**PROTOCOL NO. Amino Acid Infusion for Renal Protection in Lutetium-177 PSMA I&T Therapy for Metastatic Prostate Cancer: A Study on Renal Dosimetry Using 3D SPECT/CT Imaging - 01**:

A PROSPECTIVE, OPEN-LABEL, SINGLE CENTER, TWO ARMS STUDY OF AMINO ACIDS INFUSION AS RENAL PROTECTION DURING Lutetium-177 PSMA-I&T THERAPY: RENAL DOSIMETRY ASSESSMENT IN PATIENTS WITH METASTATIC CASTRATE-RESISTANT PROSTATE CANCER.

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| Clinical Protocol No. | Amino Acid Infusion for Renal Protection in Lutetium-177 PSMA I&T- 01 |
| Version/Date | V4 / 15th November 2023 |
| Investigational Products | SYNTHAMIN 17 (Amino acids 10%) without electrolytes |
| Sponsor | Fiona Stanley Hospital |
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# Trial Details

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| Protocol title: | A PROSPECTIVE, OPEN-LABEL, SINGLE CENTER, TWO ARMS STUDY OF AMINO ACID INFUSION AS RENAL PROTECTION DURING LUTETIUM-177 PSMA-I&T THERAPY: RENAL DOSIMETRY ASSESSMENT IN PATIENTS WITH METASTATIC CASTRATE-RESISTANT PROSTATE CANCER. |
| Rationale  Objectives  Design  Investigational Product | Despite the therapeutic potential of Radioligand therapies, including PRRT, there is evidence of associated renal injuries. Chronic renal injuries, especially in patients undergoing extended treatments with Lutetium-177 PSMA-I&T, highlight the risks. With differences in the pharmacodynamic properties between the 617 and I&T molecules, there's a need for better renal protection, especially for those patients with prolonged response to treatment.  To evaluate the efficacy of amino acid infusion as a renal protective measure during Lutetium-177 PSMA-I&T therapy, assess renal dosimetry using 3D SPECT/CT imaging, and monitor nephrotoxicity in metastatic castrate-resistant prostate cancer patients.  The study will focus on patients receiving Lutetium-177 PSMA-I&T therapy. The intervention group will receive an amino acid infusion before their 4th, 5th, or 6th treatment cycle. Renal dosimetry will be assessed using 3D SPECT/CT imaging after this cycle and compared to the renal dosimetry of the same patients at the preceding cycle without amino acid infusion.  This study introduces the amino acid infusion as a renal protective measure during Lutetium-177 PSMA-I&T treatment. The primary concern arises from the recent reports of severe long-term nephrotoxicity in patients subjected to prolonged Lutetium-177 PSMA-I&T treatment. The infusion aims to mitigate this nephrotoxicity and enhance the therapeutic benefits of the Lutetium-177 PSMA-I&T treatment, with an emphasis on its distinct pharmacodynamics compared to the Lutetium-177 PSMA-617 compound. All infusions and treatments will be conducted under strict guidelines and protocols, ensuring patient safety. |

# List of Abbreviations and Definition of Terms

| **Abbreviation** | **Definition** |
| --- | --- |
| AE | Adverse Event |
| GCP | Good Clinical Practice |
| HREC | Human Research Ethics Committee |
| NHMRC | National Health and Medical Research Council |
| PI | Principal Investigator |
| PSMA | Prostate-Specific Membrane Antigen |
| SPECT | Single-Photon Emission Computerized Tomography |
| SPECT/CT | Single-Photon Emission Computerized Tomography / Computerized Tomography |

# 3. RATIONALE / BACKGROUND

# 1. Introduction

# 3.1.1. Background and Significance

The therapeutic landscape of metastatic prostate cancer has witnessed significant advances over the past few years. Among these advancements, radioligand therapy, specifically with Lutetium-177 PSMA (Jang, Kendi, and Sartor 2023; Sartor et al. 2021; Hofman et al. 2021), offers a targeted treatment approach that has demonstrated promise in both improved survival and quality of life. However, the potential therapeutic benefits of these agents come with associated risks, given the intrinsic radiosensitivity of certain organs, notably the kidneys.

# 3.1.2. Radiosensitivity of Kidneys

The kidneys are integral to various bodily functions, including waste elimination and fluid balance regulation. Their vulnerability to ionizing radiation is well-documented. Studies involving external beam radiotherapy have identified specific thresholds of renal tolerance, emphasizing the organ's sensitivity (Cassady 1995). In the realm of peptide-receptor radionuclide therapy (PRRT), the kidneys experience exposure due to their role in filtering and reabsorbing radiopeptides (Geenen et al. 2021; Bodei, Cremonesi, and Paganelli 2014). This prolonged renal exposure to ionising radiation underscores the critical need for protective measures.

