UCSF Helen Diller Family Comprehensive Cancer Center

NCT#02918357

Gallium-68 PSMA-11 PET in patients with biochemical recurrence

Protocol Number: CC #165510
Study Drug: Gallium-68 PSMA-11

Version Number: Version 1.1
Version Date: 08/21/2016

IND Number: 127621

Principal Investigator (Sponsor-Investigator)

Thomas Hope, MD

[redacted]

Co-Investigators

Dr. Rahul Aggarwal, MD
Dr. Peter Carroll, MD
Dr. Albert Chang, MD
Dr. Matthew Cooperberg, MD
Dr. Michael Evans, PhD
Dr. Felix Feng, MD
Dr. Larry Fong, MD
Dr. Terence Friedlander, MD
Dr. Kirsten Greene, MD
Dr. Won Kim, MD
Dr. John Kurhanewicz, PhD
Dr. Amy Lin, MD
Dr. Hao Nguyen, MD
Dr. Mack Roach, MD
Dr. Chuck Ryan, MD
Dr. Jim Slater, PhD
Dr. Eric Small, MD
Dr. Li Zhang, PhD (Statistician)

Clinical Research Coordinator

[redacted]

UCSF Helen Diller Family Comprehensive Cancer Center

Protocol Signature Page

Protocol No.: **Version Date:**

1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Committee on Human Research (CHR), and Data Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with applicable CHR requirements, Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.
3. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.
4. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), and with local regulatory requirements. In accordance with the FDA Modernization Act, I will ensure the registration of the trial on the www.clinicaltrials.gov website.
5. I agree to maintain adequate and accurate records in accordance with CHR policies, Federal, state and local laws and regulations.

UCSF Principal Investigator / Study Chair

Thomas A. Hope

_____
Printed Name

_____ _____
Signature Date

Abstract

Title	Gallium-68 PSMA-11 PET in patients with biochemical recurrence

Patient population	• Rising PSA after definitive therapy with prostatectomy or radiation therapy (external beam or brachytherapy):
	  ○ Post radical prostatectomy (RP) – AUA recommendation
	  ▪ PSA greater than 0.2 ng/mL measured more than 6 weeks after RP and,
	  ▪ Confirmatory persistent PSA greater than 0.2 ng/mL
	  ○ Post-radiation therapy – ASTRO-Phoenix consensus definition
	  ▪ Nadir + greater than or equal to 2 ng/mL rise in PSA

Rationale for Study	Gallium-68 HBED-CC PSMA has been shown to have a higher sensitivity for the detection of metastatic prostate cancer compared to choline based imaging.
Primary Objective	• Sensitivity and positive predictive value (PPV) on a per-patient and per-region-basis of ^{68}Ga-PSMA-11 PET for detection of tumor location confirmed by histopathology/biopsy.
Secondary Objectives	• Sensitivity and PPV on a per-patient and per-region-basis of ^{68}Ga-PSMA-11 PET for detection of tumor location confirmed by histopathology/biopsy and conventional imaging follow-up. • Sensitivity, specificity, and negative predictive value (NPV) on a per-patient basis of ^{68}Ga-PSMA-11 PET for detection of tumor location confirmed by histopathology/biopsy and conventional imaging follow-up. • Detection rates on a per-patient basis of ^{68}Ga-PSMA-11 PET stratified by PSA value (0.2 - <0.5, 0.5 - <1.0, 1.0 - <2.0, 2.0 - <5.0, 5.0). • Impact of ^{68}Ga-PSMA-11 PET on clinical management in BCR patients. • Inter-reader reproducibility. • Safety.
Study Design	This is a phase 1/2 multi-center open label study.
Number of patients	125 patients per year, for three years, giving a total of 375 patients at UCSF. Total population of patients will be 1,500 patients across all institutions.
Duration of Therapy	The study will involve a single imaging study.

Duration of Follow up	The patients will be followed-up by phone one day after the study completion.
Duration of study	The study will reach completion three years from the time the study opens to accrual.
Study Drugs	Gallium-68 labeled PSMA-11 (PSMA-HBED-CC)
Safety Assessments	Patient vital signs will be taken immediately before and after the administration of the radiopharmaceutical. The patients will also be asked to report adverse events.

List of Abbreviations

AE	adverse event
CHR	Committee on Human Research (UCSF IRB)
CRC	Clinical Research Coordinator
CRF	case report form
CT	computerized tomography
CTCEA	Common Terminology Criteria for Adverse Events
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
Ga-68	Gallium 68
HDFCCC	Helen Diller Family Comprehensive Cancer Center
ICH	International Conference on Harmonization
IND	investigational new drug application
IRB	Institutional Review Board
IV	intravenous
MRI	magnetic resonance imaging
NCI	National Cancer Institute
PET	Positron Emission Tomography
PK	pharmacokinetics
PRC	Protocol Review Committee (UCSF)
PSA	Prostate specific antigen
PSMA	Prostate specific membrane antigen
SD	standard deviation

Table of Contents

Protocol Signature Page 0
Abstract 1
List of Abbreviations 3
Table of Contents 4
1 Introduction 6
1.1 Overview 6
1.2 Background 6
1.3 Patient Population 7
2 Objectives of the Study 7
2.1 Primary 7
2.2 Secondary 7
2.3 Endpoints 8
2.3.1 Primary Endpoints 8
2.3.2 Secondary endpoints 8
3 Study Design 8
3.1 Characteristics 8
3.2 Number of Subjects 8
3.3 Eligibility Criteria 8
3.3.1 Inclusion Criteria 8
3.3.2 Exclusion Criteria 9
3.4 Duration of Follow Up 9
3.5 Study Timeline 9
3.5.1 Primary Completion 9
3.5.2 Study Completion 9
4 Study Drugs 9
4.1 Description, Supply and Storage of Investigational Drugs 9
4.1.1 Investigational Drug #1 9
5 Treatment Plan 10
5.1 Dosage and Administration 10
5.1.1 Other Modality(ies) or Procedures 10
5.2 Monitoring and Toxicity Management 10
6 Study Procedures and Observations 11
6.1 Schedule of Procedures and Observations 11
6.1.2 Treatment Period 12
6.1.3 Post-treatment Follow Up Visits 12
6.2 Prohibited Medications 13
7 Reporting and Documentation of Results 13
7.1 Evaluation of Efficacy (or Activity) 13
7.2 Evaluation of Safety 13
7.3 Definitions of Adverse Events 13
7.3.1 Adverse Event 13
7.3.2 Adverse reaction 13
7.4 Recording of an Adverse Event 14
7.5 Follow-up of Adverse Events 15

