PROTOCOL 0002	
PROTOCOL TITLE	^{68}Ga-PSMA-11 PET in Patients with Prostate Cancer
STUDY PHASE	Open-Label Phase III Expanded Access
IND NUMBER	IND #154593
INVESTIGATIONAL PRODUCT	^{68}Ga-PSMA-11 prepared using a Sterile Cold Kit PSMA-11
SPONSOR	Bennett Chin, MD Professor, Department of Radiology 12401 East 17th Avenue, Mail Stop L954A Aurora, CO 80045
PRINCIPAL INVESTIGATOR	University of Colorado Anschutz Medical Center Department of Radiology 12401 East 17th Avenue, Mail Stop L954A Aurora, CO 80045 Phone: 720-848-6137 Email: bennett.chin@cuanschutz.edu
PROTOCOL DATE	03-Aug-2021

Good Clinical Practices

This clinical investigation will be performed in compliance with the protocol, the Declaration of Helsinki, Good Clinical Practices as set forth in the ICH Guidelines for Good Clinical Practice, and applicable local regulatory requirements.

Confidentiality Statement

This document contains confidential information of the Sponsor. This information is to be disclosed only to the recipient study staff and the Institutional Review Board or Institutional Ethics Committee reviewing this protocol. This information can be used for no other purpose than evaluation or conduct of this study without prior written consent from the Sponsor.

SPONSOR APPROVAL

Title:	^{68}Ga-PSMA-11 PET in Patients with Prostate Cancer
Sponsor:	Bennett Chin, MD University of Colorado Anschutz Medical Center Department of Radiology 12401 East 17th Avenue, Mail Stop L954A Aurora, CO 80045

[Signature]

Bennett Chin, MD

Date

INVESTIGATOR SIGNATURE

Title: ^{68}Ga-PSMA-11 PET in Patients with Prostate Cancer

Protocol Number: 21-4070

My signature below confirms that I have read and approved this protocol and assures that this clinical study will be conducted according to all requirements of this protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and ICH guidelines.

[Signature]

Bennett Chin, MD

Date

SYNOPSIS

Name of Sponsor	Bennett Chin, MD
Investigational Product	^{68} Ga-PSMA-11 prepared using a PSMA-11 Sterile Cold Kit
Indication (phase)	Open Label Phase III
Title of Study	^{68}Ga-PSMA-11 PET imaging in Patients with Prostate Cancer
Protocol Date	03-Aug-2021
STUDY LOCATIONS	
University of Colorado Health Anschutz Medical Center Anschutz Outpatient Center Aurora, CO 80045 University of Colorado Research Imaging Center 2115 North Scranton Street Aurora, CO 80045	
STUDY OBJECTIVES	

Primary Objective(s):

To provide clinical access to ^{68}Ga-PSMA-11 PET at the University of Colorado. Patients will be monitored for safety.

Secondary Objective(s):

To compare the diagnostic impact of ^{68}Ga-PSMA-11 PET/CT imaging over current standard of care imaging modalities.

To compare the impact of ^{68}Ga-PSMA-11 PET/CT imaging over standard of care imaging on the therapeutic decision or change in management with regards to the number and/or lesion location and PSA levels.

Exploratory Objective(s):

Obtain preliminary data on accuracy of 68Ga-PSMA-11 PET/CT imaging PET / MRI in patients with intermediate and high-risk prostate cancer patients prior to prostatectomy.

METHODOLOGY	
Study Design	This is a prospective, Phase III, single-center, open-label to provide extended access in patients with biochemically recurrent prostate cancer. Eligible patients will undergo baseline assessments as per the Schedule of Study Activities in Appendix A. Approximately 100 patients are planned for enrollment in this study. Patients will receive a single dose of ^{68}Ga-PSMA-11 and undergo a PET/CT or PET/MRI imaging study.
Intervention	The intervention is a PET scan with the radiolabelled PSMA ligand, ^{68}Ga-PSMA-11. The PET may be combined with a CT scan as a PET/CT or an MRI scan as PET/MRI. ^{68}Ga-PSMA-11 PET/CT will be acquired using a modern digital GE PET/CT scanner or a modern digital PET / MRI scanner.
Intervention Duration	AEs will be collected during injection and uptake phase (45-120 min posts infusion) of Ga-68 PSMA-11 PET/CT scan. All safety events will be recorded up to 120 min post injection.
Population	Men with pathologically proven prostate adenocarcinoma, high risk cancer at diagnosis, evidence of biochemical recurrence, or known metastatic disease planned to start and change systemic therapy regimen
Investigational Agent and Formulation	A description of the components of the PSMA-11 Sterile Cold Kit can be found in Section 5.1 of the protocol and in the initial IND submission.
Dose and Route of Administration	One intravenous catheter will be placed for radiopharmaceutical administration. Patients will be injected with 100 MBq (3mCi)-300 MBq(7mCi) of ^{68}Ga-PSMA-11 via this catheter.

SUBJECT POPULATION	
Number of Patients Planned for Enrollment	Approximately 100 patients are planned for enrollment in this study.
Major Inclusion Criteria	Patients must meet all inclusion criteria to be considered eligible for participation in the study. • Histopathologically proven prostate adenocarcinoma. • Age ≥ 18 years • 1) Patients with newly diagnosed with prostate cancer: Primary Staging: high / intermediate risk per NCCN guidelines <u>or</u> 2) Biochemical Recurrence: Rising PSA after definitive therapy with prostatectomy or radiation therapy (external beam or brachytherapy) or other local therapies: • Post radical prostatectomy (RP) – AUA recommendation PSA greater than or equal to 0.2 ng/mL measured more than 6-13 weeks after RP and confirmed by a second determination of a PSA level of >0.2 ng/mL • Post-radiation therapy – ASTRO-Phoenix consensus definition Nadir + greater than or equal to 2 ng/mL rise in PSA • After Local Therapies Nadir + greater than or equal to 2 ng/mL rise in PSA <u>or</u> 3) Metastatic prostate cancer, castrate naïve or castrate resistant: • To confirm suspected metastatic disease in patients with recurrent prostate cancer • To assess treatment response of metastatic disease • Ability to understand a written informed consent document, and the willingness to sign it.

