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| **Protocol Title:** | Feasibility Assessment of Next-generation PET Technology and Procedures |
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## I. Objectives

The purpose of this study is to assess the feasibility of investigational Positron Emission Tomography (PET) imaging using the new generation digital detector PET technology for new procedures beyond the current standard of care:

1. To enable innovative PET imaging in association with a clinical trial to add potential future biomarker readouts for disease characterization and therapy management.
2. To generate preliminary and comparative imaging data for potential confirmatory clinical trials using innovative imaging timepoints, acquisition, dose, and timing approaches, and/or post-processing procedures.
3. To explore digital PET imaging for new indications where PET is not currently considered a standard of care diagnostic procedure in order to be able to design future clinical trials.

## II. Background and Rationale

PET imaging is increasingly being used as a diagnostic modality in cancer detection and staging, neuro-molecular assessment, cardiovascular-molecular imaging, physiological/musculoskeletal imaging, and response assessment. Additionally, PET imaging is utilized in the detection and assessment of inflammatory processes. Constant advances in detector techonology, image acquisition, and post-processing approaches could lead to the increased utility of PET in many currently unmet clinical scenarios.

We have already performed an intra-individual comparison trial demonstrating advanced capabilities of digital PET technology in regard to lesion detection, lesion characterization, quantification, duration of scan time, and reduction of radiation dose. The digital PET is now fully FDA approved and in this trial we need to generate preliminary data in order to design prospective clinical trials that allow the validation of a hypothesis. We have demonstrated the safety of the system [now FDA approved] and the overall efficacy in relation to current clinical care practice standards, however, the technology enables the change of those standards for which we need to demonstrate the clinical feasibility that we have either shown in pre-clinical PET imaging or via simulations.

This research focuses on evaluating the new capabilities of PET imaging which may be improved or enabled by a new generation of fully digital PET systems. In order to change clinical practice, we need to first generate data on the potential capabilities of this major technology improvement. We will be performing and evaluating investigational PET/CT imaging beyond the current standard of care practice. Prior studies by our team have already performed comparisons between the new and current PET imaging, however the digital PET studies were constrained by being performed as a comparison to standard of care. In this clinical trial, we can conduct research studies at innovative time points or using innovative procedures currently not covered by insurance, such as repeat imaging prior to treatment or midway through treatment for replanning purposes or to find better quantitative readouts to improve diagnosis and disease management. We intend to conduct PET imaging also for indications not typically covered by insurance, such as cardiac, neuro-related, or orthopeadic/sportsmedicine indications. We may also perform imaging with FDA approved radiotracers beyond their normal use (off-label) to explore the synergistic capabilities of the new generation of PET imaging.

# III. Procedures

## A. Research Design

This prospective study will utilize investigational PET acquisitions on the newly available digital photon counting detector platform to develop and optimize PET acquisition and post-processing techniques as well as to generate preliminary and comparative data for potential confirmatory clinical trials. We will assess these innovations in regard but not limited to visual inspection of lesions, normal tissue, sentinel nodes and imaging artifacts, semi-quantitative and blinded reader analysis. The PET methodologies we plan to use as part of this study will allow us to obtain morphological, functional and molecular information in ways beyond any current standard of care imaging procedures.

We anticipate recruiting patients from 3 general populations. 1 – Patients enrolled in a clinical trial where innovative PET imaging may be beneficial to the trial, although not necessarily the individual patient. This would include patients enrolled in a clinical trial exploring a new treatment approach for whom imaging at other timepoints in treatment would not be covered by insurance and therefore not considered standard of care (SOC). 2 – Any patient with a concern for a medical condition / question not yet fully resolved by SOC practice for whom a treating physician believes that a research PET may have a potential to address the medical question and help for future patients with similar questions. For example, this could include a patient presenting with heel pain for whom standard x-ray shows no confirmation of injury, but the physician feels an innovative PET bone scan could help identify the cause of the pain. 3 – Any patient having a SOC PET scan who would be interested in receiving an investigational scan, either as part of or in addition to the SOC scan. This would include patients already scheduled for a SOC scan who would be willing to have an investigational PET acquisition immediately following the standard acquisition for example acquired with a shorter scan time. This would also include patients who have already had a SOC PET examination, but would be willing to have a second, investigational PET exam, with a significantly reduced radiotracer dose for example.Thus the radiation dose and exposure associated with the investigational imaging would be in addition to any standard of care imaging, although the two will be combined whenever appropriate.

