TITLE: Evaluation of a ^{68}Ga Small Molecule PSMA Antagonist Produced by Two Different Methods

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Participating Sites: Single site study

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Statement of Compliance

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the <specify NIH Institute or Center (IC) > Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.]

Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from WCM.

Joseph R. Osborne

_____	_____	_____
Principal Investigator's Name	**Principal Investigator's Signature**	**Date**

List of Abbreviations

AE	Adverse Event
CBIC	Citigroup Biomedical Imaging Center
CFR	Code of Federal Regulations
CRF	Case Report Form
CTSC	Clinical Translational Science Center
DSMB	Data Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HRBFA	Human Research Billing Analysis Form
HUD	Humanitarian Use Device
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
UIRTSO	Unanticipated Problem Involving Risks to Subjects or Others
WCM	Weill Cornell Medicine
WCINYP	Weill Cornell Imaging NewYork Presbyterian
PCa	Prostate Adenocarcinoma
^{68}Ga	Gallium-68
PET	Positron Emission Tomography
ROI	Regions of Interest
PSMA	Prostate Specific Membrane Antigen
Ga-PSMAcyc	Ga-PSMA cyclotron
Ga-PSMAgen	Ga-PSMA generator

1. Protocol Summary

Full Title:	Evaluation of a ^{68}Ga Small Molecule PSMA Antagonist Produced by two different Methods
Clinical Phase:	I/II
Principal Investigator:	Dr. Joseph R. Osborne
Study Description:	Patients with metastatic prostate cancer will undergo two protocol ^{68}Ga-PET scans within 24-48h with ^{68}Ga-PSMA-cyclotron and ^{68}Ga-PSMA-generator radiotracers. The goal of the study is to evaluate repeatability and equivalence across the different ^{68}Ga-PSMA production methods.
Sample Size:	Up to 30 patients will be enrolled in the study as defined by protocol criteria.
Enrollment:	30 patients will be enrolled in this study
Study Population:	Patients with metastatic prostate adenocarcinoma
Enrollment Period:	2 years
Study Design:	Single-dose, non-randomized design. Patients with metastatic prostate adenocarcinoma will be administered a single intravenous dose of each of the study drugs ^{68}Ga-PSMA-cyclotron and ^{68}Ga-PSMA-generator 24-48 hours apart.
Description of Sites/ Facilities Enrolling Participants:	This is a single site study. All study procedures will be performed in the NYP/WCMC facilities, CBIC, and WCINYP.
Study Duration:	2 years
Participant Duration:	3 Visits: 1 screening/consent and 2-infusions imaging. The duration of patient participation can be up to 4 weeks, depending on eligibility, and the scheduling and completion of required study visits
Study Agent/Device Name Intervention Description:	^{68}Ga-PSMA-cyclotron and ^{68}Ga-PSMA-generator; single dose each, approximately 100-300 mBq.

Primary Objective:

- To evaluate equivalence of two processes to create ^{68}Ga-HBED-PSMA (^{68}GA-PSMA-cyclotron vs. ^{68}Ga-PSMA-generator)

Secondary Objectives:

- Comparative dosimetry and biodistribution (^{68}GA-PSMA-cyclotron vs. ^{68}Ga-PSMA-generator), whole body excretion/ metabolism in patients with confirmed metastatic PCa

Exploratory Objectives:

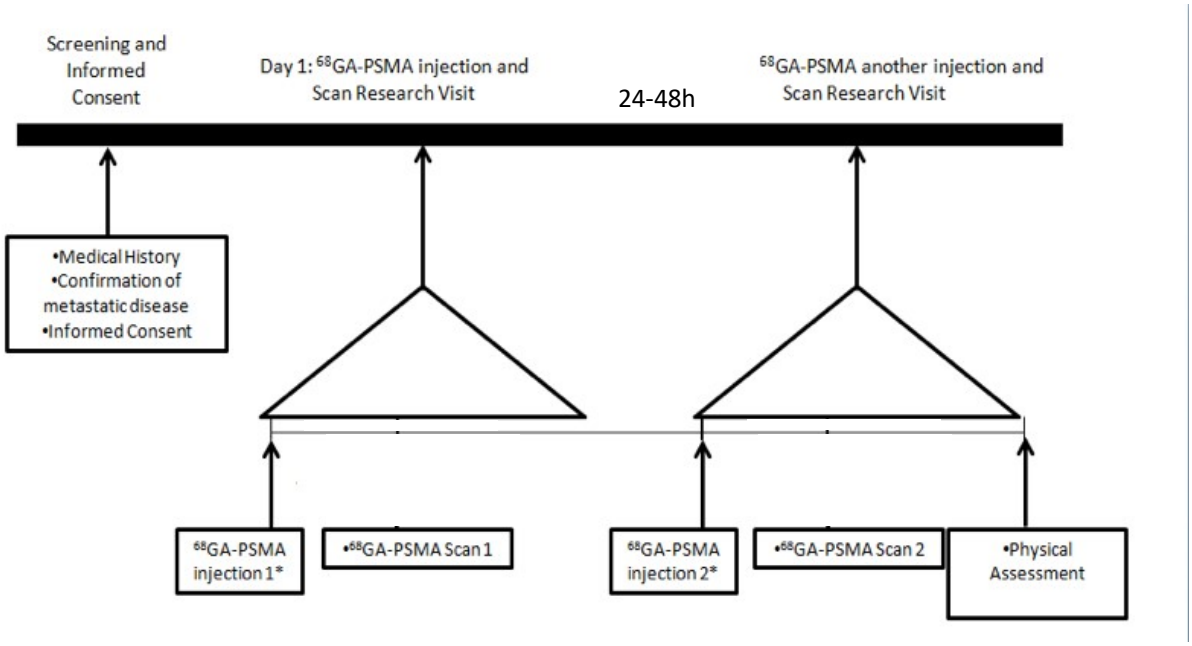
- Investigate repeatability of whole-body 68Ga-PSMA-generator Ki Patlak imaging against that of conventional whole-body ^{68}Ga-PSMA- SUV imaging in patients with confirmed metastatic prostate adenocarcinoma.