Name of Sponsor	Bennett Chin, MD
Investigational Product	^{68} Ga-PSMA-11 prepared using a PSMA-11 Sterile Cold Kit
Major Exclusion Criteria	• Unable to lie flat, still or tolerate a PET/CT scan, or any other condition that would preclude PET/CT imaging. • Patients with any medical condition or circumstance that the investigator believes may compromise the data collection or lead to a failure to fulfil the study requirements. • Patients with known hypersensitivity to the active substance or to any of the excipients of the investigational product.
ASSESSMENTS	
Efficacy	Standard of care imaging, clinical assessment, PSA.
Safety	Safety of the drug has been established (11). AEs will be collected during injection and uptake phase (45-120 min post infusion) of Ga-68 PSMA-11 PET/CT scan. All safety events will be recorded up to 120 min post injection.

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ABBREVIATIONS AND DEFINITIONS

Abbreviation	Term
AE	Adverse event
CFR	*Code of Federal Regulations*
CT	Computerized tomography
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous(ly)
MBq	Megabecquerel
MRI	Magnetic resonance imaging
PC	Prostate cancer
PET	Positron emission tomography
PSA	Prostate-specific antigen
PSMA	Prostate-specific membrane antigen
SAE	Serious adverse event
SRT	Salvage radiation therapy
T_{max}	Time to maximum plasma concentration
$t_{1/2}$	Half-life
US	United States

1. BACKGROUND AND RATIONALE

In the past several years, there has been an increasing volume of patients in the United States (US) who undergo open radical prostatectomy or robotic-assisted radical prostatectomy for high-risk prostate cancer. Based on several published retrospective reports [1, 2], there may be evidence of improved disease-free survival outcomes for this high-risk cohort compared to outcomes obtained with conventional radiotherapy approaches in conjunction with long-term androgen deprivation therapy. Concomitant with these practice trends in the US, there has been an increasing number of referrals for salvage radiotherapy due to the manifestation of detectable prostate-specific antigen (PSA) levels, which become apparent after surgery. The observation of an increased number of cases with relapsing disease is not surprising, as the risk of biochemical failure among patients with high-grade disease or other high-risk factors treated with surgery alone have ranged from 40-80% in published reports [3-5]. While such patients are often subsequently treated with salvage radiotherapy, the likelihood of maintaining an undetectable PSA at two years after such treatment is often less than 40% in treated patients [6, 7]. As evidenced from the relatively low biochemical control rates for this cohort of patients, we believe that a significant percentage of patients do not benefit from salvage radiation therapy (SRT) using standard treatment techniques because of the presence of extra-pelvic micro-metastatic disease. The increasing number of high-risk patients who develop relapsing disease after surgery currently represents a serious clinical problem. Thus, superior imaging modality for advanced newly diagnosed prostate cancer is clearly needed.

The primary barrier and challenge facing urologic oncologists is the accurate identification of the source of the rising PSA in the post-prostatectomy setting. Current imaging modalities do not perform with high sensitivity, as far as detecting local or regional recurrence with sensitivity or specificity. This concern is further compounded by the fact that several reports have demonstrated that SRT is more effective in achieving durable PSA suppression when treating patients with lower PSA baseline levels. Based on published guidelines [4 8], SRT is routinely administered to patients with the manifestation of a rising detectable PSA, which is often noted at levels of 0.1-0.5 ng/ml. Especially at these low PSA levels indicative of early relapse, standard imaging studies such as MRI, CT scans, and bone scans are often associated with a low yield of detecting positive imaging findings of < 10% and it is unclear if the more recent use of whole body MRIs provide any further information as to the sites of metastatic disease especially in the setting of early biochemical relapse. Clearly, improved and more sensitive imaging modalities are desperately needed to help identify patients with early disease relapse that is non-metastatic, who would then be suitable candidates for local-regional SRT.

We can hypothesize that the use of PSMA PET imaging will provide information about the site of recurrence that can be used to select patient for SRT and adjust SRT target volumes. It should be noted that especially for high-risk patients with biochemically relapsing disease, routine staging work-up would include bone scan and CT/MRI imaging. Nevertheless, the yield on these studies in the setting of early relapse disease has been low.

Although choline or fluciclovine have improved our ability to detect recurrent and metastatic prostate cancer by interrogating the metabolome that is upregulated in prostate cancer. Specifically, fluciclovine (18F) uptake is related to increased amino acid transport that has been demonstrated to occur with

prostate cancer (14). Both C-11 choline and fluciclovine (18F) are now FDA approved and have become a de-facto standard of care. Yet, there are additional cell level imaging biomarkers that are also upregulated in prostate cancer and may be exploited for imaging. One of these promising new targets is prostate specific membrane antigen (PSMA) (15). PSMA is a Type 2 transmembrane glycoprotein of the M28 peptidase family and is significantly overexpressed on the cell surface of prostate cancer (16,17). PSMA therefore provides a promising target for PC-specific imaging and therapy. ^{68}Ga-labelled PSMA ligand suggests that this novel tracer can detect PC relapses and metastases with high contrast by binding to the extracellular domain of PSMA, followed by internalization. A meta-analysis published in 2016 (9) describing 18 studies with efficacy and safety, 5 of which, with histopathology correlation of the positive lesions, reported an improved sensitivity and specificity of PSMA radiolabeled with ^{68}Ga (^{68}Ga-PSMA-HBED-CC or [^{68}Ga]-PSMA-11) over choline.

