORER. Built by United Imaging Healthcare (UIH)[1] in collaboration with investigators at UC Davis, EXPLORER has the potential to significantly alter the practice of PET/CT[2,3]. This initial pilot study will have the following broad objectives:

Objective 1: To obtain preliminary data on (a) delayed, (b) low-dose and (c) total body dynamic acquisitions on the EXPLORER PET/CT scanner.

Objective 2: (d) To obtain preliminary data regarding possible impacts on ^{18}F fluorodeoxyglucose (FDG) PET image quantification related to use of intravenous iodinated contrast agent with the EXPLORER PET/CT scanner.

3) Background

The 194 cm long EXPLORER total-body PET scanner is the world's first device to offer the ability to tomographically image all parts of the body simultaneously. It has the potential for a signal sensitivity gain of ~40-fold compared to existing commercially available devices for total-body applications. Spatial resolution is also comparable to or better than all other commercially available clinical devices available today.[2-4] Answering the basic questions that this new equipment poses constitutes an important advancement for both clinical and academic settings.

(A) The distribution of radiotracer activity depends on post-injection imaging time for both anatomical structure and pathologic processes. Different anatomic structures and different pathologic abnormalities are characterized by different time-activity curves.[5] However, delayed imaging results in lower signal due to radioactive decay and physiological washout, which has so far limited the evaluation of late time-to-activity curves due to the low sensitivity of conventional scanners[6]. The increased sensitivity of EXPLORER has the potential to overcome this limitation and allow for high-quality delayed scans.[7] We seek to obtain preliminary data regarding the time-course of the most commonly-used PET radiotracer ^{18}F fluorodeoxyglucose (FDG) concentration in tissues over a twelve-hour period. In addition, for precise characterization of FDG clearance through the urinary system we will assess radiotracer activity in urine collected from

subjects. Assessment of excreted FDG will increase the precision of estimated SUV values. For analysis of small structures in the brain, we will use MRI to guide region of interest placement - this has been standard practice in multiple studies for the last 25 years[8].

(B) EXPLORER PET/CT allows for the possibility of very low-dose imaging. [7] This is clinically important for pediatric patients who may have multiple scans and are more impacted by the stochastic effects of radiation than the adult population.[9] It is also important for research, where the subjects receive no benefit from the radiation exposure associated with the scan. However, we do not have information on the statistical quality of low-dose scans with EXPLORER and this information is essential for power calculations for future studies.

(C) EXPLORER whole body PET/CT is the only scanner in the world capable of acquiring total body dynamic images. Acquisition of dynamic images will allow new applications such as organ perfusion imaging.[7] Available PET/CT scanners can obtain perfusion images only on a portion of the body as large as their axial field of view, generally anywhere between 15-30 cm. EXPLORER can cover the total body and provide useful perfusion data in addition to early FDG biodistribution data and other functional parameters. We seek to obtain preliminary data regarding perfusion and early biodistribution images; this will be vitally important for the design of future studies.

(D) Intravenous iodinated contrast is commonly used in routine CT to increase the visualization of both anatomic and pathologic processes. Physically, the presence of iodine atoms increases the attenuation coefficient for CT radiation of the tissues in which it distributes by increasing the cross-section for photoelectric interactions. Applying attenuation correction algorithms for PET using contrast CT images has the potential to overcorrect the PET emission signal (which is much less susceptible to photoelectric interactions), introducing possibly significant errors in the final uptake quantification. While several studies have demonstrated that there is no statistically significant increase in uptake values upon injection of iodinated contrast when normal anatomic structures are assessed, at the present time, there is no study validating the use of contrast enhanced CT for attenuation correction purposes on the EXPLORER PET/CT scanner. We seek to obtain preliminary data to understand the impact of intravenous iodinated contrast agent on quantification of PET images.