- Evaluate equivalence of whole-body 68Ga-PSMA Ki Patlak imaging between the two processes to create 68Ga-HBED-PSMA (68GA-PSMA-cyclotron vs. 68Ga-PSMA-generator)

Endpoints:

The primary endpoint of this study is to prove equivalence between the cyclotron and generator produced radioisotope. To meet this endpoint we will make a direct comparison of the ^{68}GA-PSMA-cyclotron vs. ^{68}Ga-PSMA-generator scans obtained within 24-48h**.** We will measure SUVmean and SUVmax of the same Regions of Interest (ROI) in both scans using the PET analysis software we use in our clinical practice. The two scans will be retrieved and the exact same ROIs will be drawn at the same time for the two scans (software offers a copy-paste function so that no discrepancies exist between the two measurements). The SUVmean and SUVmax obtained from both scans for each Region of Interest will then be analyzed to determine the within-subject coefficient of variation value as measured by the Bland Altman analysis.

1.1 Schema


Screening and Informed Consent
Day 1: 68GA-PSMA injection and Scan Research Visit
24-48h
68GA-PSMA another injection and Scan Research Visit
•Medical History
•Confirmation of metastatic disease
•Informed Consent
68GA-PSMA injection 1*
•68GA-PSMA Scan 1
68GA-PSMA injection 2*
•68GA-PSMA Scan 2
•Physical Assessment

1.2 Study Objectives

1.2.1 Primary Objectives

- To confirm ^{68}Ga-PSMA-generator repeatability in patients with confirmed metastatic PCa.

- To evaluate equivalence of two processes to create ^{68}Ga-HBED-PSMA (^{68}GA-PSMA-cyclotron vs. ^{68}Ga-PSMA-generator).

1.2.2 Secondary Objectives

- Comparative dosimetry and biodistribution (^{68}GA-PSMA-cyclotron vs. ^{68}Ga-PSMA-generator), whole body excretion/metabolism in patients with confirmed metastatic PCa.

1.2.3 Exploratory Objectives

- Investigate repeatability of whole-body ^{68}Ga-PSMA-generator Ki Patlak imaging against that of conventional whole-body ^{68}Ga-PSMA-generator SUV imaging in patients with confirmed metastatic PCa.
- Evaluate equivalence of whole-body ^{68}Ga-PSMA Ki Patlak imaging between the two processes to create ^{68}Ga-HBED-PSMA (68GA-PSMA-cyclotron vs. 68Ga-PSMA-generator).

2. Background

2.1 Prostate Cancer

PCa is the second most lethal cancer among men in the U.S. with 26,120 estimated deaths in 2016 (1). The ability to monitor the presence and progression of prostate cancer disease sites is crucial for the approximately 400,000 American men living with advanced disease. A widely available, economically-viable imaging agent with the potential to convey predictive or prognostic multi-parametric information in the metastatic setting is a clear unmet need.

2.2 FDG Positron Emission Tomography (PET)

PET has advantages over conventional imaging methods because it quantitatively assesses biologic processes in vivo and can assess different processes using specific radiotracers. Processes that can be analyzed include glucose and amino acid metabolism and proliferation, blood flow, and receptor status (i.e., androgen receptor). Most studies have focused on the accumulation of FDG. FDG-PET imaging is often used in the management of advanced disease patients; however, prostate cancer is frequently not FDG-avid and the presence of avidity does not always parallel treatment efficacy. This is particularly problematic with respect to drugs in Phase II and Phase III trials. The standard RECIST criteria are difficult to apply and thus a major aim of prostate cancer research is to identify disease-specific radiotracers as an adjunct to current imaging and histologic standards, with the ultimate

goal of implementing a biomarker driven or treatment modality sensitive tracer as may be the potential for ^{68}GA-PSMA.

2.3 Rationale- PSMA PET imaging

PSMA has been studied for several years as a target for imaging prostate cancer. An antibody targeting the intracellular portion of PSMA (^{111}In-Capromab) was FDA-approved in 1996 for prostate cancer imaging. Sensitivity has been found to be limited, probably due to limitations of the antibody and the SPECT imaging technology (2).
Recent clinical studies have shown that the extracellular portion of PSMA can be targeted not only by antibodies and antibody fragments, but also by urea-based small molecule inhibitors of the enzymatic activity of PSMA. Successful targeting has been shown for iodine-123 labeled probes for SPECT imaging as well as for ^{68}Ga- and ^{18}F-labeled compounds for PET imaging (3-7).
Two recent case series including 319 and 248 patients, respectively, evaluated PET/CT with ^{68}Ga-HBED-PSMA (PSMA PET/CT) in recurrent prostate cancer (8, 9). In these two reports the frequency of positive ^{68}Ga-PSMA-generator (^{68}Ga-PSMAgen) studies at a PSA level of less than 0.5 ng/ml was 48% (13/27) and 58% (11/19), respectively.

While 68Ga-PSMA PET has shown utility in early clinical studies, the potential applicability will be limited by the availability and cost of the radioisotope due to its generator production. Proving equivalence with a cyclotron produced radioisotope could alleviate these constraints. Moreover, a ready source of 68Ga could have implications for diseases beyond prostate cancer , where more specific PET tracers can be readily generated by the availability of cyclotron-produced 68Ga.

2.4 Risk/Benefit Assessment

2.4.1 Known Potential Risks

Pharmacologic effects of HBED-PSMA
HBED-PSMA has been injected for PET imaging in more than 500 published patients. No drug related side effects have been observed. This is expected because the mass of compound is minimal, less than 10 micrograms.

Radiation exposure from PSMA PET/CT imaging
As part of this scan there is radiation delivered from the ^{68}Ga and from the low dose CT scan that are performed as part of the PET/CT for attenuation correction and co-registration. Although any exposure to ionizing radiation has the potential to cause some harm to tissue, the radiation exposures in this study are comparable to the low-level exposures associated with common diagnostic procedures such as CT scanning. There remains a low theoretical risk of developing cancer at some point later in life as a result of the radiation exposure received in this study. This risk is much smaller than the clinical risks posed by the patient's current cancer or the salvage radiation therapy the patient would be receiving. Participants should not father a baby while on this study. Acceptable birth control methods include abstinence, double barrier method, surgically sterilized patient or partner. Radiation exposure due to injection of ^{68}Ga-HBED-PSMA and CT imaging is provided in table 1.