Table of Contents

7.6 Expedited Reporting 15
8 Statistical Considerations and Evaluation of Results 16
8.1 Study Endpoints 16
8.1.1 Randomization 16
8.2 Determination of Sample Size and Accrual Rate 16
8.2.1 Sample Size and Power Estimate 16
8.2.2 Accrual estimates 17
8.3 Analyses Plans 17
8.3.1 Analysis Population 17
8.3.2 Analysis of Primary Endpoints 17
8.3.3 Analysis of Secondary Endpoints 21
9 Study Management 21
9.1 Pre-study Documentation 21
9.2 Institutional Review Board Approval 21
9.3 Informed Consent 22
9.4 Changes in the Protocol 22
10 Protection of Human Subjects 22
10.1 Protection of Privacy 22
References 23
Appendices 25
Appendix 1 Performance Status Criteria 25
Appendix 2 (flow chart) 26
Appendix 3 (pre- and post-surveys) 27

List of Tables

Table 1 5
Table 2 6
Table 3.1 Schedule of Study Procedures and Assessments 11

1 Introduction

1.1 Overview

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 (more commonly called ^{68}Ga-PSMA-11) in order to demonstrate its utility. We plan to utilize this data to obtain further approvals of the ^{68}Ga-PSMA-11 compound, so that this agent will become available for clinical imaging in prostate cancer patients.

This compound has been shown to be superior to choline based PET agents for the staging of prostate cancer, both Carbon-11 and Fluorine-18 compounds. But this compound was not patented and therefore no company or private entity will make the investment required to bring HBED-CC PSMA to market. In the vacuum of availability, academic groups must take the lead in order to collect the necessary data for future FDA approval. This protocol was developed in collaboration with the Clinical Trials Network of the Society of Nuclear Medicine and Molecular Imaging. The inclusion criteria and study endpoints have been aligned so that inter-institutional sharing of data can be performed in order to pool data for final NDA submission..

1.2 Background

Prostate cancer is the most commonly diagnosed cancer and second leading cause of cancer death in American men (1). Existing conventional imaging (CT, MRI and bone scans) has a low sensitivity in detecting local recurrence or metastatic disease (2). The one exception being NaF PET/CT for the detection of osseous metastasis. Due to this limitation, numerous approaches to stage patients have been evaluated.

Choline imaging has been frequently used, as prostate cancer exhibits increase choline uptake that has been associated with the presence of choline kinase (3). Choline uptake is increased in comparison to FDG in both androgen dependent and independent prostate cancer patients (4). Choline has also been shown to be sensitive for the detection of recurrent tumor in patients with PSA (prostate specific antigen) values of less than 1.0 ng/ml (5). There are two forms of choline that are used in imaging prostate cancer, C-11 and F-18 choline. C-11 choline has a short half-life of 20 minutes, which limits its detection for metastatic disease but results in improved local detection due to decreased urinary activity at the time of imaging. F-18 choline has significant urinary excretion that limits evaluation of the prostate but, but has been shown to have better detection rates for distant metastatic disease (6). C-11 choline has limited sensitivity for osseous metastasis, possibly due to the decreased uptake time (7). Additionally, the sensitivity of C-11 choline is limited in patients with PSA values < 1.0 ng/ml (8-10). Although choline PET may be limited in sensitivity, it clearly delineates more lesions than cross section imaging or bone scan in patients with known disease (11). In 2012, the Mayo Clinic obtained NDA (new drug application) approval from the FDA for the use of C-11 choline.

A separate approach is to image the prostate specific membrane antigen (PSMA). PSMA is expressed on the majority of prostate cancer cells, and so would be an ideal cell membrane protein to image. The initial imaging approach to PSMA imaging target the intracellular domain using Indium-111-capromab (Prostascint), a murine monoclonal antibody (12,13). Although there was early promise for the detection of nodal metastasis (14), the agent was never able to adequately visualize osseous metastasis (15). Although combination with SPECT/CT does improve lesion detection (16). One main limitation to In-111-capromab is that it takes a prolonged time to localize to the target tissue, which likely relates to both the size of the monoclonal antibody and the fact that agent targets the intracellular domain of the PSMA protein. Additionally, Prostascint also recognizes an intracellular epitope so the antibody must cross the membrane to be effective. This likely only occurs in permeable dead or dying tumor cells.

Because of the limitations of In-111 capromab, there has been continued effort to develop agents that target the extracellular domain of the PSMA protein. The Ga-68 labeled HBED-CC PSMA compound has become of particular interest because in the last year there have been two important articles. The first demonstrates that HBED-CC PSMA has a higher sensitivity for the detection of disease than F-18 choline in a head-to-head intra-patient comparison that included 37 patients (17). The second paper looked at the sensitivity of HBED-C PSMA in the detection of metastatic lesions in patients with recurrent prostate cancer (18). Their results demonstrated 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 (5).

Because of the improved resolution and image quality with PET, ability to quantitate uptake, increased sensitivity compared to choline, we intend to evaluate the utility of Ga-68 HBED-CC PSMA for the imaging of prostate cancer. We expect that the data from this study will support applications for clinical approval of this imaging agent, leading to wider availability within the United States.

Of note, although this project does not include biopsy correlation, a separate small trial is being initiated at the San Francisco VA Medical Center in pre-prostatectomy patients to determine the sensitivity and specificity of nodal uptake seen on Ga-68 HBED-CC PSMA imaging. This will help to demonstrate the specificity of imaging uptake on the PET imaging.