Patients will be asked to provide study personnel with authorization to access their medical records for follow-up on future related procedures as well as the current outcome of their standard of care imaging. Additionally, participants will be asked if their imaging data from this study can be used in a de-identified manner in the future for comparison with other imaging data or as preliminary data for the protocol development of clinical trials.

## B. Sample

The study population will include 200 evaluable patients as identified by study team members, referring physicians, or patient self-identification based on study recruitment materials or awareness from clinical trial websites such as *clinicaltrials.gov*.

***Inclusion Criteria:***

- Male and female volunteers greater than or equal to 18 years of age having a medical diagnosis which justifies exploratory PET imaging.

***Exclusion Criteria:***

- Participants who are pregnant or lactating.
- Prisoners.
- Subjects incapable of giving informed written consent or who are unlikely to complete the imaging procedure.

### C. Measurement / Instrumentation

Studies will be carried out using FDA approved PET scanners. PET is routinely used for clinical diagnostic studies.

At this time, we will be evaluating imaging using FDA approved radiopharmaceuticals at dose ranges not exceeding the label. These include Fluorine-18 florbetapir, F-18 sodium fluoride, F-18 fluorodeoxyglucose, F-18 flutemetamol, F-18 florbetaben, and Rubidium-82 chloride.

### D. Detailed study procedures

After patients have expressed interest to participate they will be provided with the informed consent and study brochure material. For each participant, written informed consent will be obtained prior to any protocol related activities in a private area with a study team member or at the time of a physician consult as part of a clinical visit. As part of this procedure, study personnel will approach eligible participants and explain verbally 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 they may withdraw from the study at any time. The patient will be given time to ask questions and review the consent form on their own. During the consent process, the patient will be asked if they are willing to provide a release of their medical records pertaining to future procedures/injuries for the next 10 years. If the patient agrees, they will undergo the non-standard of care PET/CT imaging as designated by the study PI.

***Injection:***

The PET radiopharmaceutical will be injected into a pre-positioned IV line either in a dedicated injection suite or while the patient is placed on the PET imaging system in order to enable dynamic/perfusion imaging.

***Image Collection:***

Patients will be asked to simply lie on the table of the PET system for the duration of the investigational PET/CT. The duration of the table time associated with this research study will be dependent upon the purpose of the individual study, however the procedures will be very similar to a clinical scan. Following radiotracer injection, imaging may then be performed continuously for up to 2 hours, if dynamic imaging is being performed. If static imaging is being performed, the patient may rest during the uptake period, in the normal clinical injection space. At the conclusion of the investigational imaging session, the patient will be released

with similar instructions to those given to a standard of care PET/CT patient. Participants will not undergo more than a total of 2 hours of continuous imaging time in consideration of their potential discomfort from lying still in one position.

***Release of Medical Records:***
The patient will be asked if they are interested in releasing access to their medical records for up to 10 years after their participation in this study in order to allow study personnel to track the outcome and/or related procedures in the future. The patient can revoke their consent to this question at any time by contacting the Principal Investigator.

**E. Risks, Benefits, Safety and Confidentiality:**

The patient will be injected with an FDA approved radiopharmaceutical for the PET imaging session. The dose of the radiopharmaceutical will never exceed the recommended FDA dosing limits, and we anticipate that imaging will typically be done at substantially lower than maximum levels.

