^{68}Ga PSMA-HBED-CC PET in Patients with Biochemical Recurrence

Sponsor Investigator: Michael M. Graham, PhD, MD
University of Iowa Department of Radiology
Iowa City, IA 52242
(319) 356-1616
michael-graham@uiowa.edu

Sub-Investigators: Yusuf Menda, MD
Janet Pollard, MD
Parren McNeely, MD
Yousef Zakharia, MD
Chad Tracy, MD
Mark Smith, MD
Kenneth Nepple, MD
John Sunderland, Ph.D.

Biostatistician: Timothy Ginader, MS
Biostatistician
Holden Comprehensive Cancer Center
University of Iowa Hospitals and Clinics
timothy-ginader@uiowa.edu

Protocol Number: 201709730

IND Number: 135,727

Protocol version /Date: Amendment 4 – 23 January 2018
Amendment 3 – 28 November 2017
Amendment 2 – 21 November 2017
Amendment 1 – 24 October 2017
FDA approved protocol - 20 April 2017

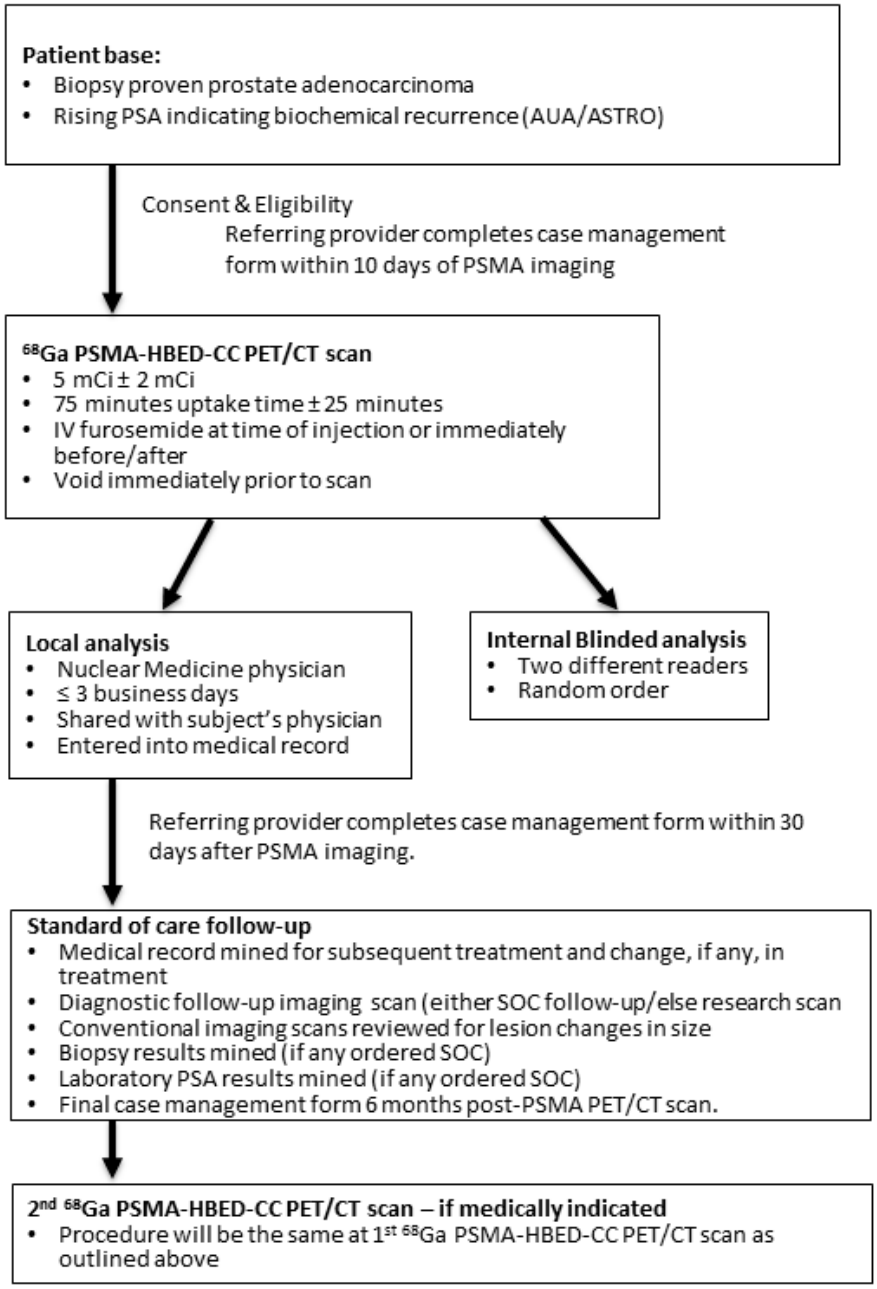
SUMMARY OF CHANGES

Section	Change
January 23, 2018	
Throughout protocol	Formatting
Cover Page	Updated version and date
Schema	Updated Schema
TOC	Updated TOC
5	Removed any mention of a 2nd research only scan during the 1st imaging PSMA imaging visit. The 2nd research only scan, detailed in Section 11-Correlative studies, is no longer part of the project.
5.1.3	Removed the option to obtain a diagnostic CT with the PSMA scan.
5.5	Updated references to tables and other sections since Correlative studies section was removed.
5.9	Removed "Extraordinary medical circumstances", not appropriate for this study.
6.1	Changed baseline data collection window from 30 day to 3 months prior to PSMA imaging.
6.2	Clarified pre-imaging assessments.
6.3	Clarified post-imaging assessments.
6.4	Added laboratory section
11	Removed Correlative studies section. The research only scan will not be obtained.
11	Study Calendar updated to reflect changes in the protocol.
12	Updated all references to tables and other sections since Correlative studies section was removed.
13	Updated all references to sections since Correlative studies section was removed.
November 28, 2017	
Cover Page	Updated version and date, and added a biostatistician
12	Added optional 2nd PSMA PET/CT scan if medically indicated
November 21, 2017	
Cover Page	Corrected IND # 135,727, updated version and date
7.1	Corrected ^{68}Ga PSMA-HBED-CC IND # 135,727
October 24, 2017	
Cover Page	Added IRB #, IND #, and updated dated version and date
Schema	Updated Schema
TOC	Updated TOC
1	Objectives updated
5.4.5	Changed from central blind reader to internal blind readers. Also clarified reference to central blind reader to internal blind readers through remainder of study protocol.
5.5	Referenced Section 13 rather than having same information in multiple places in the protocol.
6	Clarified Patient Assessment section
7.1	Added ^{68}Ga PSMA-HBED-CC IND # 135,272
12	Updated study calendar

13	Updated Efficacy Assessment – This is the same information that was in the previous section 13, however, laid out in a way to more easily evaluate the PSMA, conventional imaging and pathology assessment.
14.1	Statistical Justification added
14.2	Primary and secondary endpoints updated to match the updated objectives and analysis for this pilot study.
14.3	Updated section references throughout, as information in Section 13 was moved around.
14.4	Updated to match changes to objectives

April 20, 2017	v0.07
Receipt	Initial submission to FDA, 1571 0000

SCHEMA



End of study = 12 months after 1st 68Ga PSMA-HBED-CC PET/CT scan

TABLE OF CONTENTS

1. OBJECTIVES

1.1. Primary objective

1.1.1. Determine sensitivity on a per-subject basis of ^{68}Ga PSMA-HBED-CC PET/CT for detecting tumor location, confirming with conventional imaging, clinical follow-up, and histopathology/biopsy where available.

1.2. Secondary objective

1.2.1. Determine positive predictive value on a per-subject and per-region basis of ^{68}Ga PSMA-HBED-CC PET/CT for detecting tumor location, confirming with histopathology and conventional imaging.

1.2.2. Continue to evaluate safety of ^{68}Ga PSMA-HBED-CC injection as categorized by CTCAE 4.03.

1.3. Exploratory objective

1.3.1. Determine the impact of ^{68}Ga PSMA-HBED-CC PET/CT on clinical management in patients who have prostate cancer with biochemical recurrence.

1.3.2. Determine inter-reader reproducibility.

2. BACKGROUND AND RATIONALE

2.1. Current imaging of prostate cancer

Per NCCN guidelines,[3] at the time of biochemical recurrence, imaging is performed to detect and characterize the disease to determine treatment or guide change in management. Imaging can evaluate anatomic or functional parameters. The following imaging is recommended as standard techniques at this time-point:

- Imaging is performed for the detection and characterization of disease to select treatment or guide change in management
- Anatomic imaging techniques include plain film radiographs, ultrasound, CT, and MRI.
- Functional imaging techniques include radionuclide bone scan, PET, and advanced MRI techniques such as spectroscopy and diffusion-weighted imaging (DWI).