Evidence has demonstrated the superiority of ^{68}Ga-PSMA-11 PET/CT in staging of the high or intermediate risk prostate cancer patients (18, 19-22). In one study, ^{68}Ga-PSMA-11 PET/CT showed considerable change in staging and management of prostate cancer patients compared to conventional staging (19). The findings of this study supported the replacement of the conventional Bone scan and CT by ^{68}Ga-PSMA-11 PET/CT (19). In a prospective study, it was reported that ^{68}Ga-PSMA-11 PET/CT changed the disease stage in 69% of the patients (18). It was concluded that ^{68}Ga-PSMA-11 PET/CT can greatly impact the staging and management of prostate cancer patients outside the two classic indications (biochemical recurrence and pre-surgical staging) (18). A recent review of 11 studies including 904 patients represented ^{68}Ga-PSMA-11 PET/CT as a promising test for preoperative lymph node staging in intermediate/ high risk patients with prostate cancer (20, 21) . The results of the largest high-risk cohort for primary prostate cancer staging with ^{68}Ga-PSMA-11 PET/CT have recently been published (21). In this study comprising 691 newly diagnosed high-risk prostate cancer patients, ^{68}Ga-PSMA-11 PET/CT detected the advanced disease in 35 percent of the patients (21). The specificity for lymph node metastasis detection on ^{68}Ga-PSMA-11 PET/CT in the pelvic lymph node dissection cohort has been reported to be very high (96.6%) (21). A study on 1253 men was conducted to assess the risk of metastatic disease on ^{68}Ga-PSMA-11 PET/CT at prostate cancer diagnosis and the results supported the use of ^{68}Ga-PSMA-11 PET/CT to detect metastasis and staging (22). Finally, A multicenter, two-arm, randomized study has been conducted and investigated whether ^{68}Ga-PSMA-11 PET/CT has improved accuracy when compared to the conventional imaging (CT and bone scan) (23). Collective data from this study and others provide evidence that ^{68}Ga-PSMA-11 PET/CT is better and can replace conventional imaging with bone scan and CT for staging patients with high-risk prostate cancer before surgery or radiotherapy.

There is *significant clinical need* to provide high risk prostate cancer patients and those with biochemical relapse access to ^{68}Ga-PSMA-11 PET imaging, and because of the exceptional performance that this imaging has shown for prostate cancer staging and the detection of recurrent prostate cancer, it has clear potential to transform clinical management of patients with prostate cancer. While FDA recently approved ^{68}Ga-PSMA-11 at UCSF and UCLA, it is not approved beyond these two institutions and is not currently commercially available. This generates the need for a study at the University of Colorado Anschutz for expanded access use.

Similarly, the ^{18}F PSMA binding ligand, 18F DCF-PyL (PYLARIFY® or piflufolastat F 18), has shown high accuracy in detection of prostate cancer in the above indications (24, 25) and recently received FDA

approval. This compound, however, has not been yet made commercially available to patients by the sponsor (Lantheus), again emphasizing the need for this study for expanded access use.

1.1 NAME AND DESCRIPTION OF INVESTIGATIONAL PRODUCT

The PSMA Sterile Cold Kit, is a kit comprising all needed materials (lyophilized PSMA for PSMA reconstitution, elution vial for ^{68}Ga and ancillary materials for transfer between vials) to perform a room-temperature radiolabelling of PSMA-11 with ^{68}Ga. ^{68}Ga is not part of the kit and should be provided in the form gallium chloride solution following the requirements of the relevant local regulations. PSMA-11 radiolabelled with ^{68}Ga is administered in patients with prostate cancer recurrence after radical treatment.

1.2 RESULTS OF NONCLINICAL STUDIES

A description of the use of PSMA in non-clinical studies can be found in the Investigator's Brochure section 3 (Attachment 1).

1.3 RESULTS OF CLINICAL STUDIES

A description of the use of PSMA in clinical studies can be found in the Investigator's Brochure section 4 (Attachment 1).

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

To provide clinical access to ^{68}Ga-PSMA-11 PET at the University of Colorado Anschutz until FDA approved PSMA-based PET radiotracers become commercially available. Patients will be monitored for safety.

2.2 SECONDARY OBJECTIVES

To compare the diagnostic impact of ^{68}Ga-PSMA-11 PET/CT imaging over current standard of care imaging modalities.

To compare the impact of ^{68}Ga-PSMA-11 PET/CT imaging over standard of care imaging on the therapeutic decision (minor and major therapeutic changes) with regards to the number and/or lesion location.

2.3 EXPLORATORY OBJECTIVES

Determine the detection rate of 68Ga PSMA positive extranodal metastatic sites not seen by MRI alone in intermediate- and high-risk prostate cancer patients.

3. ENDPOINTS

3.1.1 Primary Objective

Evaluate the safety and tolerability of ^{68}Ga-PSMA-11 using the following primary safety outcome measures: Incidence and nature of AEs and change in clinical laboratory results. Incidence and severity of AEs and adverse events will be estimated with 95% confidence intervals summarized with descriptive statistics.

3.1.2 Secondary Objective

Determine the frequency of positive PSMA PET scans in relation to the PSA value before the PSMA scans and compared to conventional imaging. Results will be summarized descriptively with 95% confidence intervals.

Determine rate of major and minor changes in management by comparing planned management strategy using conventional imaging and executed management strategy incorporating information from ^{68}Ga-PSMA-11 PET/CT, regardless of treatment modality.

