Protocol Title: Validating Low FDG Dose PET/CT compared to current Standard of Care Dose PET/CT

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Principal Investigators:

Michael V. Knopp, MD, PhD
Vice Chairman and Professor, Department of Radiology
Novartis Chair of Imaging Research
The Ohio State University
395 West 12th Avenue, Room 430
Columbus, Ohio 43210
Phone: (614) 293-9998
Fax: (614) 293-9275
E-Mail: knopp.16@osu.edu

Jun Zhang, PhD, DABR
Assistant Professor of Radiology
Diagnostic Medical Physicist
395 West 12th Avenue, Room 412
Columbus, Ohio 43210
Phone: (614) 293-9998
Fax: (614) 293-9275
E-Mail: zhang.538@osu.edu

I. Overview

Positron Emission Tomography/Computed Tomography (PET/CT) imaging using ^{18}F-FDG is an important, commonly used cancer, neuroscience and cardio-vascular imaging methodology to detect disease and to monitor therapeutic interventions. While considerable technological progress of PET/CT systems has occurred over the last decade, we have not re-evaluated the ability to potentially reduce the radiation burden of the used PET imaging pharmaceutical (FDG).

This early phase trial intends to accomplish the following:

- to validate that the radiation dose burden from the PET imaging pharmaceutical (FDG) can be reduced by more than 50% from the current standard of clinical care (SOC) level without affecting the diagnostic ability;
- to confirm that a low dose approach will be feasible for response assessment;
- to validate that the difference in FDG uptake between imaging 60 min +/- 10 min post injection and 75 min +/- 10 min post injection is independent/equivalent of the injected FDG dose
- to validate a simulation methodology to streamline future dose finding studies for PET imaging pharmaceuticals.

II. Objectives

Aim 1: To validate equivalency of low dose FDG PET/CT (185 MBq [5 mCi]) compared to current standard of care FDG PET/CT dosing (481 MBq [13 mCi]).

Aim 2: To validate that the difference in FDG uptake between imaging 60 min post injection and 75 min post injection is independent/equivalent of the injected FDG dose

Aim 3: To validate equivalency of simulated FDG dose PET/CT images to effective dose reduced FDG PET/CT images

This trial seeks to finally establish in a Phase 1, single institution prospective clinical evaluation one of the key opportunities relevant to all FDG PET clinical trials and patient care examinations: Can we reliably reduce the radioactive imaging pharmaceutical (FDG) induced radiation dose for PET patient imaging by more than 50% with today's PET/CT systems, and what are the differences between a 60 min post injection and a 75 min post injection scan?

Radiotracer dose recommendations have remained unchanged despite many technological advancements, and while best practice recommendations suggest imaging 60 min of uptake time prior to whole body imaging, the current standard of care practice has been moving to longer uptake times of 75 to 90 min time post injection.

When PET images are acquired in list mode, images can be reconstructed with simulated lower PET annihilation event rates, thereby creating simulated dose equivalent images. While this approach could serve as an efficient way to help in the dose-response optimization for PET imaging agents, an equivalency has not yet been validated a clinical patient setting.

III. Background and Rationale

PET/CT imaging with ^{18}F-FDG has become an essential non-invasive tool to detect cancer, neurodegenerative, neurometabolic and cardio-vascular disease and help in the therapeutic management of many diseases. We currently perform in the US an estimated 2 million PET/CT procedures a year in more than 2,300 locations.

In 2006, the NCI Cancer Imaging Program published the current consensus recommendations for ^{18}F-FDG PET imaging [Shankar JNM 2006] which has been the foundation for its use in therapeutic response assessment trials. The workshop recommendations summarized that ^{18}F-FDG doses of 370-740 MBq (10-

20 mCi) are appropriate, but they noted, however, that no standard dose has been recommended. In another NCI effort, the Imaging Response Assessment Team (IRAT) reviewed the variations in PET/CT methodology in US academic medical centers and published their findings in 2011, in which they highlighted that the major areas of variation were in the ^{18}F-FDG doses (259–740 MBq [7–20 mCi]) and in the uptake time (45–90 min) post-injection [Graham JNM 2011].