REFERENCES

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4) Inclusion and Exclusion Criteria

Inclusion criteria:

- Men and women, 18 years of age or older
- Willing and able to fast for at least 6 hours before and for the duration of the scan
- Willing to provide urine sample throughout scan visit
- Willing and able to lay motionless in a supine position for 60 and 20 minutes at separate timepoints.
- Willing and able to give informed consent, personal contact information (phone number, email and postal address), insurance information, and primary care physician contact.

Exclusion criteria:

- No Primary Care Physician
- No health insurance
- Body weight more than 240 kg (529 pounds)
- Allergy to iodine contrast (only for subjects enrolled in Arm 3)
- Creatinine levels > 1.5 mg/dL or estimated glomerular filtration rate (eGFR) < 60 ml/minute (only for subjects enrolled in Arm 3)
- Recent (within 90 days) contrast enhanced CT (only for subjects enrolled in Arm 3)
- Any known concomitant acute infection (including upper respiratory infection, genitourinary infections, etc.
- History of metastatic or newly (last 5 years) diagnosed locally invasive cancer.
- Chemotherapy in the last 5 years
- Radiation therapy in the last 3 years
- Major surgery within the last 6 months.
- Pregnancy or breast-feeding
- Diabetes
- Fasting blood glucose level > 160 mg/dL before administration of FDG
- Prisoners
- The standard MRI contraindications will be applied, according to UC Davis Department of Radiology Magnetic Resonance Safety Policy ID 1727, which may include:
    - Having a pacemaker or other implanted electronic device,
    - Metal foreign bodies, aneurysm clips, heart valve prosthesis, vascular stents, cochlear implants, embolization coils, gunshot wounds with retained bullet fragments, certain types of penile implants, and certain types of intrauterine devices (IUDs).
    - Claustrophobia

5) Study Timelines

- Subject participation: Each subject will participate in a single arm of this three-arm study (please see below), for up to approximately 13 hours during a single study visit (Study Arm 1), 4 hours for Study Arm 2 and 2 hours for Study Arm 3.
- Enrollment duration: We anticipate completing enrollment within 8 months.
- Primary data analysis duration: We anticipate completing primary data analysis within 12 months.

6) Study Endpoints: all study endpoints are exploratory

A. To collect preliminary data regarding FDG biodistribution as a function of time

Population: Study Arm 1

Explanation: Changes are measured quantitatively from time-activity curves (TACs) generated for different organs using regions of interest (ROIs).

B. To obtain preliminary data regarding low dose EXPLORER protocols

Population: Study Arm 2

Explanation: Regions of interest (ROI) will be placed in several organs; pixel intensity and coefficient of variation within ROI will be recorded.

C. To collect preliminary data about total body FDG perfusion and early biodistribution .

Population: Study Arms 1-3

Explanation: Total body EXPLORER PET images will be obtained for the first 60 minutes following injection. Organ perfusion and early FDG biodistribution will be evaluated with time-activity curves and mathematical analysis generated for different organs using regions of interest (ROIs).

D. To obtain preliminary data to understand whether intravenous iodinated contrast agent produce a significant change in quantification of FDG uptake levels.

Population: Study Arm 3

Explanation: Regions of interest will be placed in several organs; pixel intensities within ROI will be recorded. Data reconstructed using contrast-

enhanced CT for attenuation correction will be compared to data reconstructed using non-contrast enhanced CT for attenuation correction.