2.2. Prostate Cancer, Biochemical Recurrence

Biochemical recurrence will be defined using the AUA and ASTRO-Phoenix definitions. Specifically:

2.2.1. Post radical prostatectomy (RP) – AUA recommendation[1] is PSA greater than 0.2 ng/mL measured 6–13 weeks after RP and Confirmatory persistent PSA greater than 0.2 ng/mL.

2.2.2. Post-radiation therapy – ASTRO-Phoenix consensus definition[2] nadir + greater than or equal to 2 ng/mL rise in PSA

2.3. ^{68}Ga-HBED-CC PSMA (^{68}Ga PSMA-HBED-CC)

Current evidence regarding detection rate of biochemical recurrence (BCR) with ^{68}Ga-HBED-CC PSMA (^{68}Ga PSMA-HBED-CC) PET/CT from two recent papers:

- Morigi, 2015: Detection rate was 50% when PSA was below 0.5 ng/mL, 69% for PSA 0.5–2.0 ng/mL, and 86% when PSA was above 2.0 [4].
- Eiber, 2015: Detection rate was 57.9% for PSA 0.2 to <0.5 ng/mL, 72.7% for PSA 0.5 to <1, 93.0% for 1 to <2.0, and 96.8% for ≥ 2.0 [5].

2.4. Prior human subjects experience

Safety. No adverse drug reactions have been reported in the literature for ^{68}Ga PSMA-HBED-CC. As a PET tracer, the drug should remain pharmacologically inert and not perturb the biological system. Afshar-Oromieh and colleagues[6,7] as well as Green *et al*.[8] have clearly stated that no adverse events or pharmacologic events were observed during their studies. Adverse events were not discussed in other reviewed studies[9-16] or case reports.[17,18] In total, these papers provide data regarding more than 1200 subjects without any noted adverse reactions.

Efficacy. To date, there have been 11 studies[6,7,10-12,14,15,26-29] describing use of ^{68}Ga PSMA-HBED-CC and 4 clinical trials.[8,13,16] Tables with key information of reviewed papers are provided (Tables 6.1, 6.2, and 6.3) of the IND Application

Maurer *et al.* (2014) [Germany].[11] The purpose of this retrospective study was to investigate the diagnostic efficacy of ^{68}Ga PSMA-HBED-CC -PET imaging when compared against radical prostatectomy and templated lymph node dissection as well as conventional imaging (CT, MRI). The primary inclusion criterion was intermediate-to-high risk prostate cancer scheduled to undergo radical prostatectomy. The only exclusion criterion was presence, or history, of a secondary malignancy. A total of 130 patients were reviewed. A contrast enhanced diagnostic CT was performed at the same imaging session as the PET scan. A double-trained board certified radiologist-nuclear medicine physician blinded to post-operative histopathological results analyzed all the imaging data sets (^{68}Ga PSMA-PET/CT and PET/MR). Conventional imaging was read prior to the ^{68}Ga PSMA-PET data. Results yielded a patient-based ROC AUC of 0.835 (95% CI 0.763 – 0.908) for ^{68}Ga PSMA-PET and an AUC of 0.691 (95% CI 0.592-0.789) for conventional imaging. For ^{68}Ga PSMA-PET, patient-based sensitivity was 65.9 %, specificity was 98.9%, and an overall accuracy of 88.5%. In contrast, conventional imaging had a patient-based sensitivity of 43.9%, specificity of 85.4%, and an overall accuracy of 72.3%. On a template-based analysis driven by lymph node dissection, the ^{68}Ga PSMA-PET sensitivity was calculated as 78.2%, specificity as 99.1%, and accuracy as 95.7%. Conventional imaging resulted in a sensitivity of 29.1%, specificity of 97.2%, and accuracy of 86.1%.

Van Leeuwen *et al.* (2014) [Australia].[13] The purpose of this prospective trial was to assess accuracy of ^{68}Ga PSMA-HBED-CC -PET/CT for lymph node

staging in intermediate- and high-risk prostate cancer. Criteria for selection included planned radical prostatectomy, treatment naïve, negative bone scan, no concurrent (or history of) a secondary malignancy, and at >5% risk of metastatic lymph nodes. Patients with suspected extra-nodal disease on prior contrast-enhanced CT were excluded. ^{68}Ga PSMA-HBED-CC PET/CT was performed <4 weeks before the radical prostatectomy and lymph node dissection. A total of 30 men were enrolled and evaluated. A non-contrast enhanced CT was performed at the same imaging session of the ^{68}Ga PSMA-HBED-CC -PET. Images were analyzed by two nuclear medicine physicians; it is not stated if the physicians were blinded to the pathologic results or if the scan interpretations were completed prior to surgery. Results yielded a patient-based specificity of 95%, sensitivity of 64%, positive predictive value of 88%, and negative predictive value of 82%. Lymph node analysis yielded specificity of 100%, sensitivity of 58%, PPV of 94% and NPV of 98%. The mean size of true-positive metastatic lymph nodes was 4.7 mm (± 1.4mm) and false-negative size was 2.7mm (± 1.3mm).

Eiber *et al.* (2015) [Germany].[10] The purpose of this retrospective study was to investigate the detection rate of ^{68}Ga PSMA-HBED-CC PET/CT in men with biochemical recurrence (PSA ≥ 0.2 ng/mL). Only men who had undergone a radical prostatectomy, had not received chemotherapy, and had a diagnostic CT done with the PSMA imaging study were included. Men undergoing antiandrogen therapy (n=70) were included. A total of 248 subjects were included in the analysis. The active comparator was the diagnostic CT done simultaneously with the PET imaging. Scans were interpreted by a board certified radiologist and a board certified nuclear medicine physician. The reviewers were not blinded. No significant detection effect was observed with antiandrogen use (p=0.0783). PSMA was able to identify additional areas of disease involvement in 61 subjects (24.6%) whereas CT showed additional regions in 17 subjects (6.9%). A significant limitation of the study was a lack of histopathology for outcome comparisons. Sensitivity, specificity, positive and negative predictive values are not provided.

Afshar-Oromieh *et al.* (2015) [Germany].[7] The purpose of this retrospective study was to analyze the diagnostic value of ^{68}Ga PSMA-HBED-CC PET/CT in a large cohort with multiple variables. The cohort was designed to align with a generalized population; men were included if they had suspected progressive disease following conventional therapy (radiation therapy and/or radical prostatectomy, n=292) or to determine metastatic disease burden prior to initial therapy (n=27). Of those with suspected recurrence, 86 were on antiandrogen therapy. A non-contrast enhanced diagnostic CT scan was performed at the same imaging session as the PET scan; additionally, a low-dose attenuation scan was performed for the ^{68}Ga PSMA-HBED-CC PET. Scans were interpreted by two board-certified nuclear medicine physicians. No adverse events or clinically detectable pharmacological effects were noted in any of the subjects following injection of the PSMA-HBED-CC

radiotracer. A total of 901 tumor lesions were observed in 319 subjects. Lesion-based analysis yielded sensitivity of 76.6%, specificity of 100%, negative predictive value of 91.4%, and positive predictive value of 100%. Because all patients were assumed to have tumor and therefore could not be considered 'true negative,' the authors did not provide a per-patient calculation.

Green *et al.* (2017) [Indiana University School of Medicine][8]. The purpose of this small study was to estimate human radiation dosimetry for ^{68}Ga PSMA-HBED-CC under approval of an RDRC research protocol. Both biodistribution and pharmacokinetics were evaluated in subjects (n = 9). Administered dose of ^{68}Ga PSMA-HBED-CC was 3.04 mCi and images were acquired at 15 minutes post-injection, 60 minutes post-injection, and 90 minutes post-injection. Subjects reported no symptoms or adverse reactions following radiopharmaceutical administration. Organ dose estimates are provided 22 organs and for whole body.

It should be noted that radiolabeled PSMA ligands have been shown to be taken up by rectal carcinoma,[19] gastrointestinal stromal tumors,[20] renal cell carcinoma,[21] pancreatic serous cystadenoma,[22] stromal hyperplasia of the breast,[23] B-cell follicular non-Hodgkin's lymphoma,[24] and Paget disease.[25]

Summary. To date, a prospective, well-controlled clinical trial evaluating the efficacy of ^{68}Ga PSMA-HBED-CC PET/CT has not been performed for prostate cancer. Robust trials for both initial diagnosis as well as those men with suspected recurrence needs to be designed and performed. Current retrospective review of ^{68}Ga PSMA-HBED-CC PET/CT done in foreign nations suggests strong efficacy of the ^{68}Ga PSMA-HBED-CC radiotracer. Currently, three clinical trials are underway – two foreign, one domestic.[30-32] Additional pivotal phase 3 trials should be completed in the U.S. to determine effectiveness in the generalized population and determine requirements for implementation if found effective.