Table 1: ^{68}Ga-PSMA 11 Patient Dosimetry (per session)

			Dose per CT Scan rad	# of Injections/CT scans
Activity of 68Ga-PSMA 11 (maximum)	**3.3**	mCi	~~X~~	**1**
Low dose WB CT scan	**80**	mA	**0.90**	**1**
Ultra-low dose WB CT scan	**10**	mA	**0.11**	**3**
		Total CT dose:	**1.01**	

	Absorbed Doses			
Target Organ	rad/mCi	rad/ admininstration	rad for 4 CT scans	**Total rad**
Adrenals	0.0525	0.173	1.23	**1.40**
Brain	0.0333	0.110	1.23	**1.34**
Breasts	0.0326	0.107	1.23	**1.34**
Gallbladder Wall	0.0533	0.176	1.23	**1.41**
LLI Wall	0.0455	0.150	1.23	**1.38**
Small Intestine	0.0603	0.199	1.23	**1.43**
Stomach Wall	0.0444	0.147	1.23	**1.38**
ULI Wall	0.200	0.66	1.23	**1.89**
Heart Wall	0.0403	0.133	1.23	**1.36**
Kidneys	0.969	3.20	1.23	**4.43**
Liver	0.114	0.377	1.23	**1.61**
Lungs	0.0377	0.125	1.23	**1.35**
Muscle	0.0389	0.128	1.23	**1.36**
Pancreas	0.0511	0.168	1.23	**1.40**
Red Marrow	0.0340	0.112	1.23	**1.34**
Osteogenic Cells	0.0525	0.173	1.23	**1.40**
Skin	0.327	1.08	1.23	**2.31**
Spleen	0.165	0.54	1.23	**1.77**
Testes	0.0385	0.127	1.23	**1.36**
Thymus	0.0366	0.121	1.23	**1.35**
Thyroid	0.0359	0.118	1.23	**1.35**
Urinary Bladder Wall	0.481	1.59	1.23	**2.82**
Total Body	0.0459	0.151	1.23	**1.38**
Effective Dose (rem)	0.0873	0.288	1.23	**1.52**

2.4.2 Known Potential Benefits

This is not a therapeutic study and no direct benefit exists for the participants.

2.4.3 Assessment of Potential Risks and Benefits

This study will be the basis of expanding access by enabling greater production of gallium. It will also enable our investigative team to look at the value of the information that we get from the Ga-PSMA PET scans that they may continue to have after the results of this study are documented and published.

The amount of extra radiation exposure in these scans will not significantly impact the patients in a way that has been discovered in any systematic study of PET scanning.

2.5 Correlative Studies Background- Preliminary laboratory and small animal experience

The PSMA ligand is a zinc metalloenzyme carboxypeptidase that catalyzes the hydrolysis of glutamate from the C terminus of peptides. The antagonist ^{68}Ga-HBED-PSMA targets this ligand and will be produced using the following methods.

2.5.1 Generator Production

[^{68}Ga]-gallium chloride is generated from an IGG100 Eckert and Ziegler closed system ^{68}Ga- generator consisting of a borosilicate glass column containing a titanium dioxide bed on which ^{68}Ge is absorbed and fully shielded. This study will therefore be performed under the specifications set forth by **IND 124495.** Both, the HBED-PSMA non-radioactive precursor and the ^{68}Ga radionuclide will be obtained from the ***CBIC core*** and accompanied by a certificate of analysis as described in the Chemistry, Manufacturing, and Controls (CMC) Section of the IND. A single dose will be delivered to the CBIC scanner or WCINYP with 2 h expiration.

2.5.2 Cyclotron Production

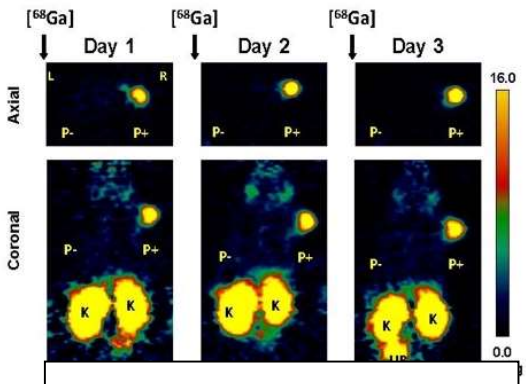
Gallium-68 *will* be produced by ***NCM USA LLC***, a NYC-based advanced PET radiopharmaceutical manufacturing and distribution company (461 Park Avenue South, New York, NY 10016) with whom we have an academic-industrial partnership NIH grant to investigate manufacturing this nuclide based on an IND held by the company. In summary, the NCM cyclotron will use enriched (>99% purity) zinc-68 target, the target will first be dissolved in 10-12 N HCl and solution will be passed on AG-50W-X8 resin to separate Zn-68 and elute gallium Gallium-68 s [^{68}Ga]-$GaCl_3$ in 3N HCl. The cyclotron produced ^{68}Ga that will be released by NCM for labeling and formulation of the ^{68}Ga-HBED-PSMA product. The radiochemical purity of the in house product will be required to match and be equivalent to the specifications of the ^{68}Ga-HBED-PSMA generator produced radiopharmaceutical.

2.5.2.1 Purity of cyclotron-produced ^{68}Ga (HPLC)

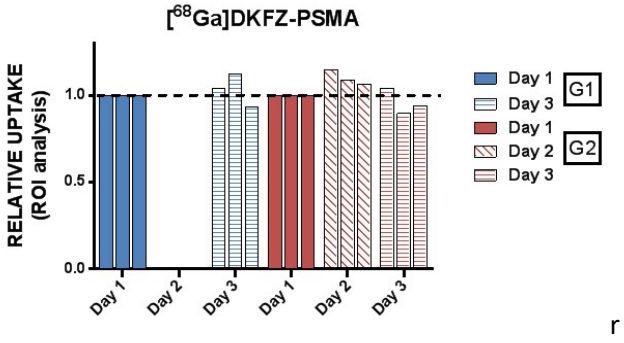
We measured radionuclide purity and identity using an ORTEC GEM series HPGe (high-purity Germanium) coaxial detector system (model GEM20-70-SMP, CFG-SV-70). The purified sample of ^{68}Ga showed only two peaks at 511 keV and 1077 keV.