7) Procedures Involved

Subject recruitment:

Up to 15 subjects per arm (please see below) will be recruited by means of a flyer posted in specific areas: the Division of Nuclear Medicine (Davis Tower, Ambulatory Care Center (ACC)), the UC Davis Explorer Molecular Imaging Center located at 3195 Folsom Blvd, Sacramento, CA, the research laboratories of Dr. John Boone and Dr. Ramsey Badawi (ACC Suite 0505), the Radiology Academic office (ACC, Suite 3100), and the research laboratories of Dr. Simon Cherry and Dr. Jinyi Qi (Main campus, GBSF). In addition, flyers will be posted in other academic offices at ACC including cardiology, ophthalmology, orthopedics, etc. Additionally, the study will be announced on the EXPLORER website: https://explorer.ucdavis.edu/

Study procedures:

At the time of the consenting and screening visit, a study-specific Inclusion/Exclusion source document will be used to determinate eligibility for this study after obtaining informed consent. The consenting and screening visit will occur at either the ACC Building Suite 3100, in the Main Hospital Nuclear Medicine Department or at EXPLORER Molecular Imaging Center (3195 Folsom Boulevard, Sacramento) not earlier than 4 weeks before the imaging visit. Study participants will be screened for eligibility at the time of the consenting and screening visit after signing the consent form. The subject can be enrolled in only one Arm; the participant can choose which Arm of the study he or she wants to be enrolled in until the recruitment for the specific Arm is completed. For participants enrolled in Arm 3, if recent (within 1 month)[10] serum creatinine and/or GFR results are not available, an order will be placed for participants to go to a UC Davis Health lab for this testing, at no charge to them prior to the imaging visit. For the subject for whom the screening requires renal function tests, the doctor will receive notification of test results through the EMR system directly from the UC Davis Health lab. The doctor will review the results (in the subjects to whom any of these tests apply) and will report on the screening form the results and will state eligibility of the subject for the study.

Participants will be asked to fast for 6 hours prior to arriving at the EXPLORER Molecular Imaging Center (3195 Folsom Blvd, Sacramento) on the day of their PET imaging study visit. A technologist will screen the participants to evaluate their readiness for PET scanning using the standard UC Davis Radiology approved form. A urine pregnancy test will be administered to all women of child-bearing potential, at no charge. Blood glucose level will be tested using the standard

fingerstick method by standard operating procedures, at no charge. Following this, an intravenous (IV) line will be placed in the forearm by the study PET/CT technologist or study physician and the participant will be positioned supine on the scanner table. From the time of injection with FDG we will collect urine from all subjects until the scan visit at EXPLORER is complete. Subjects will be asked to urinate into a portable unisex urinal. After the total amount of excreted FDG is assessed and recorded, we will dispose of the urine sample. We will also ask all subjects if they had a bowel movement from the time they are injected with FDG until they complete their scan(s).

Arm 1 (N=15; delayed imaging acquisition):

For Study Arm 1, 10 +/-2 mCi of ^{18}F fluorodeoxyglucose (FDG) will be hand injected through the IV and a 60-minute dynamic scan will begin on EXPLORER. The IV line will be removed after dynamic acquisition. The dynamic scan will be preceded by ultra low-dose (estimated dose of 1.298 mSv) CT scan. This CT scan will provide information for attenuation correction for the PET data. At 90 minutes, 3-, 6-, 9- and 12-hours, a static whole-body scan for 20 minutes will be acquired on EXPLORER. Prior to the 90-minute scan a low-dose CT (estimated dose of 7.44 mSv) will be obtained both for anatomic localization and for attenuation correction purposes. Prior to each of the later time-points (3-, 6-, 9- and 12-hours), an ultra low-dose (estimated dose of 1.298 mSv) CT scan will be acquired. This scan will be for attenuation correction purposes only. Following the 12-hour scan, the participant's study visit will be completed. Participants will be monitored for adverse reactions related to prolonged fasting (e.g. hypoglycemia) between scanning sessions. In addition, low carbohydrate snacks will be available following the 3-hour scan.

Arm 2 (N=15; low FDG dose imaging):

For Study Arm 2, 0.5 +/- 0.1 mCi of ^{18}F-FDG (1/20th of the standard dose) will be hand injected through the IV and a 60-minute dynamic scan will begin on EXPLORER. The dynamic scan will be preceded by an ultra-low-dose CT scan (estimated dose of 1.298 mSv) for attenuation correction. The standard 20-minute EXPLORER scan obtained at 90 minutes will be obtained after a low dose CT (estimated dose of 7.44 mSv) for attenuation and co-localization. The standard 20-

minute EXPLORER scan obtained at 3 hours will be preceded by an ultra-low-dose CT scan (estimated dose of 1.298 mSv) for attenuation correction only.