This project team has been serving as imaging core laboratory for pharmaceutical and national cooperative network groups, the CALGB/ALLIANCE since 2004 and for the SWOG NCI network group as of 2012 and has been also a performing site for the NIH ADNI multi-center trial. The team has constantly witnessed those variations in local practice that lead to many challenges, protocol deviations, and potentially higher than necessary radiation exposure from the radiotracer dosing. The Graham paper also highlighted that European dose recommendations are generally lower with approaches as low as (185 MBq [5 mCi]) for 3D acquisition in a 70 kg patient. Despite the increasing desire to reduce unnecessary medical imaging induced radiation exposure, no well-designed intra-individual crossover designed trial has been performed to generate the evidence and guiding methodological approach to resolve these issues using current state of the art PET/CT systems.

The guiding principal in radiation protection is as low as reasonably achievable (ALARA) [Hendee Sem Nucl Med 1986], but nevertheless objective evidence needs to be presented to change current standard of care practice policies or clinical trial recommendations for PET imaging pharmaceutical dosing.

Substantial research and advancements have been achieved to reduce the radiation burden from the associated CT attenuation scan, and rapid changes for the CT acquisition of the PET/CT imaging procedure are currently being implemented [Kinahan Phys Med Bio 2012].

While simulation approaches are available by segmenting list mode acquired image data to sub-samples, and while they use only PET events expected if a patient would have received a lower dose under the assumption that there is a linear physical and biological relationship in uptake at the relevant dose, this has never been systematically and prospectively validated.

Our goal is primarily to generate the evidence that ^{18}F-FDG PET imaging can be equivalently performed at a significant lower radioactive dose than what is currently a common US standard of care dosing at 481 MBq (13 mCi). Furthermore, we want to confirm that a change in FDG uptake that might be occurring within the 20 min window between the 60 min and 75 min p.i. whole body sweep is not impacted by reducing the dose. At the same time, we will gather important insight on the observed intra-individual uptake change occurring within that 20 min window [Beaulieu JNM 2003].

If we are able to generate this evidence, we will at a minimum facilitate that clinical trial protocols and patient care recommendations can be modified to support lower dosing, as well as having a validated simulation approach established to guide future validation trials.

Our multi-disciplinary team has extensive experience in performing prospective clinical trials and has a unique infrastructure available with access to four different current generation PET/CT systems from all three major manufacturers: Discovery PET/CT 610 (GE), Gemini 64 TOF Astonish PET/CT (Philips), Vereos 128 Digital PET/CT (Philips) and Biograph mCT 64 (Siemens). This is combined with a large comprehensive Medical Center and the James Comprehensive Cancer Center, both of which receive excellent patient participation in clinical trials.

We can summarize that we currently have substantial variation and lack of objective evidence in regard to the appropriateness to perform ^{18}F-FDG PET at lower doses than 370 MBq (10 mCi) and outside the currently recommended post injection / uptake time frame of 50 to 70 min. Furthermore, while simulations of dose reduction can be accomplished with segmented reconstruction of list mode acquired ^{18}F-FDG PET/CT scans, this methodology has also not been validated in a well-structured clinical trial.

If we are able to reduce the radiation exposure due to FDG from the current standard of care dose of 481 MBq (13 mCi) to 185 MBq (5 mCi), we will have effectively reduced the ionization dose from 9.6 mSv to 3.7 mSv per FDG PET exam, saving 5.9 mSv, which is equivalent to saving 14 month of natural radiation exposure living in the USA.

IV. Procedures

Research Design

This Phase I clinical trial is being utilized to demonstrate the feasibility of substantially lower radiation dose exposure in ^{18}F-FDG PET/CT that will be based on the intra-individual comparison of current standard of care clinical indication PET/CT using 481 MBq (13 mCi) ^{18}F-FDG with the reduced research dose of 185 MBq (5 mCi).