2.5. Rationale

Imaging and staging of prostate cancer is critical for surgical and treatment planning. We aim to image patients with suspected metastatic prostate cancer using Gallium-68 labeled HBED-CC PSMA (^{68}Ga PSMA-HBED-CC) in order to demonstrate its utility. We plan to utilize this data to obtain further approvals of the ^{68}Ga PSMA-HBED-CC compound, so that this agent will become widely available for clinical imaging in prostate cancer patients.

^{68}Ga PSMA-HBED-CC has become of particular interest due to 2 recent publications. The first article demonstrated that ^{68}Ga PSMA-HBED-CC PET/CT had a higher sensitivity for the detection of disease than F-18 choline in a head-to-head intra-patient comparison that included 37 patients[7]. The second paper looked at the sensitivity of ^{68}Ga PSMA-HBED-CC in the detection of metastatic lesions in patients with recurrent prostate cancer[8]. Their results showed a detection rate of 50% for patients with a PSA less than 1 ng/ml, and detection rate above 85% for patients with a PSA greater than 2 ng/ml. These detection rates are significantly higher than that reported by groups using choline[9]. However, ^{68}Ga PSMA-HBED-CC was not

patented and therefore no company or private entity will make the investment required to bring ^{68}Ga PSMA-HBED-CC to market. In the vacuum of availability, academic groups must take the lead in order to collect the necessary data for future FDA approval.

We aim to study the ability of ^{68}Ga PSMA-HBED-CC to detect disease at biochemical recurrence in post-prostatectomy or post-radiation patients.

3. SUBJECT SELECTION

3.1. Eligibility Criteria

3.1.1. Pathologically proven prostate adenocarcinoma.

3.1.2. Rising PSA after definitive therapy with prostatectomy or radiation therapy (external beam or brachytherapy).

- If post-radical prostatectomy, PSA > 0.2 ng/mL measured > 6 weeks post-operatively and confirmatory persistent PSA greater than 0.2 ng/mL (AUA recommendation for biochemical recurrence).
- If post-radiation therapy, PSA that is equal to, or greater than, a 2 mg/mL rise above PSA nadir (ASTRO recommendation for biochemical recurrence).

3.1.3. Not receiving any other investigational agents (i.e., unlabeled drugs or drugs under an IND for initial efficacy investigations).

3.1.4. No other malignancy within the past 2 years (skin basal cell or cutaneous superficial squamous cell carcinoma or superficial bladder cancer are exempt from this criterion).

3.1.5. Karnofsky performance status (KPS) ≥ 50 (ECOG/WHO 0, 1, or 2).

3.1.6. Ability to understand and willingness to provide informed consent.

3.2. Exclusion Criteria

3.2.1. Cannot receive furosemide.

3.2.2. History of Stevens-Johnson syndrome.

3.2.3. History or diagnosis of Paget's disease.

3.2.4. Malignancy other than current disease under study.

3.2.5. Allergy to sulfa or sulfa-containing medications.

3.2.6. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

4. REGISTRATION PROCEDURES

Once informed consent is signed:

- Attach scanned copy of completed eligibility checklist in OnCore for review by the CRSO/designated safety monitor at the time of quarterly audits.
- Enter subject into the OnCore database of the Holden Comprehensive Cancer Center.

- Scan the record of consent into the subject's medical record.

5. PROCEDURES

Protocol should not supersede standard of care procedures for patient safety.

5.1. Imaging preparation

5.1.1. **Oral hydration.** Participants will be encouraged to maximize hydration the day before and day of ^{68}Ga PSMA-HBED-CC imaging.

5.1.2. **Furosemide**. 20 mg furosemide (IV push) will be administered concurrently or immediately after radiotracer administration to minimize PET scatter artifacts from excreted radiotracer accumulation in the kidney and urinary bladder.

5.1.3. **Contrast**. Imaging contrast will not be ordered as part of this study.

5.1.4. **Voiding**. Participants will be asked to void prior to radiotracer injection.

5.2. ^{68}Ga PSMA-HBED-CC administration

5.2.1. **Dose**. 3-7 mCi (111 – 259 MBq). Target 5 mCi.

5.2.2. **Route of administration**. Intravenous.

5.2.3. **Frequency**. Once per PET scan.

5.2.4. **Uptake time**. 75 minutes ± 25 minutes. Target 75 minutes

5.3. Prohibited Medications

None.

5.4. PET/CT scan

5.4.1. **Scan coverage**. Scan coverage will extend from mid-thigh to the base of the skull, starting from the mid-thighs to minimize urinary bladder radiotracer accumulation at the start of PET imaging. Subject to void immediately prior to imaging.

5.4.2. **Bed position.** Scan time will be dependent on scanner capabilities. At a minimum, 3 minutes per bed position will be used.

5.4.3. **Discharge.** Subject must be monitored for adverse events for a minimum of 2 hours post-injection.

5.4.4. **Local Analysis.** A board-certified nuclear medicine physician on-site will interpret the images within 3 business days of the imaging study. These interpretations will not be used for final evaluation, however regional positivity results will be collected as study data.

5.4.5. **Internal Blinded Reads.** Imaging data will be interpreted by two different readers in a random order at separate reading sessions. Cross sectional imaging from the CT will be available for anatomic correlate. Final reads for each subject will be interpreted as positive or negative for the presence of pelvic nodal disease, and positive or negative for the presence of osseous metastatic disease and soft tissue metastases outside of the pelvis. All readers will have undergone ^{68}Ga PSMA PET training.

5.4.6. **Results dissemination.** Local analysis will be shared with the subject's

clinician and will be included in the subject's medical record.

5.5. **Visual Interpretation of PET data (internal blind reads)**

Regions of suspected disease will be graded on a two-point scale by each reader (0=Negative or 1=Positive). A region will be judged as positive if at least one lesion in this region is visually positive. Regions are defined in Table 12.1 in Section 12. Criteria for visual interpretation positive for disease are detailed in Section 12.1.1.

5.6. **Follow-up imaging**

All subjects should be followed as per standard of care consistent with the institution/physician. Reports and copies of any conventional imaging obtained during the 12 month window following the PSMA-HBED-CC PET/CT scan will be obtained. Clinical notes will also be reviewed to identify metastatic lesions. Interpretation of follow-up imaging is performed by local institution following standard procedures. Preferable comparison imaging would be the same imaging device as the initial re-staging work-up as per RECIST guidelines.

^{68}Ga PSMA-HBED-CC PET positive findings will be validated as true positive or false positive as outlined in more detail below. False negative ^{68}Ga PSMA-HBED-CC PET findings will only be determined when positive biopsies of ^{68}Ga PSMA-HBED-CC PET negative lesions that are present on conventional imaging are performed as part of standard clinical care. This scenario is uncommon.

^{68}Ga PSMA-HBED-CC PET validation based on follow-up imaging (CT, MRI, bone scan):

5.6.1. **Lymph nodes** ^{68}Ga PSMA-HBED-CC positive nodes will be assessed for change in size using standard of care follow-up imaging.

5.6.2. **PSMA-positive osseous or metastatic lesions.** ^{68}Ga PSMA-HBED-CC positive osseous or distant metastatic lesions will be followed by other imaging (bone scan, NaF PET, CT or MRI) at the treating physician's discretion and local standard of care.

5.6.3. **Biopsy.** Biopsies to determine metastases or provide information for re-staging should be performed at treating physician's discretion and per local standard of care.

5.7. **General Concomitant Medication and Supportive Care Guidelines**

In general, subjects may receive full concomitant and supportive care throughout this trial.

5.8. **Follow-Up**

5.8.1. **Active follow-up.** Subjects will be actively followed for acute adverse events for 10 radioactive half-lives rounded up to the calendar day (as per the established standard). With a half-life of 67.71 minute for ^{68}gallium, the active follow-up will be a minimum of 1 calendar day.

5.8.2. **Long term follow-up.** After the active follow-up period, the subject will return to standard follow-up with their physician. Subject's outcome will be followed through passive chart review. Contact with subject and/or subject's treating physicians may occur to better define treatment outcomes.

5.9. **Criteria for removal from study**

- **Consent**. Subjects must be able to continue to provide consent for this study. If a treating physician or study team member believes a subject can no longer provide prospective consent, the investigator will be contacted to determine if the subject can provide consent and is able continue on study.
- **Refusal to continue in the study.** In this event, the reasons for withdrawal will be documented.