Arm 3 (N=15; comparison PET images reconstructed using CT-based attenuation correction acquired with and without iodinated contrast enhancement):

For Study Arm 3, 10 +/-2 mCi of ^{18}F-FDG will be hand injected through the IV and a 60-minute dynamic scan will begin on EXPLORER. Prior to the dynamic scan, an ultra-low-dose CT scan (estimated dose of 1.298 mSv) will be acquired for attenuation correction purposes only. At 90 mins, a low dose non contrast enhancement CT (estimated dose of 7.44 mSv) will be acquired vertex to toes. Iodinated contrast (150 cc of iodine Omnipaque 350) will then be intravenously injected (through the same IV placed to inject FDG) at 3 ml/sec while the patient remains still on the scanner and a second low-dose CT will be acquired. Finally, a 20-minute PET acquisition will be performed. The IV line will be removed after completion of the study.

Patients on all arms

All patients will undergo a brain MRI scan (without contrast), within 90 days of the PET/CT visits. The rationale for the MRI study is to provide a detailed anatomical map, which is not obtainable by CT.[8] MRI will be acquired using head coil on one of the clinical FDA-approved MRI scanners at UC Davis Medical Center. Several gradient echo, spin echo and fast spin echo sequences will be obtained.

The PET/CT images created for this study are for research and are not meant to evaluate subject health, as they would be if they were part of a clinical (non-research) visit to the doctor or hospital. The images will not receive any routine clinical review by radiologists who interpret PET/CT scans. This means that some findings may be overlooked or misinterpreted. However, if the PET/CT technologists do notice findings that cause concern, they will notify the Study Radiologist. Additionally, if a member of the research team notices any findings that cause concern while conducting image review for study purposes, they will notify the Study Radiologist. The Study Radiologist will conduct a brief review of part of the study images for quality purposes. If the Study Radiologist thinks a clinical problem is present, one of the IRB-approved study physicians will discuss these possible problems with the subject within 8 weeks or immediately upon recognition of any critical finding that requires immediate and/or urgent intervention as described in the Department of Radiology Critical Findings policy (full dataset of images are sometimes not available for review in less than 3 days). Upon written request, we will provide the subject with a copy of a subset of their CT images to take to the physician of their choosing. A subset of PET images may also be shared with the subject unless the images from the study are clinically

uninterpretable. In addition, the sponsor may restrict sharing of PET images due to the nature of the research protocol or to protect intellectual property (e.g. proprietary radiotracers). We will send a standard letter to the designated licensed medical provider identified by the subject along with a copy of the subject's radiology report. The standard letter will state that (i) the subject's images were acquired exclusively for a research study and incidental findings that may be related to a medical condition were observed by a UC Davis radiologist; (ii) the images did not receive any dedicated routine clinical review and findings may have been overlooked or misinterpreted; (iii) the subject's physician can contact the study doctor at any time if there are any concerns regarding the study or the subject's findings. In addition, Dr. Lorenzo Nardo or a designee will contact the research subjects and ask what type of medical follow-up, if any, they received. They will also ask questions related to subject's history of cancer, history of respiratory disease, and cigarette smoking history.