Patients who received a physician prescription/order to schedule an ^{18}F-FDG PET/CT at the Ohio State University Wexner Medical Center will be contacted if they would be willing to participate in this trial. On day one patients would receive their normal standard of care ^{18}F-FDG PET/CT, and on an additional visit, a PET/CT with a 60% reduced radiation dose. Furthermore, the patients would be asked if they would like to volunteer to have an additional whole body sweep acquired at 60 min +/- 10 min post injection to the current standard of care whole body sweep at 75 min +/- 10 min. The additional sweep is a PET-only acquisition, so there would be no additional radiation exposure. If patients opt out of this additional option, they will have only a single whole body sweep performed at 75 min +/- 10 min post injection, which is consistent with our clinical standard of care procedure.

Once participants have agreed and signed the informed consent, they would be randomized to determine if they would receive the standard of care dose or the lower investigational dose first. This crossover design is necessary to blind the patient and the technologist to be unbiased during the performance of the imaging, as motion artifacts, positioning, and other aspects can influence image quality to some extent.

With a half-life of ^{18}F of just under two hours (109 min), we will wait for ten half-life's (20 hours) before we perform the second scan session. At this time, the physical radioactivity will have decayed to less than 0.5%, which considering the additional biological elimination will be less than measureable. Out target is to perform the second scan between one to four days after the first, but the protocol will allow patients to participate if they have the second scan within no more than two weeks.

The standard of care examination will be used for clinical care, and the investigational examination will only be used for clinical research evaluations. Our trial protocol will ensure that we achieve a consistent blinding of the patient, scan performing technologist, and image assessor/reader.

After appropriate patient consent and preparation, we will randomize the order in which the patient will receive the Standard of Care PET/CT and the Low Dose PET/CT (i.e. Standard of Care PET/CT on day 1 and Low Dose PET/CT on day 2, or vice versa). If the patient has requested to opt out of the additional whole-body sweep, the patient will be imaged at both examination days at 75 min +/- 10 min post injection. Otherwise, the patient imaging will start with the voluntary whole-body sweep at 60 min +/- 10 min, followed by the standard of care whole-body sweep at 75 min +/- 10 min.

It is well established that the image quality in patients that are classified by the WHO Body Mass Index (BMI) criteria as => obese (BMI => 30) is reduced and that longer bed volume acquisition times improves image quality [JNM Tech 2014 Sanchez-Jurado]. We will therefore increase the otherwise constant acquisition time per bed volume from 90 s to 120 s in those patients for both dose levels.

Using segmented reconstruction, we will be able to down sample the acquisition to be simulated as a 90 s acquisition for overall consistency.

As we are using four different current technology PET/CT systems, we will perform 4 sub-studies that are otherwise fully equivalent.

Sub-Study A: 481 MBq (13 mCi) ^{18}F-FDG vs. 185 MBq (5 mCi) using Gemini Astonish PET/CT
Sub-Study B: 481 MBq (13 mCi) ^{18}F-FDG vs. 185 MBq (5 mCi) using Biograph mCT
Sub-Study C: 481 MBq (13 mCi) ^{18}F-FDG vs. 185 MBq (5 mCi) using Discovery PET/CT
Sub-Study D: 481 MBq (13 mCi) ^{18}F-FDG vs. 185 MBq (5 mCi) using Vereos 128 digital PET/CT

We are furthermore planning two additional sub-studies.

Current simulations indicate that we should be able to further reduce the FDG imaging pharmaceutical dose to an even lower level. We will determine that comparison level after completing of Sub-Study D. At this time we would assume that the clinical SOC dose would have been already reduced to 240.5 MBq (6.5 mCi), and we would then compare it to 92.5 MBq (2.5 mCi).

Sub-Study E: 241 MBq (6.5 mCi) ^{18}F-FDG vs. 93 MBq (2.5 mCi) using Vereos 128 digital PET/CT

We plan for the possibility that one of the three-Sub-Studies (A-B) would not demonstrate equivalency, and we would then perform a modified protocol in which the SOC dosing is compared to a lower and higher dose than originally tested.