1.3 Patient Population

Patients with biochemical recurrence after prostatectomy or radiation therapy:

(a) Post radical prostatectomy (RP) – AUA recommendation

- PSA greater than 0.2 ng/mL measured more than 6–13 weeks after RP and,
- Confirmatory persistent PSA greater than 0.2 ng/mL

(b) Post-radiation therapy –ASTRO-Phoenix consensus definition

- Nadir + greater than or equal to 2 ng/mL rise in PSA

2 Objectives of the Study

2.1 Primary

- Sensitivity and positive predictive value (PPV) on a per-patient and per-region-basis (Table 1) of ^{68}Ga-PSMA-11 PET for detection of tumor location confirmed by histopathology/biopsy.

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

2.2 Secondary

- Sensitivity and PPV on a per-patient and per-region-basis (Table 1) of ^{68}Ga-PSMA-11 PET for detection of tumor location confirmed by histopathology/biopsy *and* conventional imaging follow-up.

- Sensitivity, specificity, and negative predictive value (NPV) on a per-patient basis of ^{68}Ga-PSMA-11 PET for detection of tumor location confirmed by histopathology/biopsy and conventional imaging follow-up.
- Detection rates on a per-patient basis of ^{68}Ga-PSMA-11 PET stratified by PSA value (0.2 - <0.5, 0.5 - <1.0, 1.0 - <2.0, 2.0 - <5.0, 5.0).
- Impact of ^{68}Ga-PSMA-11 PET on clinical management in BCR patients.
- Inter-reader reproducibility
- Safety.

2.3 Endpoints

2.3.1 Primary Endpoints

- Per patient and per region ^{68}Ga-PSMA-11 positivity.
- Biopsy correlation.

2.3.2 Secondary endpoints

- Per patient and per region detection sensitivity using a combined histology and conventional imaging correlate
- Sensitivity, specificity and negative predictive value on a per-patient basis.
- Change in management: survey based results
- Inter-reader reproducibility
- Safety: blood pressure, heart rate, self reported adverse events

3 Study Design

3.1 Characteristics

This is a prospective, Phase 1/2, multi-center, open-label study in patients with prostate cancer. Eligible participants will undergo baseline assessments at enrollment. Study participants will receive a one-time administration of Ga-68 PSMA-11 and undergo a PET/CT or PET/MRI imaging study.

3.2 Number of Subjects

It is anticipated that 125 patients per year over three years will be enrolled in this study, for a total of 375 at UCSF. In total we aim to enroll 1,500 patients across all sites.

3.3 Eligibility Criteria

Patients must have baseline evaluations performed prior to the administration of the radiopharmaceutical and must meet all inclusion and exclusion criteria. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

3.3.1 Inclusion Criteria

1. Histopathological proven prostate adenocarcinoma.
2. Rising PSA after definitive therapy with prostatectomy or radiation therapy (external beam or brachytherapy).

a. Post radical prostatectomy (RP) – AUA recommendation

i. PSA greater than 0.2 ng/mL measured more than 6 weeks after RP and,

ii. Confirmatory persistent PSA greater than 0.2 ng/mL

b. Post-radiation therapy –ASTRO-Phoenix consensus definition

i. Nadir + greater than or equal to 2 ng/mL rise in PSA

3. Karnofsky performance status of ≥50 (or ECOG/WHO equivalent).
4. Age > 18.
5. Ability to understand a written informed consent document, and the willingness to sign it.

3.3.2 Exclusion Criteria

1. Investigational therapy for prostate cancer.
2. Unable to lie flat, still or tolerate a PET scan.
3. Prior history of any other malignancy within the last 2 years, other than skin basal cell or cutaneous superficial squamous cell carcinoma that has not metastasized and superficial bladder cancer.
4. Contraindication to furosemide administration including prior allergy or adverse reaction to furosemide or sulfa drugs. (Note: This exclusion criteria can be removed if Furosemide is omitted as part of the PET imaging protocol if a second-generation scatter correction is available for the used PET device).

3.4 Duration of Follow Up

Patients will be followed for one day after the administration of the radiopharmaceutical.

3.5 Study Timeline

3.5.1 Primary Completion

The study will reach primary completion 36 months from the time the study opens to accrual.

3.5.2 Study Completion

The study will reach study completion 48 months from the time the study opens to accrual.

4 Study Drugs

4.1 Description, Supply and Storage of Investigational Drugs

4.1.1 Investigational Drug #1

Ga-68 labeled PSMA-11 (or PSMA-HBED-CC) is a radiopharmaceutical that will be produced under cGMP by a research pharmacists certified and highly experienced in the Department of Radiology and Biomedical Engineering, [redacted]. The radiopharmaceutical will be made at the China Basin Imaging Center. Imaging will occur at both the China Basin Imaging Center and the San Francisco VA Medical Center.

5 Treatment Plan

5.1 Dosage and Administration

The imaging agent (Ga-68 PSMA-11 or PSMA-HBED-CC) will be administered on an outpatient basis. It will be administered a single time intravenously prior to the PET imaging. The one-time nominal injected dose will be 3 to 7 mCi of ^{68}Ga-PSMA-11.

5.1.1 Other Modality(ies) or Procedures

5.1.1.1 Change in management surveys

Referring clinicians will be required to fill out a pre-imaging survey within 30 days of imaging. Please see Appendix 3. Additionally within 30 days of the completion of imaging, the referring physician will be requested to fill out a post-imaging survey, and finally six months after imaging, a third survey will be filled out.