2.5.2.2 Small animal ^{68}Ga-HBED-CC and repeatability

Several experiments were performed in mice to determine repeatability of the ^{68}Ga- HBED-CC which are published at Molecular Imaging and Biology with the following figures representing a synopsis of the results.



Representative PET images of mice bearing PC3-PIP xenografts imaged with ^{68}Ga-HBED-PSMA on three consecutive days



Normalized uptake values in mice bearing PC3-PIP tumor xenografts that were imaged using ^{68}Ga-HBED-PSMA either consecutively for three days (Group 2, mice 4, 5, and 6) or alternative days with ^{68}Ga-HBED-PSMA and administered with ^{68}Ga-HBED-PSMA on day 2 (Group 1, mice 1, 2, and 3) one hour post-administration of tracer.

3. Study Design

3.1 Overall Design

Thirty patients with metastatic prostate cancer that have undergone standard-of-care staging at WCMC will be considered for enrollment. For this study, enrolled patients will undergo a total of two whole-body dynamic ^{68}Ga-PET scan protocols of at least 0-75 min and at most 0-90 min scan time post injection, depending on the amount of injected dosage. A 6 to 48 hour gap will be introduced between the two scans. The first scan will occur after a baseline clinical evaluation, which will include a history, physical, and baseline lab draw. Blood work will be obtained before, during and after the scan. The radiotracers will be evaluated for repeatability and equivalence across the different production methods. This will include basic pharmacokinetics, distribution, metabolism and excretion.
Up to 30 patients will undergo each two whole-body dynamic scans, initially with ^{68}Ga-PSMAcyc and later with ^{68}Ga-PSMAgen (with a minimum time of 6 h and maximum time of 2 days between the two injections). All patients will receive ^{68}Ga-PSMAgen from the CBIC core and ^{68}Ga-PSMAcyc from NCM pharmaceuticals at a specific activity of 1-2 Ci/µmol, the typical specific activity used in published clinical trials with ^{68}Ga-PSMA (10).

3.2 Scientific Rationale for Study Design

This is a single-arm study.

3.3 Justification for Dose

Patients will be injected with 100-300 MBq of ^{68}Ga-HBED-PSMA (from either the generator or cyclotron source) via a catheter. ^{68}Ga-PSMA PET/CT will be acquired using a Siemens Biograph mCT™ PET/CT scanner. Please see details in section 7.1.

The goal is to administer this amount of the imaging probe labeled with 2.5 MBq of ^{68}Ga per kg body weight with a minimum of 100 MBq and maximum of 300 MBq ^{68}Ga per patient.

The whole-body dynamic ^{68}Ga-PSMA scans will involve an initial dynamic scan at a pelvic scanner bed position centered over the prostate tissues for the first 10min post injection (p.i.), followed by multiple successive whole-body scans (passes) at least 10-75 min and at most 10-90 min post injection, depending on the amount of injected dosage. A fixed scan time of 30sec per bed position per pass will be used with an adjustable total number of passes. The PET data collected from at least the last six passes will be summed at each bed position and combined over all bed positions to produce whole-body static ^{68}Ga-PSMA images equivalent of a total acquisition time of 6 x 30 sec = 180sec or 3 min/bed position from all summed passes.

Due to the short physical half-life of ^{68}Ga and the decreasing elution efficiency of the ^{68}Ge/^{68}Ga generator during its lifetime, the amount of radioactivity injected per patient will necessarily vary. If the amount of activity per kg body weight differs by more than 25% from the recommended dose of 2.5MBq/kg of body weight, the effective total acquisition time per bed position from all passes will be adjusted by increasing the total number of passes, in increments of one pass, while keeping fixed the scan time per bed per pass. The adjustment of the total number of passes will result in the respective adjustment of the total scan time up to 90 min post injection. The total number of passes will be adjusted such that the product of total acquisition time per bed position from all summed passes participating in the synthesis of the equivalent static PET images and of the injected activity is at least 7.5 MBq/kg*min or the total scan time reached 90 min.

In the meantime, the dynamic PET data from all passes will also be analyzed at each bed position on voxel-by-voxel analysis according to the Patlak graphical model to estimate ^{68}Ga-PSMA net uptake rate (Ki) whole-body images. The acquired PET data will be corrected for attenuation and scatter and adjusted for system sensitivity. Multiple parametric PET images in terms of standardized uptake values (SUV) (= MBq measured/gm tissue / MBq injected/gm body mass) and net tissue uptake rate Ki (= (MBq measured in tissue/gm tissue / MBq measured in blood plasma/ ml plasma) / post injection time) will be provided.

3.4 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including follow-up visit which is the standard of care imaging preformed after treatment. This follow-up visit does not require that the patient physically comes back for an in-trial procedure. The end of the study is defined as completion of the last visit or procedure shown in the SoA.

4. Subject Selection

4.1 Study Population

Subjects with a diagnosis of metastatic prostatic adenocarcinoma who meet the inclusion and exclusion criteria will be eligible for participation in this study.

4.2 Inclusion Criteria

Subjects must meet all of the following criteria to be enrolled in this study:

- Aged 21 years or older and below 100 years of age.
- Signed written informed consent and willingness to comply with protocol requirements.
    - Histologically confirmed diagnosis of metastatic prostate cancer
- Staging imaging exam confirming metastatic disease, e.g. total body MRI, or CT chest/abdomen/pelvis, 99mTc bone scan, NaF PET.