6. PATIENT ASSESSMENTS

6.1. **Post-consent Baseline Data Collection**

Post-consent, the following data should be collected

6.1.1. **Serial PSA.** Most recent serial PSA values defining biochemical recurrence (i.e., two PSA values meeting AUA or ASTRO recurrence criteria).

6.1.2. **PSA.** Baseline PSA levels within 3 months of ^{68}Ga PSMA-HBED-CC PET/CT should be obtained.

6.1.3. **Pathology**. Copy of original pathology report documenting Gleason score and date sample obtained. Also, obtain a copy of any pathology reports 3 months prior to the ^{68}Ga PSMA-HBED-CC PET/CT.

6.1.4. **Bone scan.** If a bone scan was performed within 3 months of ^{68}Ga PSMA-HBED-CC PET/CT, obtain a copy of the images and the report.

6.1.5. **MRI**. If an MRI was performed within 3 months of ^{68}Ga PSMA-HBED-CC PET/CT, obtain a copy of the images and the report.

6.1.6. **CT scan**. If a CT was performed within 3 months of ^{68}Ga PSMA-HBED-CC PET/CT, obtain a copy of the images and the report.

6.1.7. **Change in management.** A pre-imaging survey of planned clinical management will be performed ≤ 10 days prior to ^{68}Ga PSMA-HBED-CC PET/CT imaging.

6.2. **Pre-Imaging Assessments (Baselines)**

6.2.1. **Constitutional adverse events.** A baseline evaluation will be obtained prior to injection and will be graded against CTCAE.

6.2.2. **Vital signs**. Heart rate, blood pressure, and temperature will be obtained immediately before and after injection of ^{68}Ga PSMA-HBED-CC, in a supine position.

6.3. **Post-Imaging Assessments**

6.3.1. **Vital signs**. Heart rate, blood pressure, and temperature will be obtained when subject is supine immediately after the imaging.

6.3.2. **Constitutional adverse events.** Prior to discharge from the PET Imaging Center, the subject will be assessed for untoward medical event(s) that have occurred since injection of ^{68}Ga PSMA-HBED-CC. These will be graded with CTCAE.

6.3.3. **Symptom review**. Subject will be contacted by telephone or in person between 1 to 3 business days after PSMA-HBED-CC imaging to screen for

adverse events. Subject must be contacted at least once after 24h post-injection.

6.4. **Follow-up**

6.4.1. **Change in management.** A post-imaging survey of clinical management using PSMA-HBED-CC PET/CT information will be performed ≤ 30 days of PSMA-HBED-CC PET/CT imaging for assessment of change in clinical management.

6.4.2. **Change in management 6 months post imaging.** A survey of clinical management will be performed approximately 6 month after the PSMA-HBED-CC PET/CT imaging for assessment of change in clinical management.

6.4.3. **Follow-up imaging**. Conventional imaging ordered per standard of care up to 12 months post ^{68}Ga PSMA-HBED-CC PET/CT, will be obtained for study analysis. If imaging is NOT obtained per standard of care the research study will obtain a CT (abdomen and pelvis w/ contrast if contrast not contraindicated). Readers will be unblinded to all results and will be specifically informed of the location of the ^{68}Ga PSMA-HBED-CC PET positive lesions so follow-up measurements may be performed on the same lesions.

6.4.4. **Pathology**. Results from pathology ordered per standard of care up to 12 months post ^{68}Ga PSMA-HBED-CC PET/CT, will be obtained for study analysis.

6.4.5. **Laboratory**. Results from laboratory reports related to prostate cancer monitoring (e.g. PSA levels) ordered per standard of care up to 12 months post ^{68}Ga PSMA-HBED-CC PET/CT, will be obtained for study analysis.

6.4.6. **Second ^{68}Ga PSMA-HBED-CC PET/CT (if medically indicated)**. If the 1st ^{68}Ga PSMA-HBED-CC PET/CT scan shows lymph nodes or visceral (soft tissue) lesions positive for prostate cancer disease, but surgery or biopsy results in negative pathology; the subject may be asked to return to complete a 2nd Ga-68 PSMA-HBED-CC PET/CT imaging visit.

7. DRUG INFORMATION

7.1. **^{68}Ga PSMA-HBED-CC IND 135,727 (M. Graham, sponsor)**

7.1.1. **Availability**. Drug is available from the P E T Drug Manufacturing Unit at the University of Iowa Hospitals & Clinics.

7.1.2. **Compatibility**. No known compatibility issues.

7.1.3. **Storage and stability**. Store drug in shielded container as per local institutional guidelines. Drug has a 3 hour stability. Expiration is provided on label.

7.1.4. **Toxicities**. No known toxicities.

8. DOSE MODIFICATIONS & DELAYS

Not applicable.

9. ADVERSE EVENTS: REPORTING REQUIREMENTS

This study will also be monitored by internal oversight specialists at the University of Iowa. The Data and Safety Monitoring Plan of the Holden Comprehensive Cancer Center provides standard operating procedures to monitor all clinical cancer trials at the UIHC. All investigator-initiated trials are automatically monitored by the Data and Safety Monitoring Committee (DSMC). A detailed data and safety monitoring plan for this study is on file with the DSMC. This study has been assigned as a risk level 4 as an IND phase 2b/3 study

9.1. Determination of Reporting Requirements

The clinical research team is responsible for collecting and recording the research data. As these results are collected, all toxicities and adverse events will be identified and reported to the principal investigator (PI). The PI will determine final relationship of the event to the investigational products (^{68}Ga PSMA-HBED-CC):

- Grade 1 and 2 events do not require attributions assigned.
- Grade 3 and higher adverse events require attribution determination.
- All serious adverse events (SAEs) require attribution determination.

Toxicity will be graded according to NCI's Common Toxicity Criteria (CTCAE v4). The principal investigator will have final responsibility for determining the attribution of toxicity as it is related to the investigational product.

9.2. Institutional Review Board reporting requirements

Adverse events that meet criteria of both *serious* and *attributed* (possible, probable, or definite) to the study agent. Thus:

- Serious adverse events *and*
- Attributable to ^{68}Ga PSMA-HBED-CC

Report to the IRB *via* HawkIRB within 10 business days of event

9.3. FDA reporting requirements [M. Graham, sponsor]

Adverse events that meet criteria of *serious, unexpected,* and *attributed* (possible, probable, or definite) to ^{68}Ga PSMA-HBED-CC must be reported to the sponsor or the sponsor's appointed designee:

- Only serious adverse events are reported to FDA[21 CFR 312.32]
- Attributable to 68Ga PSMA-HBED-CC with a causal relationship as described [21 CFR 312.32 (c)(1)(i)]
- Unexpected, as defined by the FDA: "…not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended."

9.4. Routine Adverse Event Reporting Requirements to DSMC

For non-serious adverse events, documentation must begin at radiotracer injection and continue through 24 hours post injection.

Routine adverse events will be reported by submission of an adverse events log to the DSMC at the time of DSMC review.

9.5. Serious Adverse Event Reporting to DSMC

Serious adverse events occurring after ^{68}Ga PSMA-HBED-CC injection will require a notification to the DSMC within 1 business day of learning of the event. The SAE capture window will be from the administration of ^{68}Ga PSMA-HBED-CC through 24 hours after administration. Serious adverse events that occur after this window are reportable if they are deemed reasonably attributed to the investigational drug, ^{68}Ga PSMA-HBED-CC.

10. CLINICAL TRIAL MONITORING

Clinical trial monitoring will be conducted to ensure the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol and/or amendment, with good clinical practice (GCP), and with applicable regulatory requirement(s).

10.1. University of Iowa's Human Subjects Office

The University of Iowa's Human Subjects Office (HSO) provides five different types of monitoring visits (post-approval responsibilities review, post-approval monitoring and education visit, directed monitoring, department of defense sponsored research monitoring, student principal investigator review). The HSO also provides an IND educational visit combined with a post-approval responsibilities review.

- Monitoring is performed by the HSO from their roster of qualified individuals.
- Monitoring is on-site.
- An educational IND visit will be requested by the PI. This will be done after IRB approval. The IRB indicate if accrual can begin prior to this visit.
- For the educational IND visit, if subjects have been consented, all signed consent documents will be reviewed.
- For the educational IND visit, the principal investigator will be provided a copy of the report documenting the visit within 1 month.
- Monitoring plans are not study specific. The plans are maintained by the HSO and are available for public review on-line.