5.1.1.2 PET imaging

a) ^{68}Ga-PSMA-11 PET preparation and injection:

   The injected dose will be 111-259 MBq (3-7 mCi) of ^{68}Ga-PSMA-11 PET. A dose of 20 mg of Furosemide (Lasix) is recommended to be injected together with, shortly before or after administration of the radiotracer in order to minimize PET scatter artifacts from excreted radiotracer accumulation in the kidney and urinary bladder that can occur with the gallium-68 radionuclide. Oral hydration and voiding is recommended immediately before start of the scan. Furosemide should not be administered in patients with medical contraindications to Furosemide administration including allergies and adverse reactions including sulfa allergies. (Note: Application of Furosemide can be omitted as part of the PET imaging protocol if a second-generation scatter correction algorithm is available for the PET scanner used in this protocol). PET imaging will begin 50-100 minutes after injection. Scan time per bed position will be determined based on each sites PET scanner capabilities.

b) Patient preparation: no fasting is required.

c) PET protocol: Scan coverage will extend from mid thigh to the base of the skull, starting from the mid-thighs to prevent urinary bladder radiotracer accumulation at the start of PET imaging. Bed position scan time will be dependent on each sites scanner capabilities. At a minimum, 3 minutes per bed position will be used. In certain circumstances, coverage may be extended to the toes. Contrast may be administered if requested by the referring clinician and is decided site dependent.

d) Patient monitoring: Vital signs will be assessed immediately before and after injection of ^{68}Ga-PSMA-11 (HR and supine BP). Patients will be monitored for adverse events during injection and for two hours after radiotracer administration. Additionally, patient's vitals (HR and supine BP) will be checked at the completion of the imaging study prior to leaving the imaging center.

e) Patient follow-up: Patients will be contacted by phone one to three days after ^{68}Ga-PSMA-11 PET to assess for the development of delayed adverse events. Patients will be seen in the clinic if there are any concerning study related adverse events requiring further evaluation.

5.2 Monitoring and Toxicity Management

Each patient receiving Ga-68 PSMA-11 will be evaluable for safety. The safety parameters include physical findings and spontaneous reports of adverse events reported to the investigator by patients.

6 Study Procedures and Observations

6.1 Schedule of Procedures and Observations

Screening assessments must be performed within 30 days prior to the first dose of investigational product. Any results falling outside of the reference ranges may be repeated at the discretion of the investigator. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

A written, signed, informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

Table 1.1 Schedule of Study Procedures and Assessments

Period/ Procedure	Screening	Imaging day 1	One day post imaging	Follow-up surveys
Study Day/Visit Day	-30 to 1	1	2	2 to 30 days and six months
Informed consent	X			
Laboratory values, history from medical record	X			
Pre-survey	X			
Performance status	X			
Blood Pressure, HR	X	X		
Imaging Procedure				
^{68}Ga-PSMA-11		X		
PET/CT or PET/MRI		X		
Follow-up				
Adverse event reporting			X	
Post-survey				XX

6.1.1.1 Screening Assessments

The Screening procedures and assessments must be completed within 30 days of the day 1 Visit.

- Laboratory values: all patients must have a recent PSA (within 30 days prior to study enrollment) consistent with BCR

- Pathology: all patients must have histopathology/biopsy of the prostate with a documented Gleason score
- Performance status: all patients must have their Karnofsky performance status (or ECOG/WHO equivalent) evaluated (Appendix A).

6.1.2 Treatment Period

6.1.2.1 Study Procedures, Imaging Day 1

- Vital signs
- Evaluation of adverse events

6.1.3 Post-treatment Follow Up Visits

Patients will be followed for two weeks after enrollment, by phone. The following procedure will be performed at two weeks:

- Evaluation of adverse events

6.2 Prohibited Medications

There are no prohibited medications.

7 Reporting and Documentation of Results

7.1 Evaluation of Efficacy (or Activity)

7.1.1.1 Definitions

Evaluable for toxicity

All patients will be evaluable for toxicity from the time of ^{68}Ga-PSMA-11.

7.2 Evaluation of Safety

Analyses will be performed for all patients receiving ^{68}Ga-PSMA-11. The study will use the CTCAE v4.0 for reporting of adverse events.

7.3 Definitions of Adverse Events

7.3.1 Adverse Event

An adverse event (also known as an adverse experience) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. More specifically, an adverse event (can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

7.3.2 Adverse reaction

An adverse reaction is defined as any adverse event caused by the use of a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

7.3.2.1 Suspected

A suspected adverse reaction is defined as any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, “reasonable possibility” indicates that there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

7.3.2.2 Unexpected

An adverse event or suspected adverse reaction is considered *unexpected* if it is not listed in the investigator brochure or package insert(s), or is not listed at the specificity or severity that has been observed, 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.

“Unexpected,” as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or

as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Adverse events that would be anticipated to occur as part of the disease process are considered *unexpected* for the purposes of reporting because they would not be listed in the investigator brochure. For example, a certain number of non-acute deaths in a cancer trial would be anticipated as an outcome of the underlying disease, but such deaths would generally not be listed as a suspected adverse reaction in the investigator brochure.

7.3.2.3 Serious

An adverse event or suspected adverse reaction is considered *serious* if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
- Congenital anomaly/birth defect

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

7.3.2.4 Life-threatening

An adverse event or suspected adverse reaction is considered *life-threatening* if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

7.4 Recording of an Adverse Event

All grade 3 and above adverse events will be recorded using the NCI CTCAE v4.0. The Investigator will assign attribution of the possible association of the event with use of the investigational drug.

Relationship	Attribution	Description
Unrelated to investigational drug/intervention	Unrelated	The AE *is clearly NOT related* to the intervention
	Unlikely	The AE *is doubtfully related* to the intervention
Related to investigational drug/intervention	Possible	The AE *may be related* to the intervention
	Probable	The AE *is likely related* to the intervention
	Definite	The AE *is clearly related* to the intervention

Signs or symptoms reported as adverse events will be graded and recorded by the Investigator according to the CTCAE. When specific adverse events are not listed in the CTCAE they will be graded by the Investigator as *none*, *mild*, *moderate* or *severe* according to the following grades and definitions:

Grade 0	No AE (or within normal limits)
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL)
Grade 3:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4:	Life-threatening consequences; urgent intervention indicated
Grade 5:	Death related to AE

7.5 Follow-up of Adverse Events

All adverse events will be followed with appropriate medical management until resolved. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. For selected adverse events for which administration of the investigational drug was stopped, a re-challenge of the subject with the investigational drug may be conducted if considered both safe and ethical by the Investigator.