Sub-Study F: 481 MBq (13 mCi) ^{18}F-FDG vs. tbd MBq using the system that did not show equivalency in Sub-Study A-C

Figure 1 charts the study protocol and randomization.

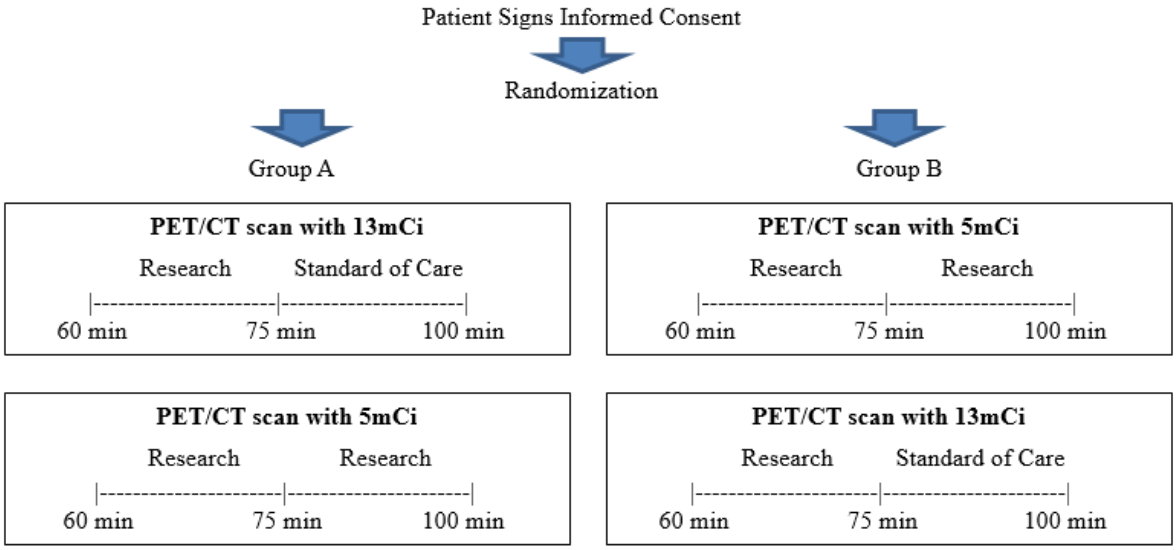

Figure 1: Flowchart of the protocol. After consent, the subject is randomized to the order of low and standard of care dose PET/CT. If the patient opts out of the second whole-body sweep, both exams will be performed at 75 min +/- 10 min p.i., otherwise the 1st sweep will be performed at 60 min +/- 10 min, followed by the 2nd at 75 min +/- 10 min.

Sample Size Considerations

The project statistician has calculated a required sample size of 33 evaluable subjects per imaging modality if we assess tracer uptake (FDG) using both a quantitative (SUVmax) and a visual quality assessment. Based on the literature and our preliminary work, we assume that the coefficient of variation (COV) is 12% and the equivalence limit is 10%. With a total sample size of 33 patients we will achieve 80% power in an equivalence test of means using two one-sided tests (TOST) on data from a two-period cross-over design, using an alpha level of 0.025 (0.05/2) after Bonferroni adjustment each system, respectively. We assume a drop-out rate of 10% (4 subjects) which leads to our target population of 37 enrolled subjects per unique sub-study.

Four imaging systems will be utilized in this study:

- Gemini TOF Astonish system from Philips Healthcare Cleveland
- Biograph mCT from Siemens Knoxville
- Discovery PET/CT from General Electric, Milwaukee
- Vereos 128 PET/CT from Philips Healthcare Cleveland (this is the first commercial digital PET detector system)

The subjects imaged at each of the four PET/CT systems will treated as its own sub-study. Each sub-study will follow the same imaging protocol.

We will evaluate four different state of the art PET/CT system in the above defined six sub-studies which then leads to the overall study population estimate of 204 subjects.