4.3 Exclusion Criteria

- Laboratory values:
    - Serum creatinine >2.5 mg/dL
    - AST (SGOT) >2.5x ULN
    - Bilirubin (total) >1.5x ULN
    - Serum calcium >11 mg/dL
- Presence of any other co-existing condition which, in the judgment of the investigator, might increase the risk to the subject.
- Presence of serious systemic illness, including: uncontrolled inter-current infection, uncontrolled malignancy, significant renal disease, or psychiatric/social situations, which might limit compliance with study requirements.
- Other severe acute or chronic medical condition(s) or laboratory abnormality(ies) that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and in the judgment of the investigator, would make the patient inappropriate for entry into this study.
- Inability to lay on the scanner table for the required period of time, e.g., due to bone pain or claustrophobia.

4.4 Lifestyle Considerations

No specific patient preparation is required before injection. One intravenous catheter (Hep-Lock) will be placed by staff in the CBIC or WCINYP. This will remain in place for the duration of the encounter.

4.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure

transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

4.6 Strategies for Recruitment and Retention

Patients will be recruited through the outpatient clinics of the Department of Radiation Oncology and Genitourinary Medicine at WCMC. Members of the treatment team and research staff will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study. If the investigator is a member of the treatment team, s/he will screen their patients' medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study. During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes. In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team.
Patients will be required to sign a statement of informed consent that meets the requirements of the code of Federal Regulations (11) and the IRB of this center. A consent form is appended. The medical record will include a statement that written informed consent was obtained (and document in the record the date written consent was obtained before) and the patient is enrolled in the study.

5. Registration Procedures

5.1 Subject Registration (WCM only)

Subjects will be registered within the WRG-CT as per the standard operating procedure for Subject Registration.

6. Study Procedures

6.1 Schedule of Assessments

Table 1. Schedule of trial events

	Screening- Visit 1 (Baseline or D0)	Imaging 1* (Visit 2 or D1)	Imaging 2* (Visit 3 or D2)
ICF	X		
Medical History	X		
Physical Exam	X		X
Review medications	X		
CBC	X		
Serum BUN and Creatinine	X		
AST, ALT, ALP, bil, albumin	X		
Review of prior imaging	X		
Adverse event monitoring		X	X
^{68}Ga-PSMA administration		X	X
^{68}Ga-PSMA PET scans		X	X
Research Blood draws **		X	X
*Two scans *with* ^{68}Ga-PSMA-cyclotron and ^{68}Ga-PSMA-generator radiotracers will be performed at least 24h apart (max 48h) ** Research blood draws will be performed only in a subset of patients (3-5) and are not required for participation in the study. The planned timepoints are as follows: pre tracer injection, 5 minutes (+/- 10 minutes) 15 minutes (+/- 10 minutes), 30 minutes (+/-10 minutes), 60 minutes (+/-10 minutes). A blood draw will also be performed after each scan (12 blood draws in total per patient at most) (for details refer to section 6.1.2.2).			

6.1.1 Screening Visit

Once a patient signs informed consent, but prior to the initiation of neoadjuvant ADT for prostate cancer the following standard of care tests and procedures will be performed prior to the administration of the investigational diagnostic agent:

- Obtain written informed consent
- Obtain medical history
- Physical exam including Karnofsky performance status
- Confirm adequate venous access
- Review medications
- Laboratory studies:
    - CBC, Serum BUN and creatinine, AST, ALT, alkaline phosphatase, bilirubin and albumin
- Review of prior imaging studies to confirm metastatic disease status (e.g. 99mTc bone scan (prostate cancer), NaF PET (prostate cancer), MRI, or CT)

6.1.2 Intervention Phase

6.1.2.1 Patient scans

Two ^{68}Ga-PSMA PET/CT scans will be performed successively at least 6 hours apart.

6.1.2.2 Serum Blood Draws

A subset of patients will have serum blood draws (approximately 5 ml) for pharmacokinetic analysis. This is **only** required in a subset (3-5 patients) as a smaller number of patients will be needed to generalize organ and lesional dosimetry. The planned timepoints are as follows: pre tracer injection, 5 minutes (+/- 10 minutes) 15 minutes (+/- 10 minutes), 30 minutes (+/-10 minutes), 60 minutes (+/-10 minutes). A blood draw will also be performed after each scan (12 blood draws in total per patient at most). This will be done through the IV placed to administer the PET tracer during the imaging visit. Apart from routine laboratory tests, samples will also be evaluated for the presence of ^{68}Ga, as well as ^{66}Ga, potential contaminants for generator-produced and cyclotron-produced products. Blood counts, liver function tests, and creatinine levels will also be monitored before, during, and after imaging evaluation/radiotracer injection. Apart from routine laboratory tests, samples will also be evaluated for the presence of ^{68}Ga, as well as ^{66}Ga, potential contaminants for generator-produced and cyclotron-produced radiotracers, respectively. Images will also be evaluated for location of radiotracer uptake, as well as excretion and organ-specific dosimetry.

6.1.3 Evaluation during intervention

Performance Status
Performance status will be assessed using the Karnofsky Performance Status scale.

Vital Signs
Blood pressure and heart rate will be obtained prior to each PET scan.

Serum Blood Draws
As described above

6.1.4 Follow- up

The patients that are enrolled in the study will afterwards undergo treatment for metastatic prostate cancer disease either as per standard of care or after enrollment in clinical trials. During completion of the treatment, there is usually a follow- up scan approximately 3mo after treatment where additional imaging is performed. This additional imaging will be considered the follow- up visit and will be used to correlate imaging with reported outcomes as well as biochemical and genomic analysis.

7. Study Intervention

7.1 Study Intervention/Patient scans

Protocol initiation quality assurance

Patient scans will be acquired on one of the Siemens Biograph mCT™ PET/CT scanners with a preference for the same instrument on all scans. Quality assurance images from each system will be acquired at the beginning of the protocol on all mCT scanners using a ^{68}Ga-filled 20-cm-diameter cylindrical water phantom with average SUVs in the range 1.0 +/- 0.5 g/ml with no artifacts on visual inspection.
Individual patients preferably use the same scanner system for both scans.
Prior to imaging evaluation, patients will be permitted to eat a light meal.
An intravenous catheter (Hep-Lock) will be placed in the CBIC or WCINYP for radiopharmaceutical administration, scans, and blood sampling.