***Risks:***
The occurance of any adverse events due to the conduct of the study is not forseen. Risks associated with the investigational PET are considered very rare and are the same type of physical events that could occur in any normal PET scan. These would include pinching of skin, minor falls or bumps. Normal risks of a nuclear medicine scan from injection of a radiopharmaceutical include allergic reactions, swelling, infections, intravenous injuries, bruising, pain, and discomfort. Clinical guidelines for the PET will be followed according to OSUWMC hospital policy.

The CT scan performed will be used for attenuation correction of the PET imaging and for anatomic correlation of the PET images. The CT scan also involves radiation exposure. Long term exposure to radiation may slightly increase one's risk for cancer. The exposure risk is cumulative over a lifetime, and the total should be kept as low as possible. The exact long-term risks from radiation are not known. To give the participant an idea about how much radiation they will receive from PET/CT scan we will make a comparison with an every-day situation. Everyone is exposed to unavoidable radiation each year, known as background raditaion. Some of this radiation comes from space and some from naturally-occurring radioactive forms of water and minerals. This research gives the participant's body at most the equivalent of about 5 extra years' worth of this natural radiation.

***Benefits:***
It is hoped that the information from this study will provide preliminary, investigational information regarding the pathophysiological status of the disease/ailment/injury and may contribute to a more personalized diagnostic and/or therapeutic management in the future. All information obtained will be labeled as investigational in any communication to participating and/or referring physicians. The subject can request that a research report is provided to their healthcare provider of choice.

***Safety Monitoring:***

The well being of the subject will be monitored in a similar manner to all non-invasive imaging methodologies as participation does not present more than minimal risk. The Principal Investigators or Co-Investigators or Key Personnel 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 PET acquisitions to ensure this.

The duration of data acquisition in the PET system per patient is limited to no more than 2 hours total consisting of one or more acquisition series. There is no limit to the number of times an individual patient may participate in this study.

In the event of any medical emergency, accident or trauma while the subject is in the facility, our contingency plans for emergency situations are as they would be for any medical facility and clinical 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 de-identified 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 de-identified manner on password protected servers with limited access in the Department of Radiology at The Ohio State University. In the Informed Consent, we are asking subjects for release of medical records for up to ten years, as well as the use of de-identified data for other future studies. This data may be kept indefinitely by the Wright Center of Innovation for further assessment or reference. No individual identities will be used in any publications resulting from this study. If the subject has authorized the use of de-identified data for other research studies as comparative data, the de-identified data may be shared with collaborative investigators as well as research databases. The established processes to verify de-identified data will always be adhered to. Officials from examining bodies such as the U.S. Food and Drug Administration or NIH may inspect records pertaining to this study.

## F. Internal Validity

Image data will be evaluated at a minimum following standard published procedures. This includes but is not limited to visual evaluation of lesions, normal tissue, sentinel nodes and imaging artifacts, semi-quantitative analysis, blinded reader analysis, and using various methods for image post-processing. This should ensure internal and external validity of the data and avoid study bias. Functional and molecular read outs will be developed according to established methodologies.

Managing and verifying the internal validity is an important task in this exploratory research program in order to develop the appropriate methodology to be validated in prospective clinical trials.

As there is an opportunity that the staff member administering the facility experience can potentially bias the subject, we will perform training sessions with the staff prior to them administering the facility experience. We will also perform from time to time an observational

assessment by a study member participating in the subject facility experience with the task to observe the team member administering the facility experience in order to ensure that no bias or systematic errors occur.

In this exploratory study where we use perception and observation-based assessments, we will have to constantly assess the potential sources of systematic errors or bias in order to ensure that we may derive conclusions that warrant generalization to other contexts.
We will assess the different factors impacting internal validity of the data sets we generate. For the specific factors we will address the following considerations. The following text uses material presented at https://en.wikipedia.org/wiki/Internal_validity and is hereby specifically acknowledged.

***Temporal precedence:***
Potential lack of clarity how one experience may influence a subsequent experience as that might be a cause and effect relationship.