10.2. The Holden Comprehensive Cancer Center

The Holden Comprehensive Cancer Center (HCCC) will provide monitoring for this investigator-initiated trial in compliance with their overarching monitoring plan on file with the National Cancer Institute (NCI) as well as with the individual clinical monitoring plan on file for this trial. Specifically:

- Monitoring is performed by the HCCC from their roster of qualified individuals.
- Eligibility review is ongoing, through remote review from OnCore, the clinical trials software.

- Monitoring is on-site and begins with the accrual of the first subject and will be performed at least twice per year. Frequency is adjusted based on risk, reported SAEs, compliance, patient population, and accrual rate.
- A minimum of 25% of subjects will be monitored for the entire study.
- Items reviewed include: eligibility, consent document, compliance to protocol, SAE reporting per institutional and federal requirements, accuracy of data against primary source, and investigational drug documentation.
- The sponsor-investigator will be provided draft copies of the report within one month of the visit.
- Independent audits will be conducted by the HCCC to verify monitoring is being performed per the filed clinical monitoring plan. The audit procedures are documented in their Quality Assurance Management Plan on file with the NCI.

11. STUDY CALENDAR

	Screening[a]	Baseline	V1 - PSMA-HBED-CC PET/CT [b,c]		Follow-up	
			Injection	Scan	Immediate	Long-term
Karnofsky PS	X					
informed consent	X					
PSA		≤3 mo V1				X[d]
imaging pull		≤3 mo V1				X[d]
pathology pull	X	≤3 mo V1				X[d]
serial PSA pull	X[e]					
change in management[f]		≤10d V1			≤30d V1	6 months V1
^{68}Ga PSMA-HBED-CC			5 mCi			
20 mg IV furosemide			X			
HR, BP, Temp			supine[g]	supine[g]		
voiding				X[h]		
Adverse event query[i]		X	X	X[i]		

a 30 days window before the ^{68}Ga PSMA-HBED-CC scans

b Scan will be clinically interpreted, and entered into the medical record.

c A 2nd ^{68}Ga PSMA-HBED-CC PET/CT imaging visit may occur, if medically indicated. The 2nd scan will be obtained identical to 1st scan.

d data from follow-up imaging, laboratory PSA levels, and pathology as ordered for standard of care or study purposes will be analyzed and mined for outcomes

e serial PSA documenting biochemical recurrence as defined by AUA and/or ASTRO (as appropriate)

f change in management forms completed by referring/treating physician at three timepoints: within 10 days prior to imaging, within 30 days post-imaging, and then approximately 6 months post-imaging

g HR, BP, temp performed with subject supine immediately before and after injection and post-imaging of the scan

h subject should void immediately prior to the scan.

i final adverse event assessment is done 1 to 3 days post-injection but no earlier than 24 hours post-injection

12. EFFICACY ASSESSMENTS

Determination of efficacy requires two primary assessments.

The first assessment is the clinical read of the ^{68}Ga-PSMA-HBED-CC PET/CT scan. Trained readers will identify lesions positive for prostate cancer disease, and based on these results, will categorize specifically defined anatomical regions of the subject (Table 12.2) as positive for disease by ^{68}Ga-PSMA-HBED-CC PET/CT. Criteria are described in Section 12.1 below.

The second assessment is the reference standard determination of disease positivity or negativity also performed on the same specifically defined anatomical regions (Table 12.2). The reference standard definitions are described below, and consist of a combination of pathological confirmation, conventional imaging follow-up evidence, and serial PSA measurements. Criteria are described in Section 12.2 below.

For purposes of endpoints, four major regions are identified for final analysis as defined in Table 12.1. Each region is divided into subregions as defined in Table 12.2. All primary data from ^{68}Ga-PSMA-HBED-CC PET interpretations, pathology results, and conventional imaging results, will be collected per the subregions defined below. The final region assignments and results will be derived from the subregion data as applicable.

Region	Description
1	Prostate Bed
2	Pelvis outside of prostate bed including lymph nodes
3	Extrapelvic soft tissue, lymph nodes and organ metastases (non-bone)
4	Bone metastases

Table 12-1. Major Analysis Regions

Region 2: Pelvis outside of prostate bed	Region 3: Extrapelvic soft tissue	Region 4: Bone metastases
Right obturator	Lung	Spine
Left obturator	Liver	Ribs
Right external iliac	Pancreas	Pelvis
Left external iliac	Spleen	Extremities
Right internal iliac	Intestine	Skull
Left internal iliac	Mesentary	Sternum
Other pelvic regions	Brain	Clavicle
	Other soft tissue	Other bone
	Abdominal nodes	
	Thoracic nodes	
	Other nodes	

Table 12-2. Subregion Classification

12.1. **^{68}Ga-PSMA-HBED-CC PET Results Definition**

Imaging interpretation ^{68}Ga-PSMA-HBED-CC PET:

Local Interpretations: PET images will initially be interpreted by a board certified nuclear medicine physician or a board-certified radiologist experienced in reading PET at the time of the imaging study at the institution that the study is being performed. These interpretations will not be used for evaluation of the primary endpoint.

Blinded Read Logistics: Imaging data will be de-identified. PET data will be interpreted by two different readers in a random order at separate reading sessions. Cross sectional imaging (CT or MRI) from the ^{68}Ga-PSMA-HBED-CC PET will be available for anatomic correlate. The blinded readers will be blinded to all other imaging results and all other clinical data.

Reader Positivity and Negativity Definition: Sub-regions defined in Table 12.2 will be graded for the presence of suspected disease on a two-point scale by each reader (0=Negative or 1=Positive). A region will be judged as positive if at least one lesion in this region is visually positive..

12.1.1. Criteria for visual interpretation:

Sub-regions of suspected disease will be graded on a two-point scale by each blinded reader (0=Negative or 1= Positive). A region will be judged as positive if at least one lesion in this region is visually positive.

12.1.1.1. Lymph nodes will be considered positive if the ^{68}Ga-PSMA-HBED-CC uptake is focal and greater than blood pool (adjacent or mediastinal blood pool).

- Lymph nodes will be classified further by region: pelvic, retroperitoneal, thoracic and other. Additionally, pelvic lymph nodes will be sub-classified according to their localization as follows: R/L obturator, R/L external iliac, R/L internal iliac and other (total of 7 subgroups). These pelvic sub-regions will be correlated with reference standard results in these sub-regions, however this sub-region data will not be directly used for evaluation of the primary or secondary endpoints, but for exploratory analysis.

12.1.1.2. Visceral lesions will be considered positive if the ^{68}Ga-PSMA-HBED-CC uptake is focal and greater than physiologic background activity of the involvement organ or anatomic site.

- Visceral lesions will be classified further by major organ: lung, liver, pancreas... as defined in Table 2. These sub-regions will be correlated with reference standard results in these sub-regions, however this sub-region data will not be directly used for evaluation of the primary or secondary endpoints, but for exploratory analysis.

12.1.1.3. Bone lesions will be considered positive if the ^{68}Ga-PSMA-

HBED-CC uptake is focal and greater than physiologic bone marrow.

- Bone lesions will be classified by further by region: spine, ribs, pelvis, extremities, skull, sternum, and clavicle, as Defined in Table 12.2. These sub-regions will be correlated with reference standard results in these sub-regions, however this sub-region data will not be directly used for evaluation of the primary or secondary endpoints, but for exploratory analysis.

12.1.1.4. Prostate bed and prostate lesions will be considered positive if the ^{68}Ga-PSMA-HBED-CC uptake is focal and greater than physiologic background activity of the involvement organ or anatomic site.

12.2. **Reference standard definition:**

12.2.1. Histopathology/Biopsy will be the primary determinate of tissue positivity and negativity for prostate cancer disease. Pathology date, organ, and location as well as any notes related to the pathology will be obtained from the subject chart. The anatomical region/sub-region the pathology occurred in will be assigned by the investigator team:

^{68}Ga-PSMA-HBED-CC positive findings are aimed to be confirmed by histopathology/biopsy if clinically feasible. Pathology performed 60 days before or after the ^{68}Ga-PSMA-HBED-CC PET will be available for correlation.

Histopathological procedures and biopsies will be performed as clinically indicated and as per institutional protocol.

12.2.1.1. Lymph Nodes, Visceral Lesions, and Bone Lesions positive for disease by pathology.

– Lesions with positive pathologic confirmation will be regarded as positive for disease. The regionality of the resected tissue will be assigned into respective regions and sub-regions as described above in Table 12.2.