4. INVESTIGATIONAL PLAN

4.1 SUBJECT SELECTION

4.1.1 Eligibility Criteria

- Histopathologically proven prostate adenocarcinoma
- Age ≥ 18 years
- Patients already diagnosed with prostate cancer: Primary Staging: intermediate and high-risk patients per NCCN guidelines
- Biochemical Recurrence: 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 or equal to 0.2 ng/mL measured more than 6-13 weeks after RP and confirmed by a second determination of a PSA level of >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
- Ability to understand a written informed consent document, and the willingness to sign it.

4.1.2 Exclusion Criteria

- Unable to lie flat, still or tolerate a PET/CT scan, or any other condition that would preclude PET/CT imaging.
- Patients with any medical condition or circumstance that the investigator believes may compromise the data collection or lead to a failure to fulfil the study requirements.
- Patients with known hypersensitivity to the active substance or to any of the excipients of the investigational product.

4.2 PATIENT ASSESSMENTS

4.2.1 Symptom assessment pre- and post-imaging

A directed review of symptoms (nausea, fatigue, pain) will be graded against CTCAE to provide baseline evaluation prior to injection and assess for adverse events post-injection.

4.2.2 Change in management surveys.

Referring clinicians will be queried in providing information on how PSMA PET/CT results impacted the clinical management of patients.

4.2.3 Selection and Timing of Dose for Each Subject

No specific patient preparation is required before ^{68}Ga-PSMA-11 injection. The imaging agent (Ga-68 PSMA-11) will be administered on an outpatient basis. It will be administered a single time intravenously prior to the PET imaging. The injected dose will be 100 to 300 MBq (~3-7 mCi) of ^{68}Ga-PSMA-11.

Following a waiting period of 60 minutes post 68Ga-PSMA-11 administration, patients will be scanned from mid thighs to base of the skull. Images will be acquired with patients in a supine position with their arms raised above their head. If patients cannot raise their arms above the head, the arms will be comfortably positioned and secured by the side of the patient. The goal is to administer this amount of the imaging probe labeled with 2.5 MBq of ^{68}Ga per kg body weight with a minimum of 100 MBq (3mCi) and maximum of 300 MBq (7mCi) 68Ga per patient. The typical acquisition time per bed position will be 3 min and the typical number of bed positions is 4.

4.3 PET IMAGING

a) ^{68}Ga-PSMA-11 PET preparation: Oral hydration is recommended on the day of the scan. No fasting is required.

b) Contrast administration: Imaging contrast will not be ordered as part of this study. However, if a clinically indicated diagnostic CT scan is ordered with intravenous iodinated contrast, it can be added at the end of the ^{68}Ga PSMA-11 PET imaging.

c) Voiding: Voiding is recommended immediately before start of the scan.

d) ^{68}Ga-PSMA-11 injection: The intravenously injected dose will be 100-300 MBq (~3-7 mCi) of ^{68}Ga-PSMA-11 PET.

e) PET imaging protocol: 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. At a minimum, 3 minutes per bed position will be used. In certain circumstances, coverage may be extended to the toes.

f) Patient monitoring: Patients will be monitored for adverse events during injection and uptake phase of the radiotracer.

4.4 IMAGE ANALYSIS AND INTERPRETATION

A board-certified nuclear medicine physician or nuclear radiologist on-site will interpret the images of the ^{68}Ga-PSMA-11 PET/CT scan. Images will be corrected for attenuation and scatter and adjusted for system sensitivity and will provide parametric images in terms of standardized uptake values (SUV) (= MBq found/gm tissue / MBq injected/gm body mass).

PET imaging can be combined with a low-dose CT for attenuation correction, a diagnostic CT (PET/CT), or MRI (PET/MR). Patients may undergo a diagnostic MRI of the prostate, other body parts or a whole-body MRI at the same imaging session as clinically indicated. Contrast material may be administered for the CT or MRI as clinically indicated.

Imaging will be initiated at approximately 60 minutes (45-120 minutes) following administration of the PSMA radiopharmaceutical. At the discretion of the investigator, an additional image of the pelvis may be obtained.

Patients will receive a single dose of ^{68}Ga-PSMA-11 and undergo a PET/CT or PET/MRI imaging study. At the time of interpretation of the ^{68}Ga-PSMA-11 PET study, the reviewing nuclear medicine physician and/or radiologist will compare the ^{68}Ga-PSMA-11 PET findings with the results from previously performed standard-of-care imaging for prostate cancer staging. The presence or absence of sites suspicious for recurrent prostate cancer will be documented. (e.g., prostate bed, lymph nodes, metastases to bone or other organs).

4.5 STATISTICAL CONSIDERATIONS

4.5.1 Primary Objective

Determine the safety and tolerability of ^{68}Ga-PSMA-11 using the following primary safety outcome measures: Incidence and nature of AEs and change in clinical laboratory results. Incidence and severity of AEs and adverse events will be estimated with 95% confidence intervals summarized with descriptive statistics.

4.5.2 Secondary Objective

Determine rate of overall changes in management by comparing planned management strategy using conventional imaging with executed management strategy incorporating information from ^{68}Ga-PSMA-11 PET/CT, regardless of treatment modality.

Analysis: The rate of change in management based on the incorporation of^{68}Ga-PSMA-11 PET/CT results will be expressed as the percentage of total patients imaged in which change in management occurred, regardless of treatment modality. The rate of change in management will also be estimated within each group (initial staging, biochemical recurrence, and pre/post treatment). 95% confidence intervals (CIs) will be used to express precision of the estimates.

4.5.3 Sample Size and Power Estimate

Since this protocol is for clinical access only, there is no need for sample size and power estimation calculations. It is anticipated that 100 patients will be imaged with primary diagnosis of prostate cancer or biochemically recurrent prostate cancer. There will likely be a ramp up period in the number of patients who will be scanned.

4.5.4 Accrual estimates

Clinically eligible patients with prostate cancer.