Participants in the research imaging will be predominately recruited from patients seen at the OSU Wexner Medical Center, including its outpatient facilities. Flyers will be available to patients that are seen in clinic offices typically referring patients for PET/CT examinations. This study will be published at clinicaltrials.gov. Potential participants will be identified by study team members at the time of the patient's standard of care imaging procedure. The patient population will include a variety of disease entities; therefore, enrollment will be monitored for relative distribution across disease categories, and the Principal Investigator's discretion will be utilized regarding the number of patients enrolled and their disease types in order to ensure a representative sample.

Randomization: Patients will be randomized in a 1:1 ratio to receive either standard of care FDG PET/CT dosing (481 MBq [13 mCi]) followed by the low dose FDG PET/CT (185 MBq [5 mCi]), or the low dose FDG PET/CT followed by the standard of care dosing using a randomized permuted block scheme in a blinded fashion. The block sizes will not be known to the investigator. No stratification factor will be included. We will, however, have the option of a randomization waiver if there are reasons that would otherwise delay patient care or prevent the patient from participating in the study.

Inclusion Criteria:

- Male and female patients greater than or equal to 18 years of age.
- Patients scheduled for a standard of care PET/CT scan.
- For female patients of child-bearing potential, the OSUWMC requirements for receiving the standard of care PET imaging agent and CT examination need to be met.

Since the patient will receive a standard of care scan as part of the protocol, we will follow the OSUWMC Imaging Services Departmental Policy and Procedure, which states that all females of child-bearing age (12-55 years old), will receive urine HCG pregnancy testing within seven days prior to imaging. While the policy also states that patients may refuse the testing by completing the pregnancy testing refusal form, we **will not** accept the form for this trial. All female patients of child-bearing age will be required to have the urine HCG test on the day of imaging or no more than 7 days prior to the imaging.

Exclusion Criteria:

- Participants who are pregnant or lactating.
- Prisoners.
- Participants incapable of giving informed consent.
- Patients unable to lie flat on the scanner for extended periods of time.

Measurement / Instrumentation

Our assessment approaches will be guided by recent community efforts established via the QIBA (RSNA) effort, PET recommendations (SNM), the QIN (NCI) and IROC (NCTN).

In this study, we will not evaluate the impact of the CT-based attenuation scan, as in recent years extensive efforts in CT dose reduction have also translated to substantially lower CT doses for attenuation scans, unless diagnostic read quality is needed to simultaneously replace an additional diagnostic CT scan. We will perform all CT-based attenuation scans at the lowest dose we established for our standard of care PET/CT protocol for each specific PET/CT system.

We currently have four different state of the art PET/CT systems within the OSU Wexner Medical Center. We therefore plan to perform this trial in four separate sub-studies, each being independent for each device, with everything else being standardized. With this unique ability to evaluate the dose and timing impact and to prove equivalency using four distinct platforms in parallel, we will achieve the most meaningful outcome and impact. This will allow us to achieve the desired changes of reducing radiation dose and enabling more flexibility in the imaging time post injection.

The imaging data will be assessed in a fully blinded fashion. Our primary endpoint will be the statistical confirmation that the SUV max measured in the regions of interest (ROI) in the target region will reveal a variation of less than 10%. The project statistician has calculated a required sample size of 37 evaluable subjects per sub-study (See section Statistical Considerations). We will treat each of the four PET/CT system as its own sub-study; however, we will perform each of the first four sub-studies identically other than the manufacturer system-induced differences.

For secondary assessments, we will determine by three independent, blinded readers the image quality for a diagnostic interpretation with a linear 10 cm scale from exceptional to unacceptable. We will use the same approach to assess the diagnostic confidence and occurrence of image artifacts and to allow for any additional comments desired. For the read assessment, each PET/CT exam will be individually assessed in a randomized order. Upon completion of this assessment and after a duration of several weeks, a matched pair assessment will be performed to assess equivalency during a side-by-side comparison using the same assessment scales. If those assessments confirm equivalency, we plan to add a full diagnostic read of each exam separately with blinded dosing information.