7.6 Expedited Reporting

Reporting to the Data and Safety Monitoring Committee

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, the Investigator or his/her designee must notify the DSMC Chair (or qualified alternate) within 1 business day of knowledge of the event. The contact may be by phone or e-mail.

Reporting to UCSF Committee on Human Research (Institutional Review Board)

The Principal Investigator must report events meeting the UCSF CHR definition of "Unanticipated Problem" (UP) and the San Francisco VA Medical Center within 5 business days of his/her awareness of the event.

Expedited Reporting to the Food and Drug Administration

If the study is being conducted under an IND, the Sponsor-Investigator is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with Federal Regulations (21 CFR §312.32).

The Investigator must report in an IND safety report any suspected adverse reaction that is both serious and unexpected. The Sponsor-Investigator needs to ensure that the event meets all three definitions:

- Suspected adverse reaction (as defined in 6.1.30)
- Unexpected (as defined in 0)
- Serious (as defined in 6.1.5)

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The timeline for submitting an IND safety report to FDA is no later than **15 calendar days** after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)).

Any unexpected fatal or life-threatening suspected adverse reaction will be reported to FDA no later than **7 calendar days** after the Investigator's initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

8 Statistical Considerations and Evaluation of Results

8.1 Study Endpoints

- Per patient and per region ^{68}Ga-PSMA-11 positivity.
- Biopsy correlation.

8.1.1 Randomization

There will be no randomization performed. There will be no blinding performed.

8.2 Determination of Sample Size and Accrual Rate

8.2.1 Sample Size and Power Estimate

The primary endpoint is to evaluate the positive predictive value (PPV) on a (1) per-patient and (2) per-region-basis (prostate bed, pelvis, extrapelvic soft tissue, and bone metastases) of ^{68}Ga-PSMA-11 PET for detection of tumor location confirmed by histopathology/biopsy. Based on the results of previous studies, the following distribution of disease across the four regions are anticipated (19-21):

a) Prostate bed: 30%
b) Pelvis: 15%
c) Extrapelvic soft tissue: 20%
d) Bone metastases: 35%

It is anticipated that the PPV for the four regions and for all regions combined using conventional imaging ranges from 30-60%. An overall PPV for ^{68}Ga-PSMA-11 PET of at most 50% will be considered as unacceptably low. Hence, the null hypothesis that the PPV is at most 50% will be tested against the alternative hypothesis that the PPV is greater than 50%. It is hypothesized that ^{68}Ga-PSMA-11 PET imaging on the per-region and per-patient basis will substantially increase the PPV for the four regions to at least 70%. A sample size of 75 true positives is required for rejecting the null hypothesis that the PPV is at most 50% with 90% power at the one-sided 0.01 (=0.05/5 – a Bonferroni adjustment for evaluating the PPV for the four regions and for all regions combined) significance level, assuming an average regions specific prevalence of 20%. It is expected that approximately 25% of the accrued patients will undergo a biopsy. Hence, the proposed total number of patients requiring a biopsy is 375 in

order to power the analysis at a per region level. Assuming a prevalence rate of 20% for disease in each individual region, a total sample size of 1,500 patients is required. The following table shows the attainable power levels for detecting an increase in the PPV from 50% to 70% at the one-sided 0.01 significance level for the four disease regions and for all regions combined with the proposed sample size of 1500 patients:

Table: *Attainable power levels for detecting an increase in PPV from 50% to 70% with sample size of 1,500 patients (375 biopsies)*

	Prevalence	Number of Biopsies with True Positives	Power
Prostate bed	30%	113	98%
Pelvis	15%	56	78%
Extrapelvic soft tissue	20%	75	90%
Bone metastases	35%	131	>99%
All regions combined	100%	375	>99%

In summary, the proposed target accrual of 1,500 patients (375 with biopsies) will provide adequate power for detecting the anticipated improvement in the PPV for both the per-patient and per-region based ^{68}Ga-PSMA-11 PET imaging when compared to conventional imaging. However, a sample size of 107 patients with biopsies in total is sufficient for detecting the anticipated improvement in PPV when evaluating per-patient based positive predictive value.

8.2.2 Accrual estimates

We estimate that roughly 125 patients with prostate cancer will be enrolled in this trial per year. Over a four-year period this will result in up to 375 patients being enrolled in the study.

8.3 Analyses Plans

8.3.1 Analysis Population

Patients with histopathology correlates will be analyzed for the Primary Aim. All remaining patients will be analyzed for the secondary endpoints.

8.3.2 Analysis of Primary Endpoints

PPVs on a per-patient and per-region-basis of ^{68}Ga-PSMA-11 PET for detection of tumor location confirmed by histopathology/biopsy 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.

a) Imaging interpretation ^{68}Ga-PSMA-11 PET:

   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 final evaluation. For the data sets included in the analysis for the Primary Endpoint, imaging data will be anonymized and collected at a central site. PET data will be interpreted by three different readers in a random order at separate reading sessions. ^{68}Ga-PSMA PET/CT reading training set and guides will be provided and completion of this training will be required for all central review readers.

Visual interpretation:

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.

i) Lymph nodes will be considered positive if the ^{68}Ga-PSMA-11 uptake is focal and greater than blood pool (adjacent or mediastinal blood pool). Pelvic lymph nodes will be subclassified according to their localization as follows: R/L obturator, R/L external iliac, R/L internal iliac and other (total of 7 subgroups).

ii) Visceral lesions will be considered positive if the ^{68}Ga-PSMA-11 uptake is focal and greater than physiologic background activity of the involvement organ or anatomic site.

iii) Bone lesions will be considered positive if the ^{68}Ga-PSMA-11 uptake is focal and greater than physiologic bone marrow.

iv) Prostate bed and prostate lesions will be considered positive if the ^{68}Ga-PSMA-11 uptake is focal and greater than physiologic background activity of the involvement organ or anatomic site.

b) Follow-up Imaging:

All patients will be followed up 3-12 months with conventional imaging (dedicated CT, MRI and/or bone scan). Interpretation of follow-up imaging will be performed by local read. The follow-up conventional imaging should be the same modality/modalities as the initial staging work-up to allow for reproducible and accurate comparisons.