5. INVESTIGATIONAL DRUG

5.1 GA68 PSMA-11

5.1.1 The PSMA-11 Sterile Cold Kit

The final drug product is the ^{68}Ga-PSMA-11 Prostate-Specific Membrane Antigen (PSMA)- prepared using the Telix cold sterile kit labeled with the Gallium-68. The full description of the investigational drug is described in the CMC section of the initial submission packet.

5.1.2 Formulation and preparation

The final dosage form of Ga68-PSMA-11 is an intravenous solution. Ga68-PSMA-11 will be aseptically prepared in the PharmaLogic radiopharmacy as described in the CMC section of the IND. Subject specific doses will be aseptically withdrawn from the vial of the sterile cold kit into a sterile syringe. The radioactive dose will be calibrated for the appropriate scan time with the use of a dose calibrator. The syringe containing the study drug will be placed in a syringe shield with the approved IND prescription label as in the initial IND submission and then delivered to the University of Colorado Anschutz Outpatient Center for PET/CT imaging or the University of Colorado Research Imaging Center (CURIC) for PET / MRI imaging.

5.1.3 Administration

Ga68-PSMA-11 will be administered intravenously with a dose of 2.5 MBq of ^{68}Ga per kg body weight with a minimum of 100 MBq (3mCi) and maximum of 300 MBq (7mCi) 68Ga per patient.

6. ADVERSE EVENTS AND REPORTING REQUIREMENTS

6.1 ASSESSMENT OF SAFETY

Pharmacologic effects of ^{68}Ga-PSMA-11

^{68}Ga-PSMA-11 has been injected for PET imaging in more than 2,616 published patients [11] and the safety profile has been well established. Currently, no serious adverse events related to drug have been reported. This is expected because the mass of compound is minimal, less than 25 micrograms. There is a potential small risk of infection at the site of injection.

Safety evaluation

AEs will be collected during injection and uptake phase (50-100 min) of Ga-68 PSMA-11 PET/CT scan. All safety events will be recorded up to 120 min post injection.

Analyses will be performed for all patients receiving Ga-68 PSMA-11. The study will use the CTCAE v5.0 for reporting of adverse events.

Radiation exposure from PSMA PET/CT imaging

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

In a phase 1 clinical trial (EudraCT: 2016-004971-32) conducted with the PSMA-11 sterile cold kit as Investigational Medicinal Product (IMP), physiological uptake of [68Ga] PSMA-11 was observed in kidneys, urinary bladder, salivary glands and small intestines. The kidneys were the organs receiving the highest absorbed dose. Additional organs with higher dose were the bladder, small intestines, and salivary glands. Estimated radiation absorbed doses in selected organs and tissues are presented in the Table 1 below.

Table 1 summarizes the expected radiation exposure for the planned study and is consistent with biodistribution data published by Afshar-Oromieh et al. [12] and assuming a voiding interval of 2 h, i.e., the patient is asked to void the bladder after completion of the PSMA PET/CT study. ^{68}Ga has a short half-life of 68 minutes.

Table 1. Estimated Radiation Absorbed Dose per Injection Activity in Selected Organs and Tissues of Adults after a Gallium (68Ga) PSMA-11 Injection Dose

Absorbed Doses

Organ/Tissue	Estimated Radiation Absorbed Dose per Injection Activity (µGy/MBq)
Adrenals	12
Brain	1
Breasts	6
Gallbladder	12
Lower colon	12
Small intestine	58
Stomach	9
Upper Colon	13
Heart	13
Kidneys	456
Liver	22
Lungs	8
Muscle	8
Pancreas	11
Red marrow	12
Osteogenic cells	13
Skin	6
Spleen	37
Testes	8
Thymus	7
Thyroid	7
Bladder	241
Salivary glands	96
Total body	11
Effective dose	**19 (µSv/MBq)**

Monitoring and Oversight

The sponsor investigator will be responsible for monitoring the trial per the trial monitoring plan, in addition to overseeing the safety and efficacy of the trial including any specimens collected, executing the data and safety monitoring (DSM) plan, and complying with all reporting requirements to local and federal authorities. This oversight will be accomplished through additional oversight from the Data and Safety Monitoring Committee (DSMC) at the University of Colorado Cancer Center (CU Cancer Center). The DSMC is responsible for ensuring data quality and study participant safety for all clinical studies at the CU Cancer Center, which is the coordinating institution of this trial. A summary of the DSMC's activities is as follows:

• Conduct of internal audits

• Ongoing review of all serious adverse events (SAEs) and unanticipated problems (UAPs)

• May submit recommendations for corrective actions to the CU Cancer Center's Executive Committee

Per the CU Cancer Center Institutional DSM Plan, SAEs and UAPs are reported to the DSMC, IRB and the sponsor investigator per protocol. All SAEs and UAPs are to be reported to the DSMC within 7 (for fatal or life-threatening events) or 15 (non-life-threatening events) calendar days of the sponsor investigator receiving notification of the occurrence.

Each subject's treatment outcomes will be discussed by the site PI and appropriate staff at regularly scheduled meetings. Data regarding number of subjects, significant toxicities, dose modifications, and treatment responses will be discussed and documented in the meeting's minutes.

The sponsor investigator will provide a DSM progress report to the CU Cancer Center DSMC on a recurring basis (either every six or twelve months based on DSMC vote). The DSM report will include a protocol summary, current enrollment numbers, summary of toxicity data to include specific SAEs, UAPs and AEs, any dose modifications, all protocol deviations, and protocol amendments. The DSM progress report submitted to the DSMC will also include, if applicable, the results of any efficacy data analysis conducted. Results and recommendations from the review of this progress report by the DSMC will then be provided to the sponsor investigator in a DSMC review letter. The sponsor investigator is then responsible for ensuring this letter is submitted to the site's IRB of record at the time of IRB continuing review.