For this Phase I study, we believe that performing intra-individual comparisons on the same PET/CT system is the only way to get unconfounded, objective assessment of the equivalency of dose reduction. In case we would find difference between the four different PET/CT systems, different dose reduction schemes might be necessary.

While we cannot evaluate in this trial the equivalency for response assessment of therapy between the low dose and current standard of care dose, we do have at least the ability to evaluate that the difference in FDG uptake between the whole body sweep at 60 min +/- 10 min and 75 min +/- 10 min for the target regions is not impacted by dose. While this is our hypothesis we want to evaluate, we will at the same time gain insight into the intra-individual variability in FDG uptake within such a 15 min +/- 10 min window. The current guidelines recommend that the PET/CT whole body sweep be performed 60 min +/- 10 min post injection, giving a 20 min window to start the whole body sweep [Shankar]. Current clinical practice however is favoring imaging around 75 min p.i. which leads to a considerable number of protocol deviations in clinical trials.

As Imaging Core Laboratory for a large number of trials which include PET imaging, we see that the protocol deviation rate in time post injection is consistently the highest with rates of 15% to 40% depending on protocol, most frequently however in the time frame of 70 to 80 min post injection. By adding this aim to the protocol, we can answer another burning clinical/scientific question without adding any additional radiation exposure to the patient.

We will be giving participating subjects an opt out option, as we are certainly aware that some patients are quite uncomfortable laying on the PET/CT table but would be willing to participate in the dose reduction validation while preferring to be on the system table for the shortest time possible.

For the assessment of equivalency, we will use the same methodologies as outlined in Aim 1. We acknowledge that with the subjects opt out option, we might not achieve validation at the proposed level of power for this aim, but are otherwise confident that this comparison will deliver invaluable data to guide a pathway to resolve the discrepancy between current recommendations and clinical practice of scanning at later p.i. times.

PET/CT images are reconstructed from the simultaneous emission events recorded in the detectors accumulated over the time of acquisition over a bed volume. The level of emission events detected is relative proportional to the available radioactivity within that imaging volume. By performing additional reconstructions of a sub-sampled list mode data set, we are able to simulate a sparser count rate which then would be predict the image acquisition using a lower injected radiation dose.

Such an idealized assumption neglects any biologic or distribution differences which could additionally impact the validity of such simulations. On the other hand, if we can demonstrate that such simulated images are practically equivalent to effectively reduced radiotracer dose levels, it would revolutionize our ability to optimize dose response relations for radiotracers and substantially reduce the required subject populations for dose-finding and dose optimization studies. Considering, that radical changes in PET detector technology (digital vs. analog, crystal size and material) are occurring with the combined increase in potentially available PET tracers, a validation of such a simulation approach by comparing true low dose to simulated low dose images will be tremendously enabling and will lead to considerable future optimization of time-dose-image quality relations.

Detailed study procedures

For each participant, written informed consent will be obtained prior to any protocol related activities in a private area with a study team member. As part of this procedure, study personnel will approach eligible participants and explain orally and in writing the nature, duration, and purpose of the study as well as all associated risks and benefits. They will inform the participant that he/she may withdraw from the study at any time. If the patient agrees, he/she will have additional PET acquisitions either before or after their standard of care PET imaging.

The patient will be randomized to either Group A or Group B.

Group A will receive the standard of care 13mCi injection of the radiopharmaceutical and will begin imaging at 60 minutes post-injection.

If the patient agrees, there will be two imaging sweeps 1) 60-75 minutes post-injection and 2) 75-90 minutes post-injection. The 75-90 minute post-injection acquisitions will be utilized for the standard of care diagnostic read.

After the initial scan, the patient will be scheduled for a follow-up PET/CT scan that will take place $\geq$ 20 hours and $\leq$ 2 weeks after injection. At the follow-up exam, the patient will receive a 5mCi injection of the same radiopharmaceutical and will begin imaging at 60 minutes post-injection. If the patient agrees, there will be two imaging sweeps 1) 60-75 minutes post-injection and 2) 75-90 minutes post-injection.