***Confounding:***
A major threat to the validity of causal inferences is confounding. Observations in one variable may relate to another manipulated variable. Where spurious relationships cannot be ruled out, hypothesis would have to be appropriately developed.

***Selection bias:***
Selection bias refers to the problem that, at pre-test, differences between groups exist that may interact with the independent variable and thus be 'responsible' for the observed outcome. Researchers and participants bring to the experiment a myriad of characteristics, some learned and others inherent. For example, sex, weight, hair, eye, and skin color, personality, mental capabilities, and physical abilities, but also attitudes like motivation or willingness to participate.
During the selection step of the research study, if an unequal number of test subjects have similar subject-related variables there is a threat to the internal validity. If subjects in two groups to be compared are not alike with regard to the independent variable, but similar in one or more of the subject-related variables, it may jeopardize the internal validity.

Self-selection to participate in this research can have a negative effect on the interpretive power of the dependent variable, this is especially known for online surveys where individuals of specific demographics opt into the test at higher rates than other demographics.

***History:***
Events outside of the study/experiment or between repeated measures of the dependent variable may affect participants' responses to experimental experiences. Often, these are large scale events (natural disaster, political change, etc.) that affect participants' attitudes and behaviors such that it becomes impossible to determine whether any change on the dependent measures is due to the independent variable, or the historical event.

***Maturation:***
Subjects may change during the course of the experiment or even between measurements. Both permanent changes, such as physical growth and temporary ones like fatigue, provide "natural"

alternative explanations; thus, they may change the way a subject would react to the independent variable. So upon completion of the study, the researcher may not be able to determine if the cause of the discrepancy is due to time or the independent variable.

***Repeated testing:***
Repeatedly measuring the participants may lead to bias. Participants may remember the answers or may be conditioned to know that they are being tested. Repeatedly taking (the same or similar) tests usually leads to score gains.

***Instrument change:***
The instrument used during the testing process can change the experiment, an aspect that we will managed via device quality control to the largest extent possible. This also refers to observers being more concentrated or primed, or having unconsciously changed the criteria they use to make judgments. This can also be an issue with self-report measures such as facility perceptions given at different times. In this case the impact may be mitigated through the use of retrospective pretesting. If any instrumentation changes occur, the internal validity of the main conclusion is affected.

***Differential attrition:***
This error occurs if inferences are made on the basis of only those participants that have participated from the start to the end. However, participants may have dropped out of the study before completion, and maybe even due to the study or experiment itself. If this attrition is systematically related to any feature of the study, the administration of the independent variable, the instrumentation, or if dropping out leads to relevant bias between groups, a whole class of alternative explanations may be possible that account for the observed differences.

***Selection-maturation interaction:***
This occurs when the subject-related variables, color of hair, skin color, etc., and the time-related variables, age, physical size, etc., interact. If a discrepancy between the two groups occurs between the testing, the discrepancy may be due to the age differences in the age categories.

***Experimenter bias:***
Experimenter bias occurs when the individuals who are conducting an experiment inadvertently affect the outcome by non-consciously behaving in different ways to members of control and experimental groups. It is possible to eliminate the possibility of experimenter bias through the use of double blind study designs, in which the experimenter is not aware of the condition to which a participant belongs.

### G. Incidental Findings

Any incidental findings discovered will be correlated to any accessible standard of care imaging. If these incidental findings were not previously reported on standard of care imaging, the subject will be contacted according to the previous choice/request indicated on the informed consent form.

### H. Data Analysis

The purpose of this trial is to perform exploratory assessment and as such will only use descriptive statistics. We do not intend to perform a statistical assessment beyond classifying the characteristics of pilot data and comparing observational trends either to the standard of care imaging data or other known reference data. For our purposes, imaging that presents lower imaging quality will not be pursued for further evaluation. Only images that suggest equivalent or improved image quality or diagnostic information compared to current standard of care imaging approaches would be evaluated for the potential use as data towards the design of a formal clinical trial and/or funding applications.