6.2 DEFINITIONS

6.2.1 ADVERSE EVENTS

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

For this study, AEs are regarded as 'treatment emergent', if they occur after treatment has been administered.

Pre-planned or elective surgeries or therapies should be recorded in the patient's source documents but are not to be considered AEs unless there was any change to the patient's medical condition during the AE collection period.

Collection of AEs will occur upon signature of consent.

6.2.2 SERIOUS ADVERSE EVENTS

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon 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.

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE. SAE reporting is required as soon as the participant signs consent.

6.2.3 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.

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).

SAE reporting will comply with University of Colorado Anschutz Medical Center SOPs and with local and federal regulations.

6.2.4 EVALUATION OF ADVERSE EVENTS

Seriousness

The seriousness must be determined for each AE, according to the criteria given in Section 7.3.3.

Intensity/Severity

The intensity of an AE is classified according to NCI-CTCAE version 5.0, taking into account the possible range of the intensity of the event:

- NCI-CTCAE Grade 1 (mild)
- NCI-CTCAE Grade 2 (moderate)
- NCI-CTCAE Grade 3 (severe)
- NCI-CTCAE Grade 4 (life-threatening)
- NCI-CTCAE Grade 5 (fatal)

Study drug action

AEs requiring any action, i.e., medication or therapy for treatment, should be treated according to recognised standards of medical care to protect the health and well-being of the patient.

Any potential study drug action to resolve the AEs is to be documented as follows:

- Drug withdrawn
- Dose reduced
- Dose not changed
- Other action (stopped: definitely, temporarily with exact dates)

Any potential study drug action to resolve the AEs is to be documented in free text in the CRF, e.g., 'dose interrupted', 'dose interrupted and re-started'.

6.2.5 RELATIONSHIP TO STUDY INTERVENTION

The possible causal relationship between the AE and the administration of the study drug is classified according to the following question:

"Is there a reasonable likelihood that the event was caused by the study drug?"

Possible answers are:

- Related (plausible time relationship to the administration of IMP/RP. No plausible explanation by underlying/concurrent disease or other drugs/events),
- Possible (plausible time relationship to the administration of IMP/RP, but the AE can be also plausibly explained by the underlying/concurrent disease or other medicinal products / events),
- Unlikely (unlikely temporal relationship to the administration of IMP/RP. Other medicinal products, events, and the underlying/concurrent disease provide a plausible explanation)
- Not related (clear evidence that the AE is not connected to the IMP/RP administration)
- Not assessable (no evaluation possible based on present data, additional clarification and follow-up necessary)

Causal relationship to study conduct

The possible causal relationship between the AE and any study-conduct-related procedures and activities required by the protocol is classified according to the following question:

"*Is there a reasonable likelihood that the event was caused by the study conduct?*"

Possible answers are "related", "not related", "not assessable".

6.2.6 EXPECTEDNESS

Expected Conduct-related AEs

The use of an indwelling cannula for blood sampling and administration of study drug may be accompanied by mild bruising and also, in rare cases, by transient inflammation of the vessel wall. After

initial irritation, the presence of an indwelling cannula is usually painless and hardly noticeable. The same applies to single vein punctures for blood sampling.

Patients may also experience discomfort from lying in the camera, e.g., back pain.

Expected Adverse Drug Reactions

The definition below follows ICH-GCP (see also ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting):

Adverse drug reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established, all noxious and unintended responses to a medicinal product related to any dose should be considered as ADR. The phrase 'responses to a medicinal product' means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Unexpected Adverse Drug Reactions

An unexpected adverse drug reaction is defined as any adverse drug experience, the nature, specificity or severity of which is not consistent with the applicable product information (e.g., investigator's brochure for an unapproved investigational product or Summary of Product Characteristics for an approved product). "Unexpected" as used in this definition refers to an adverse drug experience that has not been previously observed and included in the product information, rather than from the perspective of such experience not being anticipated from the pharmacological properties of the investigational product.

6.2.7 DATA QUALITY ASSURANCE

Accurate, consistent, and reliable data will be ensured through the use of standard practices and procedures. These are described in the following sections.

6.2.8 DATA COLLECTION, MONITORING, AND TRANSFER

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data including adverse events, concomitant medications, and expected adverse reactions data and clinical laboratory data will be entered into the hospital electronic medical record system (EPIC).

The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

6.2.9 QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor will perform a clinical review to define the level of resolution required of each data field, with major safety fields (e.g., AE) given the highest importance.

The database will be 100% verified against the CRFs. A clinical review will be performed at Sponsor to identify those minor issues that could remain unresolved.

Serious AE data in the Sponsor' clinical safety database will be reconciled to the original clinical management database.

6.2.10 SAFETY ANALYSIS

All subjects who receive study drug will be analyzed for safety. Safety-related data will be summarized using tables and graphical presentations, subject listings and complete narrative descriptions of SAEs. Results of the safety-related data analysis will be expressed as medians (or means) broken down into age, sex, racial subgroups, and defined by disease severity and concurrent illness (if reported).

6.2.11 EXTENT OF EXPOSURE

A total of 100 patients are planned for exposure to a single dose of ^{68}Ga-PSMA-11 at 100MBq (3mCi)-300 MBq (7mCi).

7. ETHICS

7.1 COMPLIANCE STATEMENT

The study will be conducted in accordance with the protocol, Good Clinical Practices, the relevant ICH guidelines, the applicable regulatory requirements, and the ethical principles that have their origins in the Declaration of Helsinki. As required by United States Food and Drug Administration (FDA) Code of Federal Regulations (CFR) (21 CFR 56) and the Declaration of Helsinki, the study protocol, amendments, and Informed Consent form will be reviewed and approved, according to 21 CFR §50 and §56, respectively, by each study center's IEC or IRB.