12.2.1.2. Lymph Nodes and Visceral Lesions negative for disease by pathology.

– Tissue removed and negative for pathology are considered negative for prostate cancer disease, unless subsequent conventional imaging or ^{68}Ga-PSMA-HBED-CC PET imaging demonstrates that targeted tissue were not resected. In this case:

i. Subjects can be rescanned with dedicated CT, MRI, or ^{68}Ga-PSMA-HBED-CC PET/CT to determine if the suspicious ^{68}Ga-PSMA-HBED-CC tissue was removed. If the tissue is confirmed as removed, this is considered negative for disease.

ii. If ^{68}Ga-PSMA-HBED-CC PET/CT positive tissue is still present, a needle biopsy can be pursued at the discretion of the treating physician. Images of the procedure will be reviewed to determine if the correct tissue was biopsied.

- If the ^{68}Ga-PSMA-HBED-CC PET/CT positive tissue was biopsied, a negative pathologic finding of the biopsied tissue is considered negative for disease.

- If the ^{68}Ga-PSMA-HBED-CC PET/CT positive tissue was biopsied, a positive pathologic finding of the biopsied tissue is considered positive for disease.

- If biopsy or re-biopsy is not performed, or the wrong tissue was biopsied, change in node size as measured by conventional imaging and as defined below will be the criteria by which disease status will be defined.

12.2.1.3. Bone lesions: Given the high rate of false negative biopsies for osseous metastases in subjects with prostate cancer, subjects with negative bone biopsies of ^{68}Ga-PSMA-HBED-CC PET positive lesions will be further evaluated:

- If pathology demonstrates an alternative diagnoses that is known to be ^{68}Ga-PSMA-HBED-CC positive (eg Renal Cell Carcinoma metastases, Paget's disease), then this will be considered negative for disease.

- If pathology is indeterminate, then follow-up imaging as described below will be performed as per clinical standards at the site.

12.2.1.4. Although not routinely performed during standard practice, immunohistochemical staining for PSMA of tumor specimens (primary and lymph node metastases) may be performed, although not required.

12.2.1.5. All regions not sampled for biopsy/histopathology will be designated as indeterminate for disease by pathology. Conventional imaging follow-up may be used in these cases to determine tissue status.

12.2.2. Follow-up Imaging will be used as a secondary assessment for prostate cancer in the event pathology information is not available:

All subjects will be tracked for follow-up conventional imaging between 3-12 months post ^{68}Ga-PSMA-HBED-CC (dedicated CT, MRI and/or bone scan) as per site standard of care. If no follow-up imaging has been performed within the 9 months following the ^{68}Ga-PSMA-HBED-CC scan, then the research study will pay for an additional follow-up CT scan to be performed

in the 9-12 month window post-^{68}Ga-PSMA-HBED-CC scan. Follow up imaging will only be performed on subjects that have positive ^{68}Ga-PSMA-HBED-CC findings because conventional imaging assessment for disease is primarily targeting suspicious lesions identified by ^{68}Ga-PSMA-HBED-CC PET/CT. Interpretation of follow-up imaging will be performed by local read. Preferably, the follow-up conventional imaging should be the same modality/modalities as the initial staging work-up to allow for reproducible and accurate comparisons. Conventional imaging standards as described below will be used to determine tissue positive for prostate cancer disease. Conventional imaging will not be used to determine negative prostate cancer disease regions due to its inherently low negative predictive value.

Tissue positive for prostate cancer disease based on follow-up imaging:

12.2.2.1. Lymph nodes will be assessed by change in size.

i. Positive for disease:

a. -For subjects undergoing systemic treatment (alone or in combination with targeted treatment): If on post-treatment follow-up imaging within 3-12 months, visually suspicious lymph nodes seen on CT or MRI decrease by more than 30% in short axis diameter and PSA declines by more than 50%.

- If PSA increases by more than 25% (PCWG3 definition of recurrence) on systemic therapy, then an increase in the size of lesion by more than 20% in the short axis diameter will be considered a positive for disease.

b. In subjects with localized suspected lymph node(s) receiving targeted treatment without concomitant systemic treatment there are two ways to achieve positive for disease designation:

- If the subject shows a decrease of PSA by greater than 50% after targeted treatment and the lymph node does not enlarge (change in size less than 20% in the short axis diameter or less than 3 mm increase in short axis diameter) [*OR*]

- If on post-treatment follow-up imaging within 3-12 months, lymph nodes seen on CT or MRI decrease by more than 30% in short axis diameter (with a minimum of 3 mm in change in size)

c. For untreated subjects: If on follow-up imaging within 3-12 months, lymph nodes seen on CT or MRI increase by more than 20% in short axis diameter (with a minimum of 3 mm in change in size).

ii. Negative for disease:

- Conventional Imaging follow-up will not be used for assessment of negativity for disease.

iii. Indeterminate for disease

- Regions with no lymph nodes determined to be positive by the conventional imaging criteria described above and without pathology will be designated regions indeterminate for prostate cancer disease.

- Subjects that have had neither pathology sampling, nor conventional imaging follow up will have all regions designated as indeterminate for disease by reference standard.

12.2.2.2. Visceral lesions (non-lymph node soft tissue or organ) and prostate bed and prostate lesions will be assessed by change in size.

i. Positive for disease:

a. For subjects undergoing systemic treatment (alone or in combination with targeted treatment): If on post-treatment follow-up imaging within 3-12 months, visually conspicuous lesions seen on CT or MRI decrease by more than 30% in long axis diameter and PSA declines by more than 50%.

- If PSA increases by more than 25% (PCWG3 definition of recurrence) on systemic therapy, then an increase in the size of lesion by more than 20% in the long axis diameter will be considered positive for disease.

b. In subjects with localized suspected lesions(s) receiving targeted treatment without concomitant systemic treatment there are two ways to meet positive disease criteria:

- If the subject demonstrates a decrease of PSA by greater than 50% after targeted treatment [*OR*]

- If on post-treatment follow-up imaging within 3-12 months, lesions seen on CT or MRI decrease by more than 30% in long axis diameter (with a minimum of 3 mm in change in size)

c. For untreated subjects: If on follow-up imaging within 3-12 months, lesions seen on CT or MRI increase by more than 20%

in long axis diameter (with a minimum of 3 mm in change in size).

ii. Negative for disease:

- Conventional Imaging follow up will not be used for assessment of negativity for disease

iii. Indeterminate for disease

- Regions with no visceral lesions determined to be positive by the conventional imaging criteria described above and without pathology will be designated as visceral regions indeterminate for prostate cancer disease.

- Prostate bed and prostate regions not determined to be positive by the conventional imaging criteria described above and without pathology will be designated as prostate regions indeterminate for prostate cancer disease.

- Subjects that have had neither pathology sampling, nor conventional imaging follow up will have all prostate and visceral regions designated as indeterminate for disease by reference standard.

12.2.2.3. Bone lesions will be considered:

i. Positive for disease on baseline assessment:

- Any positive sclerotic lesion on the CT portion of the ^{68}Ga-PSMA-HBED-CC PET or on a separate CT obtained ≤ 30 days before or after the PET/CT.

- Focal uptake on the baseline bone scan performed within one month of ^{68}Ga-PSMA-HBED-CC PET.

- Any MRI lesion in bone read as positive on the initial MRI performed within one month of ^{68}Ga-PSMA-HBED-CC PET.

ii. Positive for disease on follow up:

- Any new positive sclerotic lesion on CT within 12 months of ^{68}Ga-PSMA-HBED-CC PET scan

- Any new MRI bone lesion within 12 months of ^{68}Ga-PSMA-HBED-CC PET scan

- Any new focal uptake in bone within 12 months of ^{68}Ga-PSMA-HBED-CC PET scan

- In subjects with localized suspected bone lesion(s) receiving targeted treatment without concomitant systemic treatment:

- If the subject demonstrates a decrease of PSA by greater than 50% after targeted treatment.

iii. Negative for disease:

- Conventional Imaging follow up will not be used for assessment of negativity for disease

iv. Indeterminate for disease:

- Regions with no bone lesions determined to be positive by the conventional imaging criteria described above and without pathology will be designated bone regions indeterminate for prostate cancer disease.

13. STATISTICAL CONSIDERATIONS

13.1. Statistical Justification

This study is a pilot study to determine target sensitivity for ^{68}Ga PSMA-HBED-CC for the detection of metastatic prostate cancer in the biochemical recurrent population. Based upon literature, we anticipate sensitivities of > 80% in this patient population, but there are uncertainties, particularly related to the proposed reference standard. We plan to use the results of this pilot study, potentially combined with reported results from other sites across the US performing similar studies (same patient population, same methods, same reference standard definitions…) to determine most-appropriate primary endpoint sensitivities for a larger University of Iowa study to follow this one, so as to appropriately statistically power the larger study.