# 3.1.3. Radioligand Therapy Kidney Injury

While radioligand treatments, especially PRRT, show promising therapeutic effects, they have also been linked to kidney damage. The process of this damage is complex, starting with the kidney's filtration of radiopeptides, which are then reabsorbed, resulting in the persistence of radioactive substances within the kidney's inner layers. Notably, kidney issues, such as thrombotic microangiopathy (TMA), have been observed with well-known treatments like yttrium-90 DOTATOC and Lutetium-177-PSMA (Moll et al. 2001). Consequently, the safety of these treatments, particularly over longer treatment durations, continues to be a focal point of research and scrutiny.

# 3.1.4. The Case for Renal Protection in Lutetium-177 PSMA-I&T

After documented decreases in renal function following PRRT in metastatic neuroendocrine tumours, amino acid infusion as a renal protective measure has become standard practice (Vegt et al. 2010; Bodei et al. 2022), refining and enhancing this crucial therapeutic approach.

There have been recent indications of severe long-term nephrotoxicity in patients subjected to prolonged Lutetium-177 PSMA-I&T treatment (Steinhelfer et al. 2023). Chronic renal injuries, notably from thrombotic microangiopathy, have been reported in patients who underwent more than six cycles of Lutetium-177 PSMA-I&T, underscoring potential long-term toxicities for those with extended treatment response and survival (Schäfer et al. 2023).

# 2.Rationale for Renal Protection in Patients Undergoing Lutetium-177 PSMA-I&T

# 3.2.1. Overview of Lutetium-177 PSMA Therapies

Lutetium-177 PSMA therapies represent a revolutionary approach in the treatment of metastatic prostate cancer. By targeting the prostate-specific membrane antigen (PSMA) with radionuclides, these therapies offer a more precise method of delivering radiation to malignant cells, sparing healthy tissues. Pivotal trials, including Thera-P and VISION, have shown substantial therapeutic efficacy, with patients experiencing improved survival rates and quality of life. Notably, while neither trial incorporated renal protection measures, both reported minimal serious nephrotoxicity. However, it's crucial to mention that both studies utilized the Lutetium-177 PSMA-617 compound, a Novartis property, and only reported patient outcomes for approximately 20 months. While Lutetium-177 PSMA-617 and Lutetium-177 PSMA-I&T both fall under this umbrella, there are inherent differences between the two molecules that influence their renal safety profile.

# 3.2.2. Key Differences Between Lutetium-177 PSMA-I&T and Lutetium-177 PSMA-617

The distinct pharmacodynamic attributes of the 617 and I&T molecules are well-documented in both preclinical and clinical research.

Molecular Structure and Chelation: The Lutetium-177 PSMA-I&T molecule incorporates the DOTAGA chelator, which carries a negative charge (-1). In contrast, the Lutetium-177 PSMA-617 molecule uses the DOTA chelator, which is neutrally charged (0). This distinction in charge might influence their interaction and retention within renal tissues.

Kidney Uptake and Dosimetry: Preliminary preclinical investigations indicated a potential for up to 30 times higher radiation doses to the kidneys with 177Lu PSMA-I&T compared to 177Lu PSMA-617 (Ruigrok et al. 2021; Banerjee et al. 2019). Though subsequent clinical studies using 3D SPECT/CT dosimetry revised this figure to about 1.5 times (Uijen et al. 2023), it still emphasizes the increased renal radiation exposure with Lutetium-177 PSMA-I&T. Investigating enhanced or alternative protective interventions could strike a balance—amplifying therapeutic gains while curbing potential renal toxicity risks, especially for patients with a longer life expectancy.

Renal Retention: The differential chelation and molecular properties between the two compounds could result in varying durations of renal retention. A prolonged residence of radioligands within the kidneys invariably augments the risk of radiation-induced renal injury.

# 3.2.3. Implications for Renal Protection

Given the highlighted differences, especially the potential for increased renal exposure with Lutetium-177 PSMA-I&T, there is a pressing need to incorporate robust renal protective measures for patients undergoing this therapy.

Enhanced Radiation Exposure: Even a marginally increased radiation exposure, as suggested between the two molecules, could have significant implications over multiple treatment cycles. Cumulative radiation doses might elevate the risk of chronic renal damage.

Mechanistic Insights: Understanding the mechanistic differences between Lutetium-177 PSMA-I&T and Lutetium-177 PSMA-617 could pave the way for tailored renal protection strategies. For instance, if the negative charge of DOTAGA in Lutetium-177 PSMA-I&T is identified as a significant contributor to increased renal retention, interventions targeting this mechanism might be explored.

Renal Dosimetry: Regular renal dosimetry using advanced imaging techniques like 3D SPECT/CT can aid in quantifying renal radiation exposure. This not only offers insights into the immediate therapeutic safety but can guide modifications in subsequent treatment cycles.