7.2 INFORMED CONSENT

Before protocol-specific procedures are carried out, qualified consenting professionals will explain full details of the protocol and study procedures, as well as the risks involved to patients prior to their inclusion in the study.

Patients will also be informed that they are free to withdraw from the study at any time. All patients must sign an Institutional Review Board/Privacy Board (IRB/PB) approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the IRB/PB of this Center.

Both the patient and the qualified consenting professional will sign the consent form. The patient must receive a copy of the signed informed consent form.

7.3 CHANGES IN PROTOCOL

Once the protocol has been approved by the IRB and Radiation Safety Committee, any changes to the protocol must be documented in the form of an amendment

8. PROTECTION OF HUMAN SUBJECTS

8. 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.

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10. APPENDICES

APPENDIX A: STUDY CALENDAR: SCHEDULE OF ACTIVITIES

	Screening	Day of Scan	Post Scan
Informed Consent	X		
Standard of Care Chart Review	X		
Administration of Ga-PSMA PET Imaging		X	
Safety Monitoring		X	X
Change in management surveys		X	X

COMIRB
APPROVED
For Use
29-Sep-2021
28-Sep-2022

Principal Investigator: Bennett Chin, MD
COMIRB No: 21-4070
Version Date: Version 1.0; August 3, 2021

Study Title: ^{68}Ga-PSMA-11 PET in Patients with Prostate Cancer

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You are being asked to be in a research study. This form provides you with information about the study. A member of the research team will describe this study to you and answer all of your questions. Please read the information below and ask questions about anything you don't understand before deciding whether or not to take part.

Why is this study being done?

This study is being performed to provide clinical access to the prostate cancer imaging agent 68Ga-PSMA-11 for positron emission tomography (PET) imaging in patients with prostate cancer at the University of Colorado.

You are being asked to be in this research study because this prostate cancer imaging agent, 68Ga-PSMA-11, is either currently not available for clinical use, or is not yet approved by the Food and Drug Administration (FDA).

You will be monitored by our routine procedures to ensure your safety.

Other people in this study

Up to 100 patients from your area will participate in the study. Several thousand patients of with prostate cancer have already received this 68Ga-PSMA-11 PET imaging agent with no reported serious adverse events.

What happens if I join this study?

If you join the study, you will undergo a 68Ga-PSMA-11 PET / CT or 68Ga-PSMA-11 PET/ MRI study depending upon your specific situation. In general, if your doctor suspects any cancer in your prostate gland, your doctor may recommend a PET / MRI. If have previously been treated by removal of your prostate gland your doctor may recommend a PET / CT scan.

The study will last approximately 2 hours or less. An intravenous catheter will be inserted, 3-7mCi of 68Ga-PSMA-11 will be administered through the catheter over less than 30 seconds, and then a waiting period (uptake time) of approximately 60 minutes will occur before scanning. Prior to scanning, you will be asked to empty your bladder, and then the scan will be performed which will take approximately 30-45 minutes.

We will observe you during this entire period, and then the study will be finished.

What are the discomforts and risks of the study procedures?

Risks of Insertion of the intravenous catheter. In this study we will insert an intravenous catheter, connected to a plastic tube, into a vein in your arm. We will use the tube to administer the 68Ga-PSMA-11. You will feel some pain when we first insert the tube into your vein. You may have some redness, swelling, or bruising where the tube goes under your skin. In some cases, this type of tube can cause an infection where it goes under the skin. In rare cases, it can cause a blood clot in the vein.

Risks of Computed Tomography (CT). As part of this study, we may perform a CT scan of your chest, abdomen, pelvic area. CT is a way of taking detailed pictures inside your body by using X-rays. X-rays are a type of radiation. You get some radiation from your environment. You get radiation from bricks and concrete, from some foods, and from radon gas, which is an invisible gas that seeps out of the ground. The amount of radiation that this CT scan will deliver to your body (give you) is about the same as you would get from living in your environment for **5 years**.

This is an estimate. The amount of radiation you get could be higher or lower, depending on the machine, the power setting, and your body weight. Exposure to radiation at high levels increases a risk of developing cancer. There is no evidence of such risks for diagnostic procedures.
The risk of this procedure is not equal for everyone. The risk is much lower for people over the age of 30.

Risks of Having an MRI

In this study we may perform Magnetic Resonance Images (MRIs) of your head, chest, abdomen, pelvic area and extremities, if indicated. The MRI machine uses powerful magnetic waves to take pictures inside the body. The waves themselves are not harmful, but they can cause metal to heat up and electronics to stop working.

You should NOT have an MRI if you have metal or electronic devices inside your body. Heart pacemakers and insulin pumps are examples of electronic devices.

The MRI machine is a small round tube. It might make you uncomfortable if you do not like tight spaces.

The most common side effect of having an MRI is flashing lights in the eyes. This is caused by the magnetic waves and is not harmful. Some people also experience warmth and reddening of the skin. This usually goes away after a few minutes.

MRIs may be done with or without contrast. The contrast solution may cause an allergic reaction. Severe allergic reactions can be life threatening. MRI contrast solution can cause kidney damage, especially if you are diabetic, dehydrated (lost body water) or elderly.

Risks of ^{68}Ga-PSMA-11 Positron Emission Tomography (PET)

A small amount (3-7 mCi) of radioactive substance (radiotracer) 68Ga PSMA,-11 will be injected into your bloodstream. The PET scanner works by detecting the radioactive substance inside the body and makes images that show where the radiation is concentrated.

Everyone is exposed to radiation everyday of their lives (background radiation). The doses that are used in a PET scan carry a possible risk of causing cancer at a later date (as does your exposure to background radiation), but the risk is very low. The amount of radiation that this 68Ga PSMA-11 radiotracer will deliver to your body (give you) is about the same as you would get from living in your environment for **3 years**.