The primary objective of this pilot study is to obtain preliminary information on the sensitivity of physician reads for Ga-68 PSMA post-prostatectomy biochemical recurrence; physicians' ability to correctly identify biochemical recurrence via Ga-68 PSMA relative to our pathology/conventional imaging reference standard. Due to the lack of clinical experience with this radiopharmaceutical, this pilot study is meant to gain meaningful information of the sensitivity of this agent in this patient population to generate hypotheses for further trials.

To evaluate sensitivity, patients must undergo both Ga-68 PSMA imaging and evaluation for biochemical recurrence by pathology, follow-up conventional imaging, or both. Sensitivity is defined as:

$$Sensitivity = \frac{number\ of\ true\ positives\ (TP)}{number\ of\ true\ positives\ (TP) + number\ of\ false\ positives\ (FP)}$$

The table below provides 95% confidence interval half-widths for a range of sensitivity values based on a planned sample size of 30 patients using a normal approximation.

.

Sensitivity	Half-Width
70%	16.4%
75%	15.5%
80%	14.3%
85%	12.8%
90%	10.7%

13.2. **Primary and Secondary Endpoints using histopathology/biopsy and conventional imaging follow-up**

Primary: Sensitivity on a per-subject basis of ^{68}Ga PSMA-HBED-CC PET/CT for detection of tumor location confirmed by histopathology/biopsy and conventional imaging follow-up will be calculated and reported along with the corresponding two-sided 95% confidence intervals. The confidence intervals will be constructed using the Wilson score method.

No statistical significance will be generated due to the pilot nature of the project.

Secondary: PPVs on a per-subject and per-region-basis of ^{68}Ga PSMA-HBED-CC for detection of tumor location confirmed by histopathology/biopsy and conventional imaging follow-up will be calculated and reported along with the corresponding two-sided 95% confidence intervals. The confidence intervals will be constructed using the Wilson score method.

The following definitions will define accuracy of ^{68}Ga PSMA-HBED-CC for detection of tumor location confirmed by histopathology/biopsy and conventional imaging follow-up

No statistical significance will be generated due to the pilot nature of the project.

13.3. **Definitions of ^{68}Ga PSMA-HBED-CC accuracy**

13.3.1. **True positive definitions**

13.3.1.1. **^{68}Ga PSMA-HBED-CC PET/CT positive for nodal metastases by internal blind reader** – and pathology (if available) positive for that node, or node positive for disease by imaging as defined in Section 12.2.2.1 If this criteria is met, the subject is defined as true positive for nodal disease.

13.3.1.2. **^{68}Ga PSMA-HBED-CC PET/CT positive for visceral metastases by internal blind reader** – and pathology (if available) positive for that visceral lesion, or, visceral lesion positive for disease by imaging as defined in Section 12.2.2.2. If this criteria is met, the subject is defined as true positive for visceral disease.

13.3.1.3. **^{68}Ga PSMA-HBED-CC PET/CT positive for osseous**

metastases by internal blind reader - and pathology (if available) positive for that osseous lesion, or, osseous lesion positive for disease by imaging as defined in Section 12.2.2.3. If this criteria is met, the subject is defined as true positive for osseous disease.

13.3.1.4. A single nodal, visceral, or osseous region determined as true positive as defined above is sufficient to define the subject as true positive by ^{68}Ga PSMA-HBED-CC PET/CT.

13.3.2. **True negative definitions**

13.3.2.1. **^{68}Ga PSMA-HBED-CC PET/CT negative for nodal metastases by internal blind reader** – and pathology (if available) negative for disease, and, extra-pelvic node not positive for disease by imaging. If this criteria is met, the subject is defined as true negative for nodal disease.

13.3.2.2. **^{68}Ga PSMA-HBED-CC PET/CT negative for visceral metastases by internal blind reader** – and pathology (if available) negative for disease, and, visceral lesion not positive for disease by imaging. If this criteria is met, the subject is defined as true negative for visceral disease.

13.3.2.3. **^{68}Ga PSMA-HBED-CC PET/CT negative for osseous metastases by internal blind reader** - and pathology (if available) negative for disease, and, osseous lesion not positive for disease by imaging. If this criteria is met, the subject is defined as true negative for osseous disease.

13.3.3. **False positive definitions:**

13.3.3.1. **^{68}Ga PSMA-HBED-CC PET/CT positive for nodal metastases by internal blind reader**, pathology (if available) is negative, and imaging demonstrates that node is not positive for disease. If this criteria is met, the subject is defined as false positive for nodal disease.

13.3.3.2. **^{68}Ga PSMA-HBED-CC PET/CT positive for nodal metastases by internal blind reader**, but pathology (if available) is positive for node but in a different nodal region than the node seen on PSMA PET. If this criteria is met, the subject is defined as false positive for nodal disease.

13.3.3.3. **^{68}Ga PSMA-HBED-CC PET/CT positive for visceral lesion by internal blind reader**, pathology (if available) is negative, and imaging demonstrates that the visceral lesion is not positive for disease. If this criteria is met, the subject is defined as false positive for visceral disease.

13.3.3.4. **^{68}Ga PSMA-HBED-CC PET/CT positive for visceral lesion by internal blind reader**, but pathology (if available) is positive for visceral lesion but in a different region than the visceral

region seen on PSMA PET. If this criteria is met, the subject is defined as false positive for visceral disease.

13.3.3.5. **^{68}Ga PSMA-HBED-CC PET/CT positive for osseous lesion by internal blind reader**, pathology (if available) is negative, and imaging demonstrates that the osseous lesion is not postive for disease. If this criteria is met, the subject is defined as false positive for osseous disease.

13.3.3.6. **^{68}Ga PSMA-HBED-CC PET/CT positive for osseous lesion by internal blind reader**, but pathology (if available) is positive for osseous lesion but in a different region than the osseous region seen on PSMA PET. If this criteria is met, the subject is defined as false positive for osseous disease.

13.3.3.7. A subject is defined as false positive for disease by ^{68}Ga PSMA-HBED-CC PET/CT if one or more regions as defined above are defined as false positive regions and the subject is not defined as true positive as defined in Section 13.3.1

13.3.4. **False negative definitions:**

13.3.4.1. **^{68}Ga PSMA-HBED-CC PET/CT negative for nodal metastases by internal blind reader**, and pathology (if available) positive for any node or positive for disease by imaging as defined in Section 12.2.2.1. If this criteria is met, the subject is defined as false negative for nodal disease.

13.3.4.2. **^{68}Ga PSMA-HBED-CC PET/CT negative for visceral lesion by internal blind reader**, and pathology (if available) positive for any visceral lesion, or, visceral lesion positive for disease by imaging as defined in Section 12.2.2.2. If this criteria is met, the subject is defined as false negative for visceral disease

13.3.4.3. **^{68}Ga PSMA-HBED-CC PET/CT negative for osseous lesion by internal blind reader**, and pathology (if available) positive for any osseous lesion, or, osseous lesion positive for disease by imaging as defined in Section 12.2.2.3. If this criteria is met, the subject is defined as false negative for osseous disease.

13.3.4.4. A subject is defined as false negative for disease by ^{68}Ga PSMA-HBED-CC PET/CT if the subject is negative for disease in all regions by ^{68}Ga PSMA-HBED-CC PET/CT, but positive for disease by pathology or follow-up imaging in any region.

13.3.5. **Non-evaluable definitions**:

13.3.5.1. Any region that is does not have sufficient data to meet the criteria for definition of true positive region, true negative region, false positive region, or false negative region will be classified as non-evaluable.

13.3.5.2. Any region that is does not have sufficient data to meet the

criteria for definition of true positive subject, true negative subject, false positive subject, or false negative subject will be classified as non-evaluable.

13.4. **Other statistical considerations**

13.4.1. The impact of ^{68}Ga PSMA-HBED-CC PET/CT on clinical management in BCR patients will be evaluated using descriptive statistics.

13.4.2. Inter-reader reproducibility for positivity at the patient level and region level will be reported using the Fleiss' Kappa test for multiple readers.