Group B will be identical to Group A with the exception that the first exam is performed using a 5mCi injection of the FDG radiopharmaceutical, followed by the SOC dose of 13 mCi at the second exam/

Risks:

Patients will have an additional intravenous injection of FDG at the low dose of 5/13 of the standard care dose, 5 mCi (185MBq). The radiation dose for the additional low dose FDG PET will be 4 mSv, which is equivalent to 10 month of natural radiation exposure for someone living in the USA.

There is slight risk of inflammation, infection, or hematoma from the i.v., and there is some associated discomfort. This is a standard procedure for many diagnostic tests. The i.v. will be removed prior to the

positioning of the patient within the PET scanner. There is a remote possibility of an allergic reaction to FDG, though we are unaware of any reported incidents.

Benefits:

If the lower dose PET/CT examination is determined to be equivalent to the current standard of care, we will change our standard of care and follow-up examinations maybe performed at lower dose levels.

Safety Monitoring:

The safety of data and patients will be managed consistent with the clinical protocols in place for PET imaging at The Ohio State University Wexner Medical Center. The difference compared to standard of care scans is solely in the fact that we are using a substantially lower dose of PET radiotracer compared to the current standard. All other safety aspects are equivalent.

As part of the standard of care imaging procedure, safety monitoring is in place for patients. This will include the monitoring of the physiologic parameters that are deemed appropriate in the evaluation of potential risk during the acquisition process (electrocardiogram, respiration rate, core body temperature). These parameters are monitored to ensure that they do not approach potentially hazardous levels. The Principal Investigators or Co-Investigators are able to respond immediately to ensure the safety of the patients participating in the research study. The Principal and/or Co-Investigators or Key Personnel will be present at the time of all non-standard of care PET acquisitions to ensure this.

Patient participation maximum duration and frequency is defined by protocol as follows: Duration of data acquisition in the PET system per patient is limited to no more than 2 hours total per day consisting of one or more acquisitions.

In the event of any medical emergency, accident or trauma while the subject is in the laboratory, our contingency plans for emergency situations are as they would be for any medical facility and clinical magnetic resonance imaging facility. Our emergency protocol fully prepares us to provide access to emergency treatment for our patients, resuscitation, life support and medical care as needed.

Confidentiality of Records:

All paper and electronic data/information will be coded prior to any review or analysis. All paper documents will be stored in a locked file cabinet with limited access in the Department of Radiology at The Ohio State University. All electronic data obtained through PACS or IHIS will be stored in a coded manner on password protected servers with limited access in the Department of Radiology at The Ohio State University. No individual identities will be used in any publications resulting from this study. Officials from examining bodies such as the U.S. Food and Drug Administration or NIH may inspect records pertaining to this study.

Internal Validity

This crossover design is necessary to blind the patient and the technologist to be unbiased during the performance of the imaging, as motion artifacts, positioning, and other aspects can influence image quality to some extent.

Data Analysis

Our primary hypothesis is that the SUVmax will be equivalent between standard of care dosing (13 mCi) and the low dose (5 mCi) in each PET/CT system. The two one-sided tests procedure (TOST) will be used to test the equivalence of SUVmax at 75 min post injection between the standard care of dosing and the low dose. As SUVmax is known to have lognormal distribution, the data will be log-transformed before all analysis. Holm-Bonferroni method will be used to adjust for multiple ROIs. The McNemar-Bowker's test will be used to evaluate the inter-reader reliability in image quality measured from 1-10 scale between every two readers. The average scores will be calculated among those 3 readers. The TOST test will be used to

test the equivalence in the average score of image quality between the standard care of dosing and the low dose.

The percentage of change in SUVmax measured from 60 min to 75 min will be tested first for equivalence between the standard of care dosing and the low dose target ROI in each PET/CT system. Then the SUVmax measured at 60 min will be compared to SUVmax measured at 75 min within standard care of dosing and the low dosing groups, respectively.

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