^{68}Ga-PSMA-11 PET positive findings will be validated as true or false positive as outlined in more detail below. False negative ^{68}Ga-PSMA-11 PET findings cannot be determined as this would require biopsies of ^{68}Ga-PSMA-11 negative but conventional or functional non-^{68}Ga-PSMA-11 PET positive imaging lesions. Inclusion of such patients however would be violation of the inclusion criteria.

^{68}Ga-PSMA-11 PET validation based on follow-up imaging:

i) Lymph nodes will be assessed by change in size. ^{68}Ga-PSMA-11 positive lymph nodes will be considered:

(1) True positive:

- If on follow-up imaging within 3-12 months, lymph nodes seen on CT or MRI decrease by more than 30% (for patients undergoing systemic treatment of focal therapy at this site) or increase by more than 20% in short axis diameter (with a minimum of 3 mm in change in size).

- If patients with solitary lymph node regions show a decrease of PSA by greater than 50% after targeted treatment (i.e. external beam radiation) and the lymph nodes do not change in size (less than 30% decrease or less than 20% increase in short axis diameter).

(2) False positive:

- If on follow-up imaging within 3-12 months, sites of initial ^{68}Ga-PSMA-11 positive lymph node lesions seen on CT or MRI decrease by more than 30% *without* systemic therapy or focal therapy at this site.

- If ^{68}Ga-PSMA-11 positive lymph node lesions do not meet the criteria for above false positive or true positive findings.

ii) Visceral lesions (non-lymph node soft tissue or organ) will be assessed by change in size. ^{68}Ga-PSMA-11 positive visceral lesions will be considered:

(1) True positive:

- If on follow-up imaging within 3-12 months, visceral lesions seen on CT or MRI decrease by 30% (for patients undergoing systemic treatment of focal therapy at this site)or increase by 20% in largest diameter.

- If patients with solitary visceral metastasis show a decrease of PSA by greater than 50% after targeted treatment (i.e. external beam radiation) and lesions do not change in size (less than 30% decrease or 20% increase in largest diameter).

(2) False positive:

- If on follow-up imaging within 3-12 months, sites of initial ^{68}Ga-PSMA-11 positive lymph node lesions seen on CT or MRI decrease by more than 30% *without* systemic therapy or focal therapy at this site.

- If ^{68}Ga-PSMA-11 positive lymph node lesions do not meet the criteria for above false positive or true positive findings.

iii) ^{68}Ga-PSMA-11 positive bone lesions will be considered:

(1) True positive:

- If there was a corresponding positive sclerotic lesion on the CT portion of the ^{68}Ga-PSMA-11 PET.

- If there is focal uptake seen on the baseline bone scan performed within one month of ^{68}Ga-PSMA-11 PET.

- If there is a lesion noted on the initial MRI performed within one month of ^{68}Ga-PSMA-11 PET.

- If within 12 months follow-up CT demonstrates development of sclerosis.

- If within 12 months follow-up MRI demonstrates a new bone lesion.

- If within 12 months follow-up bone scan demonstrates new focal uptake.

(2) False positive:

- If ^{68}Ga-PSMA-11 positive bone lesions do not meet the criteria for true positive findings.

iv) ^{68}Ga-PSMA-11 positive prostate bed and prostate lesions will be considered:

(1) True positive:

- If on follow-up imaging within 12 months, lesions seen on CT or MRI decrease by 30% (for patients undergoing systemic treatment of focal therapy at this site) or increase by 20% in largest diameter..

- If patients with prostate bed lesions show a decrease of PSA by greater than 50% after targeted treatment (i.e. external beam radiation) and lesions do not change in size (less than 30% decrease or 20% increase in largest diameter).

(2) False positive:

- If on follow-up imaging within 3-12 months, sites of initial ^{68}Ga-PSMA-11 positive lymph node lesions seen on CT or MRI decrease by more than 30% *without* systemic therapy or focal therapy at this site.

- If ^{68}Ga-PSMA-11 positive lymph node lesions do not meet the criteria for above false positive or true positive findings.

c) Histopathology/Biopsy:

i) Localization of lesions for histopathology/biopsy will be a classified according to the regions in table 1.

ii) ^{68}Ga-PSMA-11 positive findings are aimed to be confirmed by histopathology/biopsy if clinically feasible.

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

(1) Positive HP/Biopsy: Confirmed sites of metastatic or tumor involvement by histopathology/biopsy will be discussed with the responsible physician/surgeon.

(2) Negative Biopsy: Patients with suspected tumor recurrence on ^{68}Ga-PSMA-11 PET with negative histopathology/biopsy will be handled as outlined below:

(a) Lymph nodes:

- For patients undergoing nodal dissection: Patients will be rescanned with dedicated CT or MRI to determine if the suspicious ^{68}Ga-PSMA-11 positive node was removed.

1. If ^{68}Ga-PSMA-11 positive lymph node is still present, a repeat biopsy can be pursued if clinically feasible and applicable, or follow-up using imaging as described above will be performed.

2. If the corresponding node was removed, then this will be considered a False Positive.

- For patients undergoing needle biopsy: Images of the procedure will be reviewed to determine if the correct node was biopsied.