Patient scans

Two dynamic whole body ^{68}Ga-PSMA PET/CT scans will be performed successively at least 6 hours apart. As there will be an accumulation of activity in the urinary bladder, patients will have pre-treatment hydration and encourage voiding immediately prior to imaging, however the short half-life of ^{68}Ga should not result in imaging counts from the first scan to appear on the latter scan.
PET/CT imaging patients will be positioned on a flat couch in radiation treatment position. Custom-made immobilization devices, skin markings, PET/CT gantry, and room lasers will be used to ensure accurate and reproducible positioning. Imaging will start with low-dose CT scan (80 mA) for attenuation correction, followed by a PET scan. A low dose CT scan (80 mA) will be performed over the prostate or a pre-determined index lesion. A 10min dynamic PET scan at the pelvic bed position, centered over the prostate tissues, will be initiated concurrently with an intravenous bolus injection of approximately 2.5MBq/kg of body weight (+/- 10%) of ^{68}Ga-PSMA, followed by a time series of whole-body PET scans (passes) at least 10-75 min and at most 10-90 min post injection. The PET acquisition time per bed position per pass will be fixed at 30sec and the total number of passes summed post acquisition to produce the static ^{68}Ga-PSMA PET images will be at least six. The total number of late passes may be increased , if needed, such that the product of total acquisition time per bed position from all passes and injected activity is at least 7.5 MBq/kg*min or a total acquisition time of 90min is reached. Moreover, the number of bed positions will be adjusted to cover a field of view from top of the skull to mid-thigh of an average human adult for each pass. All PET scans will be conducted with patients in a supine position with the arms comfortably positioned and secured by the side of the patient. All whole-body PET passes of each subject will be uni-directional, i.e. they will be performed along the same axial direction (cranio-caudal or caudo-cranial).

The PET data from at least the last six whole-body scan passes will be summed up and reconstructed at each bed position such that the product of total acquisition time per bed position from all passes and injected activity is at least 7.5 MBq/kg*min or a total scan time of 90min is reached. The resulting composite static PET images will then be combined with the same method as that employed for conventional static PET images at each bed position and the composite Standardized Uptake Value (SUV) static PET images will be calculated. In the meantime, the dynamic ^{68}Ga-PSMA concentration in the blood plasma (input function) will also be derived from the dynamic PET images at the pelvis, as estimated from the 0-10min p.i. of the initial dynamic pelvic PET scan and the corresponding pelvic beds of the subsequent set of whole-body PET passes. For that purpose, regions of interest will be drawn in the lumen of the abdominal section of the descending aorta that is included in the pelvic bed position. The blood pool image regions will be drawn as far as possible from the neighboring aortic wall to minimize any partial volume effects. The image derived input function data will then be fitted to the measured blood samples data for validation and enhanced accuracy. Subsequently, the images from all the dynamic PET whole-body passes and the image-derived input function will be fitted to the Patlak graphical model on a voxel-by-voxel basis to produce whole-body ^{68}Ga-PSMA net uptake rate constant (Ki) images. During the PET scan procedure, the patient will be allowed to get off from the couch in between the dynamic whole-body passes, if required (such as for a bathroom break).

The PET data will be used to determine the repeatability of the multi-parametric (SUV and Ki) features of the ^{68}Ga-PSMA organ biodistribution between two successive ^{68}Ga-PSMA-generator and cyclotron PET/CT scans. Moreover, the same data will be utilized to evaluate the equivalence of the SUV and Ki features between the organ biodistributions of generator- and cyclotron-produced ^{68}Ga-PSMA radiopharmaceuticals as estimated from respective dynamic whole-body ^{68}Ga-PSMA PET/CT scans. Following standard image processing, regions of interest (ROI) will be drawn on the summed dynamic image data set, and then copied onto the individual dynamic frames, in order to analyze the tumor activity as a function of time. Reconstructed whole body static ^{68}Ga-PSMA PET images will be analyzed on a standard workstation.
After 24-48 hours, patients will be asked to repeat PET imaging after injection of the second experimental radiotracer. The same procedures will apply. The radiopharmacy will keep a log of all doses administered. The intravenous catheter will be removed at the conclusion of imaging.

7.2 Availability

Radiotracer production described in section 2.5

7.3 Acquisition and Accountability

Radiotracer production described in section 2.5

7.4 Formulation, Appearance, Packaging, and Labeling

Radiotracer production described in section 2.5

7.5 Product Storage and Stability

Radiotracer production described in section 2.5

7.6 Preparation

Radiotracer production described in section 2.5

7.7 Dosing and Administration

Radiotracer dose described in section 3.3

7.8 General Concomitant Medication and Supportive Care Guidelines

Not applicable

7.9 Duration of Therapy and Criteria for Removal from Study

Participation in this study is entirely voluntary. Patients may be removed from the protocol for the following reasons:

- Patient decides to withdraw from the study.
- Intercurrent illness that prevents treatment and/or follow-up imaging
- Unacceptable adverse event that may be directly related to the protocol intervention
- General or specific changes in the patient's condition that render the patient unacceptable for further treatment, in the judgment of the investigator
- Does not meet inclusion/exclusion criteria

7.10 Duration of Follow Up

Not applicable.
This is a protocol designed to conform to RDRC regulations and has the specific purpose to study the equivalence of a radiopharmaceutical made using generator and cyclotron produced ^{68}Ga. It is not a therapeutic study and therefore does not have end point of treatment outcome.

7.11 Measures to Minimize Bias: Randomization and Blinding

The patients' doses will not be randomized as per FDA guidance documents for bioequivalence -- ***21 CFR 320.24(b)*** where a crossover design would be plausible, but instead will be conducted in a parallel design since the shipments of Ga-PSMAcyc will always be in the afternoon. That said the reader will be blinded as to which of the imaging pair emanated from the Ga-PSMAcyc or PSMAgen as the images will be delivered in pairs separate from the imaging sessions. In this way, the rigor of the bioequivalence is retained in the reader/analyst being blinded to the imaging session.