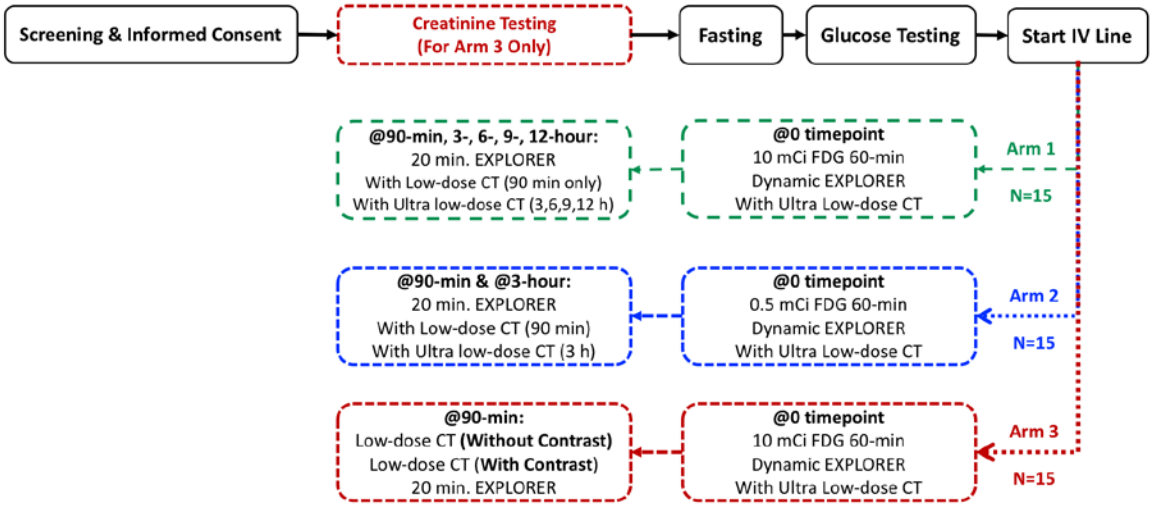
If there are findings on any of the scans that can deem the subject as not meeting the inclusion/exclusion criteria (e.g. metastatic disease, marked claustrophobia leading to incomplete scans. etc), this event will be reported and the subject will be excluded from the study. An additional participant will be added to meet the recruitment target of that specific arm.

Participants will be compensated with gift cards at a rate of $25 (upon enrollment and radiotracer injection), plus an additional $25 for each hour of participation as follows:

- *Arm 1: up to 13 hours + Brain MRI scan: 1 hour ($25); total of $375*
- *Arm 2: up to 4 hours + Brain MRI scan: 1 hour ($25); total of $150*
- *Arm 3: up to 2 hours + Brain MRI scan: 1 hour ($25) + $50 for creatinine testing; total of $150*

There is no compensation associated with initial consenting and screening visit and also with the optional visit(s) intended to discuss scan findings with study doctors.

Study Schema:



Data analysis plan:

Image reconstruction and analysis: Data from EXPLORER (all the three study arms) will be acquired in listmode. Data will be reconstructed using manufacturer's recommendations. Image quality, quantitative comparisons and preliminary biodistribution data collection will be performed by means of regions of interest (ROIs) drawn in different organs and tissue types where pixel intensity and coefficient of variation within ROIs will be computed and recorded.

Statistical considerations:

Since this is a pilot exploratory study on a first-of-its kind scanner, no formal power analysis is presented.

Exploratory data analysis will be conducted to examine the distribution of the data. Graphical methods including box-plots and histograms will be employed to examine the distributions of the measures. For all continuous variables, descriptive statistics, including means, ranges, and standard deviations will be computed. Ninety-five percent confidence intervals will be computed for means and proportions to obtain interval estimates of all measurements across image. For categorical data, frequency, proportions, and percentages will be calculated.