1. If the correct node was biopsied, then a negative biopsy will be considered a False Positive.

2. If the incorrect node was biopsied, then follow-up imaging as described above will be performed.

(b) Bone lesions: Given the high rate of false negative biopsies for osseous metastases in patients with prostate cancer, patients with negative bone biopsies of PSMA PET positive lesions will be further evaluated:

- If pathology demonstrates an alternative diagnoses that is known to be PSMA positive (eg Renal Cell Carcinoma metastases, Paget's disease), then this will be considered a False Positive.
- If pathology is indeterminate, then follow-up imaging as described above will be performed to determine if the lesion is a True Positive or False Positive.

(c) Additionally a repeat ^{68}Ga-PSMA-11 can also be obtained, as allowable, in addition to repeat conventional imaging (CT and/or MRI) in cases of negative biopsy to determine if the biopsy was true negative or false negative.

(d) 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.

8.3.3 Analysis of Secondary Endpoints

PPVs on a per-patient and per-region-basis of ^{68}Ga-PSMA-11 PET 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 paired McNemar's test will be used to compare the PPVs of ^{68}Ga-PSMA-11 PET imaging to the PPVs of conventional imaging.

Sensitivity, specificity, and NPVs on a per-patient basis of ^{68}Ga-PSMA-11 PET for detection of tumor location confirmed by histopathology/biopsy will be summarized in tabular format. Furthermore, the positive and negative likelihood ratios (LR+ and LR-) will be calculated and reported. Ninety-five confidence intervals of sensitivity, specificity, and NPV will be calculated using the Wilson score method. The comparisons of sensitivity, specificity, and NPV on a per-patient basis of ^{68}Ga-PSMA-11 PET imaging will be compared to of sensitivity, specificity, and NPV on a per-patient basis of conventional imaging using a paired McNemar's test.

Detection rates on a per-patient basis of ^{68}Ga-PSMA-11 PET stratified by PSA value (0.2 - <0.5, 0.5 - <1.0, 1.0 - <2.0, 2.0 - <5.0, 5.0) will be summarized in tabular format and compared between PSA strata using chi-square analysis. The impact of ^{68}Ga-PSMA-11 PET on clinical management in BCR patients will be evaluated using descriptive statistics.

9 Study Management

9.1 Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the Investigator will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment

materials, and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed or the Investigator has received a letter from FDA stating that the study is exempt from IND requirements.

9.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the UCSF CHR (UCSF Institutional Review Board). Prior to obtaining CHR approval, the protocol must be approved by the Helen Diller Family Comprehensive Cancer Center Site Committee and by the Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

9.3 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the CHR-approved informed consent form prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

9.4 Changes in the Protocol

Once the protocol has been approved by the UCSF CHR, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the Investigator and approved by PRC and the CHR prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to CHR approval. In this circumstance, however, the Investigator must then notify the CHR in writing within five (5) working days after implementation. The Study Chair and the UCSF study team will be responsible for updating any participating sites.

10 Protection of Human Subjects

10.1 Protection of Privacy

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

References

1. Edwards BK, Noone A-M, Mariotto AB, et al. Annual Report to the Nation on the status of cancer, 1975-2010, featuring prevalence of comorbidity and impact on survival among persons with lung, colorectal, breast, or prostate cancer. Cancer. 2014;120:1290–1314.

2. Oyen RH, Van Poppel HP, Ameye FE, Van de Voorde WA, Baert AL, Baert LV. Lymph node staging of localized prostatic carcinoma with CT and CT-guided fine-needle aspiration biopsy: prospective study of 285 patients. 1994;190:315–322.

3. Contractor K, Challapalli A, Barwick T, et al. Use of [11C]choline PET-CT as a noninvasive method for detecting pelvic lymph node status from prostate cancer and relationship with choline kinase expression. Clin Cancer Res. 2011;17:7673–7683.

4. Price DT, Coleman RE, Liao RP, Robertson CN, Polascik TJ, DeGrado TR. Comparison of [18 F]fluorocholine and [18 F]fluorodeoxyglucose for positron emission tomography of androgen dependent and androgen independent prostate cancer. J Urol. 2002;168:273–280.

5. Castellucci P, Ceci F, Graziani T, et al. Early biochemical relapse after radical prostatectomy: which prostate cancer patients may benefit from a restaging 11C-Choline PET/CT scan before salvage radiation therapy? J Nucl Med. 2014;55:1424–1429.

6. Brogsitter C, Zöphel K, Kotzerke J. 18F-Choline, 11C-choline and 11C-acetate PET/CT: comparative analysis for imaging prostate cancer patients. Eur J Nucl Med Mol Imaging. 2013;40 Suppl 1:S18–S27.

7. Picchio M, Spinapolice EG, Fallanca F, et al. [11C]Choline PET/CT detection of bone metastases in patients with PSA progression after primary treatment for prostate cancer: comparison with bone scintigraphy. Eur J Nucl Med Mol Imaging. 2011;39:13–26.

8. Souvatzoglou M, Krause BJ, Pürschel A, et al. Influence of (11)C-choline PET/CT on the treatment planning for salvage radiation therapy in patients with biochemical recurrence of prostate cancer. Radiother Oncol. 2011;99:193–200.

9. Castellucci P, Fuccio C, Rubello D, et al. Is there a role for ^{11}C-choline PET/CT in the early detection of metastatic disease in surgically treated prostate cancer patients with a mild PSA increase. Eur J Nucl Med Mol Imaging. 2011;38:55–63.

10. Giovacchini G, Picchio M, Scattoni V, et al. PSA doubling time for prediction of [(11)C]choline PET/CT findings in prostate cancer patients with biochemical failure after radical prostatectomy. Eur J Nucl Med Mol Imaging. 2010;37:1106–1116.

11. Fuccio C, Castellucci P, Schiavina R, et al. Role of 11C-choline PET/CT in the restaging of prostate cancer patients showing a single lesion on bone scintigraphy. Ann Nucl Med. 2010;24:485–492.

12. Seltzer MA, Barbaric Z, Belldegrun A, et al. Comparison of helical computerized tomography, positron emission tomography and monoclonal antibody scans for

evaluation of lymph node metastases in patients with prostate specific antigen relapse after treatment for localized prostate cancer. J Urol. 2005;162:1322–1328.