7.12 Study Intervention/Follow-up Compliance

Not applicable

8. Study Intervention Discontinuation and Participant Discontinuation/Withdrawal

Participants may withdraw voluntarily from the study. A dedicated Case Report Form (CRF) page should capture the date and the specific underlying reason for discontinuation of study intervention or participant discontinuation/withdrawal.

8.1 Discontinuation of Study Intervention

Not applicable. This is not a therapeutic study.

8.2 Participant Discontinuation/Withdrawal from the Study

This is not a therapeutic study. Participants can withdraw by refusing to perform the scans at any point during the study.

8.3 Lost to Follow Up

A participant will be considered lost to follow-up if we fail to obtain his imaging scan 3 months post-treatment.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.

9. Correlative/Special Studies

Not applicable

10. Measurement of Effect

This is a protocol designed to conform to RDRC regulations and has the specific purpose to study the equivalence of a radiopharmaceutical made using generator and cyclotron produced ^{68}Ga. It is not a therapeutic study and therefore does not have end point of treatment outcome.

10.1 Response Criteria

Not applicable. This is not a therapeutic study.

10.2 Duration of Response

Not applicable. This is not a therapeutic study.

10.3 Progression-Free Survival

Not applicable. This is not a therapeutic study.

10.4 Other Response Parameters

Not applicable. *This is not a therapeutic study.*

11. Data Reporting / Regulatory Considerations

11.1 Data Collection

The data collection plan for this study is to utilize REDCap to capture all treatment, toxicity, efficacy, and adverse event data for all enrolled subjects.

11.1.1 REDCap

REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill-Cornell Medical Center CTSC. It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

11.2 Regulatory Considerations

11.2.1 Institutional Review Board/Ethics Committee Approval

As required by local regulations, the Investigator will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, before study initiation.

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the patients, and any other relevant study documentation will be submitted to the appropriate Ethics Committee. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the IP is released to the Investigator. Any necessary extensions or renewals of IEC/IRB approval must be obtained for changes to the study, such as amendments to the protocol, the ICF, or other study documentation. The written approval of the IEC/IRB together with the approved ICF must be filed in the study files.

The Investigator will report promptly to the IEC/IRB any new information that may adversely affect the safety of the patients or the conduct of the study. The Investigator will submit written

summaries of the study status to the IEC/IRB as required. On completion of the study, the IEC/IRB will be notified that the study has ended.

Neither the Investigator nor BMS will modify or alter this protocol without the agreement of the other. All agreed protocol amendments will be clearly recorded on a protocol amendment form and will be signed and dated by the original protocol approving signatories. All protocol amendments will be submitted to the relevant institutional IEC/IRB for approval before implementation, as required by local regulations. The only exception will be when the amendment is necessary to eliminate an immediate hazard to the trial participants. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter.

Once protocol amendments or consent form modifications are implemented at the lead site, Weill Cornell Medicine, updated documents will be provided to participating sites. Weill Cornell Medicine must approve all consent form changes prior to local IRB submission.

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

11.2.2 Ethical Conduct of the Study

The Investigators and all parties involved should conduct this study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines and the applicable national and local laws and regulatory requirements.

This study will be conducted under a protocol reviewed and approved by the applicable ethics committees and investigations will be undertaken by scientifically and medically qualified persons, where the benefits of the study are in proportion to the risks.

11.2.3 Informed Consent

The investigator or qualified designee must obtain documented consent according to ICH-GCP and local regulations, as applicable, from each potential subject or each subject's legally authorized representative prior to participating in the research study. Subjects who agree to participate will sign the approved informed consent form and will be provided a copy of the signed document.

The initial ICF, any subsequent revised written ICF and any written information provided to the subject must approved by IRB prior to use. The ICF will adhere to IRB/IEC requirements, applicable laws and regulations.

If consent cannot be obtained in person, written consent can be obtained via a HIPAA-compliant method per the following procedure:

- The participant receives a copy of the informed consent document (e.g., via mail, fax or email) in advance of discussion regarding the study. If mailed, two copies must be mailed. This allows the participant to retain a copy for reference when their signed document is returned to the site. A final copy with all necessary signatures will be sent back to the participant from the site.
- The investigator or designee discusses the study with the potential participant either via telephone or video conferencing. The investigator/designee must have the same consent discussion via telephone/video conferencing that they would have had with the participant during an in-person meeting. The investigator/designee must also implement a method to ensure the identity of the participant (e.g., verification of state identification or other identifying documents or use of personal questions or visual methods). The investigator/designee will also remind the potential participant to conduct this informed consent discussion in a private location to ensure privacy.
- The investigator or designee will provide a comprehensive explanation of the purpose, procedures, and possible risks/benefits of the study in language that is understandable to a non-medically trained person; explain the participant responsibilities and the fact that participation is voluntary; that the participant may withdraw from the study at any time; and that the decision not to participate or to withdraw will not affect the patient's care in any way. The investigator or designee will provide ample opportunity for the participant to ask questions and to consider the decision.
- If the participant expresses a sustained interest, instructions will be given about how the participant needs to sign and date the consent form and how to transmit the signed form back.
- Once the research team receives the signed informed consent document from the participant, the investigator/designee who conducted the consent process must sign and date the document using the current date. Under the signature line, the investigator/designee must document whether consent was obtained over the telephone or video conferencing, the date of the telephone/video conference, and the date the signed consent was received. For example, "Discussed with [participant name] via [telephone or videoconferencing] on [insert date] and received signed consent form on [insert date]." Include a brief reason for performing the informed consent discussion over the telephone/videoconferencing.
- The date the investigator/designee signs the informed consent document, not the date the consent discussion with the participant took place, is the official date of informed consent for the participant on the trial. The informed consent

form is not valid and study enrollment cannot proceed unless all pages are received and appropriately filled out/signed/dated by the participant.

- The final informed consent document must be filed in the designated investigator/site regulatory file location. A copy of the final informed consent document, signed by the participant and the investigator or designee, must be sent back to the participant via email/scan, fax, or postal mail.