8) Data and/or Specimen Management and Confidentiality

At the time of data acquisition, identifiable information will be entered in the UC Davis system database. Electronic image files, radiation dose reports and pertinent medical information will be stored on the EXPLORER research cluster at

3195 Folsom Blvd (UC Davis facility), on dedicated encrypted password-protected hard disks and workstations at UC Davis, which project staff may access; in addition, electronic image files, radiation dose reports and pertinent medical information will be stored on the UC Davis radiology department PACS system, Radimetrics dose reporting system and Electronic Medical Record. These files will contain the patient identifiers. When this data is transferred for analysis to any other computer/device, it will be anonymized. We will assign participants a unique subject/code number that will be used to identify them in our database. Our data will be in the form of anonymized images and coded medical records reported in an Excel spreadsheet and images in electronic format. The Excel spreadsheet and the images containing the subjects coded medical records will be stored in a encrypted password-protected device. We will keep the code key containing subject names/medical record numbers and corresponding subject code numbers in a secured location separate from the data. Only study team will have access to the data. Requests to use the data will be reviewed by the PI, if approved, PI will provide only de-identified data. Quality control will include regular data verification and protocol compliance checks by the PI and the study coordinator. The PI will complete annual reports to the UC Davis IRB detailing the study progress and enrollment status.

9) Data and/or Specimen Banking

All the imaging data will be banked indefinitely for future use. Data will be saved on the EXPLORER research cluster at 3195 Folsom Boulevard and/or on dedicated encrypted password-protected hard disks and workstations at UC Davis with access limited to authorized personnel. in addition, electronic image files, radiation dose reports and pertinent medical information will be stored on the UC Davis radiology department PACS system and Electronic Medical Record. A radiation dose report will be generated. This will be part of the banked data and will contain Protected Health Information. It will be sent to Radimetrics system, which is a mandated tracking system for lifetime radiation dose.

Future use of banked data may include improved image analysis, use as a normal atlas/comparator, and use for other research purposes.

In addition, investigators from other entities may contact the study team with requests to use banked data. Anonymous data may be shared with other entities if appropriate data use agreements are in place (e.g., DTA and UC reliance) and if approved by the investigators in charge of this study.

Biological specimens (blood sample) are used only for screening purposes. Urine samples will be used for screening purposes and to assess radiotracer activity

during scanning. After the results are recorded the biological specimens will be discarded.

10) Provisions to Monitor the Data to Ensure the Safety of Subjects

Throughout the study, study personnel will consult with the UC Davis Health Radiation Safety Officer and the local IRB regarding the monitoring and reporting of adverse events and follow their recommendations. Protocol changes involving the radiation dose will first receive approvals from Radiation Use Committee prior to submitting a modification request to the IRB.

Participants will be informed about the study risks including risks related to iodine contrast media administration (Arm 3 only) during the initial consenting and screening visit. In case a contrast reaction occurs, it will be handled per departmental standard operating procedure.

Protocol changes will not be implemented prior to UC Davis IRB approval unless necessary to eliminate apparent immediate hazards to the research subjects.

If any incidental finding will be detected, they will be managed as described above in section "Procedures Involved" of this protocol.

Data safety monitoring

After acquisition of data, we will assign participants a unique subject/code number that we will use to identify them in the database used for processing, analysis, or publications. Our coded data will be in the form of elements of medical records recorded in an Excel spreadsheet saved in a encrypted password-protected device. Electronic image files, which may contain PHI, will be stored on the EXPLORER research cluster at 3195 Folsom Boulevard and/or on dedicated encrypted password-protected hard disks and workstations at UC Davis. In addition, electronic image files, radiation dose reports and pertinent medical information will be stored on the UC Davis radiology department PACS system the Radimetrics dose reporting system and the Electronic Medical Record. Quality control will include regular data verification and protocol compliance checks by the PI and the study coordinator. The PI will submit annual reports to the UC Davis IRB detailing the study progress and enrollment status.

Breach of confidentiality

Confidentiality will be protected through periodic assessment, as new study materials and communication methods among project staff develop. The PI will

report any confidentiality breaches to the IRB using the standard Reportable New Information form.

11) Withdrawal of Subjects

Subjects will be withdrawn from the study without their consent if:

- they do not follow the study rules or they no longer meet the requirements to be in the study; or
- the study is stopped by the sponsor or researchers.
- the investigators feel it is in the participants best interest to discontinue participation. Such circumstances may include unanticipated discomfort and/or fatigue from laying on the scanner table, and feelings of claustrophobia from being inside the scanner bore.