13.4.3. Safety will be reported descriptively as rates of patient reported adverse events.

15. REFERENCES

1. Cookson MS, Aus G, Burnett AL*, et al.* Variation in the definition of biochemical recurrence in patients treated for localized prostate cancer: the American Urological Association Prostate Guidelines for Localized Prostate Cancer Update Panel report and recommendations for a standard in the reporting of surgical outcomes. *J Urol.* 2007;177(2):540-545.
2. Roach M, 3rd, Hanks G, Thames H, Jr.*, et al.* Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys.* 2006;65(4):965-974.
3. National Comprehensive Cancer Network (NCCN). NCCN Guidelines®. 2016; https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site.
4. Morigi JJ, Stricker PD, van Leeuwen PJ*, et al.* Prospective Comparison of 18F-Fluoromethylcholine Versus ^{68}Ga PSMA PET/CT in Prostate Cancer Patients Who Have Rising PSA After Curative Treatment and Are Being Considered for Targeted Therapy. *J Nucl Med.* 2015;56(8):1185-1190.
5. Eiber M, Maurer T, Souvatzoglou M*, et al.* Evaluation of Hybrid ^{68}Ga PSMA Ligand PET/CT in 248 Patients with Biochemical Recurrence After Radical Prostatectomy. *J Nucl Med.* 2015;56(5):668-674.
6. Afshar-Oromieh A, Zechmann CM, Malcher A*, et al.* Comparison of PET imaging with a (68)Ga-labelled PSMA ligand and (18)F-choline-based PET/CT for the diagnosis of recurrent prostate cancer. *Eur J Nucl Med Mol Imaging.* 2014;41(1):11-20.
7. Afshar-Oromieh A, Avtzi E, Giesel FL*, et al.* The diagnostic value of PET/CT imaging with the (68)Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. *Eur J Nucl Med Mol Imaging.* 2015;42(2):197-209.
8. Green MA, Eitel JA, Fletcher JW*, et al.* Estimation of radiation dosimetry for 68Ga-HBED-CC (PSMA-HBED-CC) in patients with suspected recurrence of prostate cancer. *Nucl Med Biol.* 2017;46:32-35.
9. Rai BP, Baum RP, Patel A*, et al.* The Role of Positron Emission Tomography With (68)Gallium (Ga)-Labeled Prostate-specific Membrane Antigen (PSMA) in the Management of Patients With Organ-confined and Locally Advanced Prostate Cancer Prior to Radical Treatment and After Radical Prostatectomy. *Urology.* 2016;95:11-15.

10. Eiber M, Maurer T, Souvatzoglou M, *et al.* Evaluation of Hybrid (6)(8)Ga PSMA Ligand PET/CT in 248 Patients with Biochemical Recurrence After Radical Prostatectomy. *J Nucl Med.* 2015;56(5):668-674.
11. Maurer T, Gschwend JE, Rauscher I, *et al.* Diagnostic Efficacy of (68)Gallium-PSMA Positron Emission Tomography Compared to Conventional Imaging for Lymph Node Staging of 130 Consecutive Patients with Intermediate to High Risk Prostate Cancer. *J Urol.* 2016;195(5):1436-1443.
12. Giesel FL, Fiedler H, Stefanova M, *et al.* PSMA PET/CT with Glu-urea-Lys-(Ahx)-[(6)(8)Ga(HBED-CC)] versus 3D CT volumetric lymph node assessment in recurrent prostate cancer. *Eur J Nucl Med Mol Imaging.* 2015;42(12):1794-1800.
13. van Leeuwen PJ, Emmett L, Ho B, *et al.* Prospective evaluation of 68Gallium-prostate-specific membrane antigen positron emission tomography/computed tomography for preoperative lymph node staging in prostate cancer. *BJU Int.* 2017;119(2):209-215.
14. van Leeuwen PJ, Stricker P, Hruby G, *et al.* (68) Ga PSMA has a high detection rate of prostate cancer recurrence outside the prostatic fossa in patients being considered for salvage radiation treatment. *BJU Int.* 2016;117(5):732-739.
15. Demirkol MO, Acar O, Ucar B, Ramazanoglu SR, Saglican Y, and Esen T. Prostate-specific membrane antigen-based imaging in prostate cancer: impact on clinical decision making process. *Prostate.* 2015;75(7):748-757.
16. Bluemel C, Krebs M, Polat B, *et al.* 68Ga PSMA-PET/CT in Patients With Biochemical Prostate Cancer Recurrence and Negative 18F-Choline-PET/CT. *Clin Nucl Med.* 2016;41(7):515-521.
17. Afshar-Oromieh A, Haberkorn U, Eder M, Eisenhut M, and Zechmann CM. [68Ga]Gallium-labelled PSMA ligand as superior PET tracer for the diagnosis of prostate cancer: comparison with 18F-FECH. *Eur J Nucl Med Mol Imaging.* 2012;39(6):1085-1086.
18. Schiavina R, Ceci F, Romagnoli D, *et al.* (68)Ga PSMA-PET/CT-Guided Salvage Retroperitoneal Lymph Node Dissection for Disease Relapse After Radical Prostatectomy for Prostate Cancer. *Clin Genitourin Cancer.* 2015;13(6):e415-417.
19. Stoykow C, Huber-Schumacher S, Almanasreh N, Jilg C, and Ruf J. Strong PMSA Radioligand Uptake by Rectal Carcinoma: Who Put the "S" in PSMA? *Clin Nucl Med.* 2017;42(3):225-226.
20. Noto B, Weckesser M, Buerke B, Pixberg M, and Avramovic N. Gastrointestinal Stromal Tumor Showing Intense Tracer Uptake on PSMA PET/CT. *Clin Nucl Med.* 2017;42(3):200-202.
21. Bilgin R, Ergul N, and Cermik TF. Incidental Meningioma Mimicking Metastasis of Prostate Adenocarcinoma in 68Ga-Labeled PSMA Ligand PET/CT. *Clin Nucl Med.* 2016;41(12):956-958.
22. Chan M, Schembri GP, and Hsiao E. Serous Cystadenoma of the Pancreas Showing Uptake on 68Ga PSMA PET/CT. *Clin Nucl Med.* 2017;42(1):56-57.
23. Malik D, Basher RK, Mittal BR, Jain TK, Bal A, and Singh SK. 68Ga PSMA Expression in Pseudoangiomatous Stromal Hyperplasia of the Breast. *Clin Nucl Med.* 2017;42(1):58-60.

24. Vamadevan S, Shetty D, Le K, Bui C, Mansberg R, and Loh H. Prostate-Specific Membrane Antigen (PSMA) Avid Pancreatic Neuroendocrine Tumor. *Clin Nucl Med.* 2016;41(10):804-806.
25. Blazak JK, and Thomas P. Paget Disease: A Potential Pitfall in PSMA PET for Prostate Cancer. *Clin Nucl Med.* 2016;41(9):699-700.
26. Budaus L, Leyh-Bannurah SR, Salomon G*, et al.* Initial Experience of (68)Ga PSMA PET/CT Imaging in High-risk Prostate Cancer Patients Prior to Radical Prostatectomy. *Eur Urol.* 2016;69(3):393-396.
27. Pyka T, Okamoto S, Dahlbender M*, et al.* Comparison of bone scintigraphy and 68Ga PSMA PET for skeletal staging in prostate cancer. *Eur J Nucl Med Mol Imaging.* 2016;43(12):2114-2121.
28. Verburg FA, Pfister D, Heidenreich A*, et al.* Extent of disease in recurrent prostate cancer determined by [(68)Ga]PSMA-HBED-CC PET/CT in relation to PSA levels, PSA doubling time and Gleason score. *Eur J Nucl Med Mol Imaging.* 2016;43(3):397-403.
29. Fendler WP, Schmidt DF, Wenter V*, et al.* 68Ga PSMA PET/CT Detects the Location and Extent of Primary Prostate Cancer. *J Nucl Med.* 2016;57(11):1720-1725.
30. Australian New Zealand Clinical Trials Registry (ANZCTR). ACTRN12617000005358p: A prospective randomised multi-centre study of the impact of Ga-68 PSMA-PET/CT imaging for staging high risk prostate cancer prior to curative-intent surgery of radiotherapy. 2017; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=371669. Accessed 03 March, 2017.
31. ClinicalTrials.gov USNIoH. NCT03062254: Metabolic change in prostate bone cancer metastases on 68Ga-HBED-CC-PSMA (DKFZ-11) PET/CT following radium-223 therapy. 2017; https://clinicaltrials.gov/ct2/show/NCT03062254. Accessed 03 March, 2017.
32. European Union Clinical Trials Register. 2016-002485-31: Optimisation of [68Ga] PSMA-HBED-CC PET/CT Imaging Protocol for localizing primary prostate cancer prior to radical prostatectomy. 2017; https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-002485-31/NL. Accessed 03 March, 2017.
33. Ceci F, Uprimny C, Nilica B*, et al.* (68)Ga PSMA PET/CT for restaging recurrent prostate cancer: which factors are associated with PET/CT detection rate? *Eur J Nucl Med Mol Imaging.* 2015;42(8):1284-1294.
34. van Leeuwen PJ, Stricker P, Hruby G*, et al.* 68Ga PSMA has high detection rate of prostate cancer recurrence outside the prostatic fossa in patients being considered for salvage radiation treatment. *BJU Int.* 2015.