11.2.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor-Investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

11.2.5 Record Retention

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the IP. In addition, all subjects medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

12. Statistical Considerations

Up to 30 patients will undergo a dynamic whole-body scan with ^{68}Ga-PSMA$_{Gen}$ and later ^{68}Ga-PSMA$_{cyc}$ with a maximum time of 2 days and a minimum time of 6 h between the two injections. All 22 patients will receive ^{68}Ga-PSMA$_{Gen}$ at a specific activity of 1-2 Ci/µmol, the typical specific activity used in clinical trials with ^{68}Ga-PSMA. We expect the ^{68}Ga-PSMA$_{cyc}$ to be delivered and injected at a specific activity of 0.1- 2.0 Ci/umol given the rigors of delivery. We will accept doses in this range as the prior small animal imaging was designed to understand the affect of specific activity over a 20X range.

For a power of 80% a calculation of the sample size needed to test odds ratio (equality test) was performed. A sample size of 22 would give a power percentage of 18.47 with a type 1 error of 5%. This power percentage is sufficient in providing confidence that the findings will reflect a true effect. The median statistical power of studies in the neurosciences is between ~8% and ~31%.
We will not and should not be focusing on p-values but rather the estimates of the effect size with its confidence intervals.

Estimating repeatabilities using a mixed effects model framework has proven to be powerful, the repeatability (r)is calculated as the variance among group means (group-level variance) over the sum of group-level and data-level (residual) variance (v). A pearson's correlation coefficient will demonstrate also present the repeatability of results. Intraclass correlation values for both groups will be calculated to test if the groups differ in repeatability. These collection of tests(functions) for estimating repeatability of measurements with a single grouping factor are all performed in R statistical software.

To quantify the agreement between the two scans, we will use the repeated measures correlation coefficient to account for multiple observations per subject. We will calculate the repeated measures correlation-coefficient for the SUVmax and SUVmean for reference regions as well as regions suspicious for metastatic disease. We will measure SUVmean and SUVmax of the same Regions of Interest (ROI) in both scans using the PET analysis software we use in our clinical practice. The two scans will be retrieved and the exact same ROIs will be drawn at the same time for the two scans (software offers a copy-paste function so that no discrepancies exist between the two measurements). The SUVmean and SUVmax obtained from both scans for each Region of Interest will then be analyzed to determine the within-subject coefficient of variation value as measured by the Bland Altman analysis. If the agreement between the two scans lies within an acceptable rate (which we consider 30% based on previously published data), we will consider the two methods equivalent.

Also, as aforementioned the Bland-Altman Test presents proof of repeatability analysis.

13. Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safe use of the drug or device under investigation. Safety will be monitored by evaluation of adverse events reported by subjects or observed by investigators or research staff, as well as by other investigations such as clinical laboratory tests, x-rays, electrocardiographs, etc.

13.1 Adverse Event Definition

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

13.1.1 Investigational Agent or Device Risks (Expected Adverse Events)

The non-radiation exposure related risks that may be experienced during the scans are related to the radiotracer infusion and can be:

- Bruising or bleeding at the site of the radiotracer injection
- Infection at the site of injection
- Allergic type reaction

13.1.2 Adverse Event Characteristics and Related Attributions

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.
  -

13.1.3 Recording of Adverse Events

All adverse events will be recorded on a subject specific AE log. The AE log will be maintained by the research staff and kept in the subject's research chart.

13.1.4 Reporting of AE to WCM IRB

All AEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link:
http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

13.2 Definition of SAE

SAEs include death, life threatening adverse experiences, hospitalization or prolongation of hospitalization, disability or incapacitation, overdose, congenital anomalies and any other serious events that may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition. *(Modify as necessary)*

13.2.1 Reporting of SAE to IRB

All SAEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link:
http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

13.2.2 Reporting of SAE to FDA

IND application sponsor must report any suspected adverse reaction or adverse reaction to study intervention that is both serious and unexpected. Unexpected fatal or life-threatening suspected adverse reactions represent especially important safety information and must be reported to FDA as soon as possible but no later than 7 calendar days following the sponsor's initial receipt of the information.

i. death,
ii. a life-threatening adverse event,
iii. in-patient hospitalization or prolongation of existing hospitalization,
iv. a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
v. a congenital anomaly or birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or research subject and may require medical or surgical intervention to prevent one of the outcomes listed as serious

CDER INDs:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Investigational Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

13.3 AE/SAE Follow Up

All SAEs and AEs reported during this study will be followed until resolution or until the investigator confirms that the AE/SAE has stabilized and no more follow-up is required. This requirement indicates that follow-up may be required for some events after the subject discontinues participation from the study.

13.4 Time Period and Frequency for Event Assessment and Follow Up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

All reportable events will be recorded with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

14. Unanticipated Problems Involving Risks to Subjects or Others

14.1 Definition of Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO)

The reporting of UPIRTSOs applies to non-exempt human subjects research conducted or supported by HHS. Provide the definition of an UPIRTSO being used for this clinical trial. An incident, experience, or outcome that meets the definition of an UPIRTSO generally will warrant consideration of changes to the protocol or consent in order to protect the safety, welfare, or rights of participants or others. Other UPIRTSOs may warrant corrective actions at a specific study site. Examples of corrective actions or changes that might need to be considered in response to an UPIRTSO include:

- Modification of inclusion or exclusion criteria to mitigate the newly identified risks
- Implementation of additional safety monitoring procedures
- Suspension of enrollment of new participants or halting of study procedures for enrolled participants
- Modification of informed consent documents to include a description of newly recognized risks
- Provision of additional information about newly recognized risks to previously enrolled participants.

14.1.2 Unanticipated Problem Reporting

The investigator will report unanticipated problems (UPIRTSOs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UPIRTSO report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UPIRTSO;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UPIRTSO.

To satisfy the requirement for prompt reporting, UPIRTSOs will be reported using the following timeline:

- UPIRTSOs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the event.
- Any other UPIRTSO will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), Food and Drug Administration (FDA), and the Office for Human Research Protections (OHRP) within <insert timeline in accordance with policy> of the IRB's receipt of the report of the problem from the investigator.]

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