12) Risks to Subjects

Risks to subjects may include:

- Discomfort and/or fatigue from laying on the scanner table
- Claustrophobic symptoms
- Bruising and/or infection at the IV site
- Radiation Risks: This study involves a radiation exposure that is typical of other diagnostic tests using ionizing radiation. The amount of radiation exposure received in this study is below the levels that are thought to result in a significant risk of harmful effects.
- It is possible that EXPLORER PET/CT may detect false positive findings that may require further follow-up (clinical, imaging or surgical) with all the risks associated with these follow-up procedures. These risks range from minor risks to severe risks including death and permanent diasabilities.
- Hypoglycemia from prolonged fasting.

Iodine contrast administration related risks (only for Arm 3):

Minor/Common risks:

- Bruising and/or infection at IV site
- Nausea & vomiting
- Urticaria (hives)
- Pruritis (itching)
- Diaphoresis (sweating)

Moderate/Uncommon risks

- Faintness
- Facial edema (swelling)

- Laryngeal edema (swelling of the airway in the throat)
- Bronchospasm (tightening of the airways in the chest)

Severe/Rare risks

- Pulmonary edema (fluid in the lungs)
- Respiratory arrest (loss of breathing)
- Cardiac arrest (loss of heartbeat)
- Seizures
- Death or permanent disabilities

13) Potential Benefits to Subjects

In general, we expect there to be no benefit to the subject If any incidental finding will be detected, they will be managed as described above in section "Procedures Involved" of this protocol.

14) Multi-Site Research

This study does not involve multiple sites. Please note that EXPLORER Molecular Imaging Center at 3195 Folsom Blvd, Sacramento, CA is a UC Davis facility which is entirely administrated by UC Davis employees.

15) Community-Based Participatory Research

This study does not involve community-based participatory research.

16) Sharing of Results with Subjects

The results of this research will not be shared with subjects. However, if any incidental finding will be detected, they will be managed as described above in section "Procedures Involved" of this protocol.

17) Prior Approvals

This study has been approved by the UC Davis Health Radiation Use Committee.

18) Provisions to Protect the Privacy Interests of Subjects

The investigator obtaining consent will meet with the candidate in a private setting and will dedicate sufficient time to explain the study procedures and answer any questions. It will be explained that participation is strictly voluntary and declining to participate will not affect them in any way. A HIPAA disclosure form will be signed by the subject to allow access to their medical records.

19) Compensation for Research-Related Injury

If a subject is injured as a result of being in this study, the University of California will provide the necessary medical treatment. Depending on the circumstances, the costs of the treatment may be covered by the University or the study sponsor or may be billed to the subject's insurance company just like other medical costs. The

University and the study sponsor do not normally provide any other form of compensation for injury. For more information about compensation, the subject may contact the IRB Administration at (916) 703-9151 or HS-IRBAdmin@ucdavis.edu

20) Economic Burden to Subjects

Subjects will not be charged for their participation. In case of abnormal or unclear findings, the subject may decide in agreement with his/her Primary Care Physician to further investigate and the cost of this will be borne by the subject and/or his/her insurance.

21) Drugs or Devices

No investigational drugs or devices are involved.

☐ I confirm that all investigational drugs will be received by the Investigational Drug Service (IDS). The IDS will store, handle, and administer those drugs so that they will be used only on subjects and be used only by authorized investigators.

☐ I confirm that all investigational devices will be labelled in accordance with FDA regulations and stored and dispensed in such a manner that they will be used only on subjects and be used only by authorized investigators.

22) Review Requirements

Are there any contractual obligations or other considerations that require IRB review of this research, or review at intervals other than those required by the Common Rule or FDA? If yes, check box:

☐ Yes

☒ No