You may feel some claustrophobia, discomfort or anxiety when lying inside the scanner. Possible side effects of ^{68}Ga-PSMA-11 PET may include allergic reactions, itching, and rash.

These scans may be taken in combination with a CT or MRI scan. Please see CT and MRI risks above.

There is a risk that people outside of the research team will see your research information. We will do all that we can to protect your information, but it can not be guaranteed.

What are the possible benefits of the study?

This study is designed to provide 68Ga PSMA-11 PET imaging information for patients with prostate cancer.

The results of the 68Ga PSMA-11 PET study will be available to your doctors to use for your care.

Are there alternative treatments?

Currently, there are no alternative 68Ga PSMA-11 PET imaging agents available to detect prostate cancer at the University of Colorado. Another method to produce 68Ga PSMA-11 for PET has been shown to be safe and effective for identifying prostate cancer and has been approved by the FDA. Due to differences in manufacturing requirements, however, the currently approved formulation is not available for patients at the University of Colorado. The proposed method to produce 68Ga PSMA-11 in this study is currently under review by the FDA.

You should talk to your doctor about your choices. Make sure you understand all of your choices before you decide to take part in this study. You may leave this study and still have these other choices available to you.

Who is paying for this study?

Currently, PET imaging for prostate cancer detection is the standard of care, and is paid for by Medicare for patients over the age of 65, and by most insurance carriers.

The sponsor will only pay for procedures not considered standard of care, as detailed below.

The cost for the current 68Ga PSMA-11 PET radiopharmaceutical product, however, may not be paid for due to its current status under review by the FDA, or by Medicare payment determination. The cost of the radiotracer under this research protocol is being sponsored by the University of Colorado Health System.

Will I be paid for being in the study?

You will not be paid to be in the study.

Will I have to pay for anything?

No, participants will not be required to pay for this study.

Is my participation voluntary?

Taking part in this study is voluntary. You have the right to choose not to take part in this study. If you choose to take part, you have the right to stop at any time. If you refuse or decide to withdraw later, you will not lose any benefits or rights to which you are entitled.

Can I be removed from this study?

The study doctor may decide to stop your participation without your permission if the study doctor thinks that being in the study may cause you harm, or for any other reason. Also, the sponsor may stop the study at any time.

What happens if I am injured or hurt during the study?

If you have an injury while you are in this study, you should call Dr. Bennett Chin, and notify his study team immediately. His phone number is 720-848-6137.

We will arrange to get you medical care if you have an injury that is caused by this research. However, you or your insurance company will have to pay for that care.

Who do I call if I have questions?

The researcher carrying out this study is Dr. Bennett Chin. You may ask any questions you have now. If you have questions, concerns, or complaints later, you may call Dr. Bennett Chin at 720-848-6137. You will be given a copy of this form to keep.

You may have questions about your rights as someone in this study. You can call Dr. Bennett Chin with questions. You can also call the responsible Institutional Review Board (COMIRB). You can call them at 303-724-1055.

A description of this clinical trial will be available on http://www.Clinical Trials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Who will see my research information?

The University of Colorado Denver | Anschutz Medical Campus (the University) and its affiliated health systems have rules to protect information about you. Federal and state laws including the Health Insurance Portability and Accountability Act (HIPAA) also protect your privacy. This part of the consent form tells you what information about you may be collected in this study and who might see or use it.

The institutions involved in this study include:

- University of Colorado Denver | Anschutz Medical Campus
- University of Colorado Health

We cannot do this study without your permission to see, use and give out your information. You do not have to give us this permission. If you do not, then you may not join this study.

We will see, use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside the University and its affiliate hospitals may not be covered by this obligation.

We will do everything we can to maintain the confidentiality of your personal information, but confidentiality cannot be guaranteed.

The use and disclosure of your information has no time limit. You can cancel your permission to use and disclose your information at any time by writing to the study's Principal Investigator (PI), at the name and address listed below. If you do cancel your permission to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in this study.

Bennett Chin, MD
University of Colorado Health Anschutz Medical Center
Department of Radiology
12401 East 17th Avenue, Mail Stop L954A
Aurora, CO 80045

Both the research records that identify you and the consent form signed by you may be looked at by others who have a legal right to see that information, such as:

- Federal offices such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP) that protect research subjects like you.
- The Institutional Review Board that is responsible for overseeing this research
- The study doctor and the rest of the study team.
- Officials at the institution where the research is conducted and officials at other institutions involved in this study who are in charge of making sure that we follow all of the rules for research

We might talk about this research study at meetings. We might also print the results of this research study in relevant journals. But we will always keep the names of the research subjects, like you, private.

You have the right to request access to your personal health information from the Investigator

What happens to Data, Tissue, Blood and Specimens that are collected in this study?

Scientists at the University and the health systems involved in this study work to find the causes and cures of disease. The data collected from you during this study are important to this study and to future research. If you join this study:

- The data given by you to the investigators for this research no longer belong to you.
- The investigators may study your data collected from you.
- If data are in a form that identifies you, the University or the health systems involved in this study may use them for future research only with your consent or Institutional Review Board (IRB) approval.
- Any product or idea created by the researchers working on this study will not belong to you.
- There is no plan for you to receive any financial benefit from the creation, use or sale of such a product or idea.

Agreement to be in this study and use my data

I have read this paper about the study, or it was read to me. I understand the possible risks and benefits of this study. I understand and authorize the access, use and disclosure of my information as stated in this form. I know that being in this study is voluntary. I choose to be in this study: I will get a signed and dated copy of this consent form.

Signature:_____ Date:_____

Print Name:_____

Consent form explained by:_____ Date:_____

Print Name:_____