13. Kahn D, Williams RD, Manyak MJ, et al. 111Indium-capromab pendetide in the evaluation of patients with residual or recurrent prostate cancer after radical prostatectomy. The ProstaScint Study Group. J Urol. 1998;159:2041–6–discussion2046–7.

14. Manyak MJ, Hinkle GH, Olsen JO, et al. Immunoscintigraphy with indium-111-capromab pendetide: evaluation before definitive therapy in patients with prostate cancer. Urology. 1999;54:1058–1063.

15. Raj GV, Partin AW, Polascik TJ. Clinical utility of indium 111-capromab pendetide immunoscintigraphy in the detection of early, recurrent prostate carcinoma after radical prostatectomy. Cancer. 2002;94:987–996.

16. Aparici CM, Carlson D, Nguyen N, Hawkins RA, Seo Y. Combined SPECT and Multidetector CT for Prostate Cancer Evaluations. Am J Nucl Med Mol Imaging. 2012;2:48–54.

17. 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;41:11–20.

18. 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;42:197–209.

19. 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. Society of Nuclear Medicine. 2015;56:668–674.

20. 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;42:1284–1294.

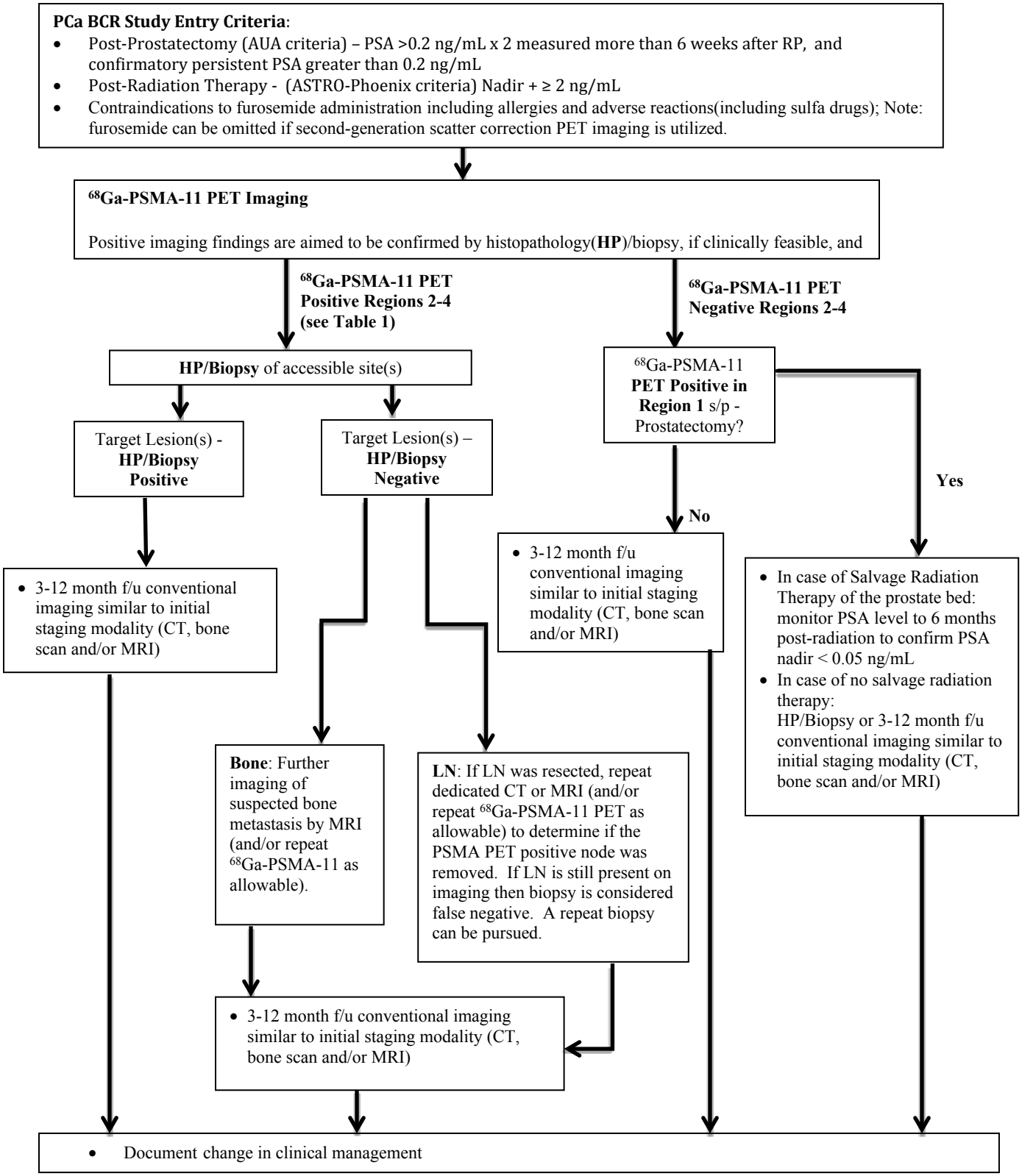
21. van Leeuwen PJ, Stricker P, Hruby G, et al. (68) Ga-PSMA has a high detection rate of prostate cancer recurrence outside the prostatic fossa in patients being considered for salvage radiation treatment. BJU Int. 2016;117:732–739.

Appendices

Appendix 1 Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity Fully active, able to carry on all pre-disease performance without restriction	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
1	Symptoms, but ambulatory Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work)	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self, unable to carry on normal activity or to do active work
2	In bed < 50% of the time Ambulatory and capable of all self-care, but unable to carry out any work activities Up and about more than 50% of waking hours	60	Requires occasional assistance, but is able to care for most of his/her needs
		50	Requires considerable assistance and frequent medical care
3	In bed > 50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated Death not imminent
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair	20	Very sick, hospitalization indicated Death not imminent
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

Appendix 2 (flow chart)



Appendix 3 (pre- and post-surveys)