In conclusion, while both Lutetium-177 PSMA-I&T and Lutetium-177 PSMA-617 have demonstrated therapeutic promise, the nuanced differences between them, especially concerning renal safety, mandate a keen emphasis on renal protection for patients undergoing the former therapy. The journey towards harnessing the full potential of Lutetium-177 PSMA-I&T in prostate cancer treatment would invariably involve meticulous strategies to safeguard kidney function.

## 3.2 Name and description of the intervention or product(s) used in this trial

SYNTHAMIN 17 (Amino acids 10%) without electrolytes solution infusion @Baxter

Administered as IV infusion at 250 mL/h over a four-hour period, commencing 30 – 60 minutes prior to Lutetium-177 PSMA-I&T infusion.

# 4. AIMS / OBJECTIVES / HYPOTHESES

## 4.1 Aims

In light of the above, this study seeks to investigate the potential of amino-acid infusion as a renal protective measure during Lutetium-177 PSMA-I&T treatment for metastatic prostate cancer. By focusing on renal dosimetry using 3D SPECT/CT imaging, we aim to furnish a clearer understanding of the intervention's effects, thereby guiding future therapeutic strategies.

## 4.2 Primary Objective

• To investigate the potential of amino-acid infusion as a means to provide renal protection by reducing renal radiation dose from Lutetium-177 PSMA-I&T treatment for metastatic prostate cancer.

## 4.3 Hypotheses

The hypothesis of the trial is:

The use of amino acid infusion as a renal protective measure before the 4th, 5th or 6th cycle of Lutetium-177 PSMA-I&T therapy will reduce renal radiation dose, as measured by renal dosimetry using 3D SPECT/CT imaging, when compared to the renal dosimetry from the preceding cycle without amino acid infusion in patients with metastatic castrate-resistant prostate cancer. This protective measure aims to optimize therapeutic benefits while minimizing potential nephrotoxic side effects, especially given the distinct pharmacodynamics of the Lutetium-177 PSMA-I&T compared to the Lutetium-177 PSMA-617 compound.

# 5. TRIAL DESIGN

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# 5.1 Primary Endpoint

• The primary endpoint is the comparative analysis of renal dosimetry, as quantified by 3D SPECT/CT imaging, following a cycle of Lutetium-177 PSMA-I&T therapy with a standard amino acid infusion (intervention cycle) versus the renal dosimetry obtained from the immediate preceding cycle without amino acid infusion (control cycle) in patients with metastatic castration-resistant prostate cancer (mCRPC).

# 5.2 Secondary Endpoints

• Assessment of nephrotoxicity rates, including changes in serum creatinine and estimated glomerular filtration rate (eGFR), in patients following cycles of Lutetium-177 PSMA-I&T therapy with and without amino acid infusion.

• Comprehensive documentation of any adverse events or reactions related to Lutetium-177 PSMA-I&T therapy and the accompanying amino acid infusion, with a particular focus on elucidating any potential renal protective effects and delineating the safety profile of the intervention.

## 5.3 Study design

This is a pilot, two-arms, prospective trial. Ten men with metastatic castrate-resistant prostate cancer will be recruited for the study. The primary objective is to assess the renal dosimetry effects of Lutetium-177 PSMA-I&T therapy with amino acid infusion as a renal protective measure. All patients will be informed about the procedures, the intention to use their data for research purposes, and potential risks. They will provide written consent before participation. The study will secure approval from the local ethics committee.

Lutetium PSMA-I&T therapy is a form of internal radioligand therapy. It is typically administered intravenously every six weeks. Upon patients enrollment, baseline renal function tests (e.g., serum creatinine, creatinine clearance) and 3D SPECT/CT imaging for renal dosimetry will be conducted following their 3rd, 4th or 5th cycle of Lutetium-177 PSMA-I&T therapy without amino acid infusion.

Subsequently, these patients will receive their 4th, 5th or 6th cycle of Lutetium-177 PSMA-I&T therapy, but this time with an amino acid infusion as a renal protective measure. Post-therapy renal function tests and 3D SPECT/CT imaging will be repeated.

All patients will be closely monitored for signs of nephrotoxicity and any other adverse events associated with the therapy. Any documented cases of reduced renal function will be noted.

**Renal dosimetry** will be undertaken by a qualified medical physicist at three specific time points: 4 ±1 hour, 24 ±2 hours, and 120 ±24 hours post-treatment using planar imaging, and at the 24-hour mark using 3D SPECT/CT. Analysis and interpretation of the results will be performed with the aid of specialized MIM software.

Participants may be requested to measure total urinary volume and to take a ~20 mL sample for approximately 120 hours post-therapy. The activity in the excreted 177Lu in the samples will be measured in a gamma counter. Data collected will be used to calculate the whole-body retained activity which will be compared and used as a cross-check to the whole body retained activity as determined by the SPECT/CT imaging. The data may also provide extra useful information of renal radiation dose in the 24-hour period immediately following therapy as this is when the greatest activity of Luetium-177 passes through the kidneys.

The entire duration of the trial for each patient will span the time from baseline evaluation until the post-final cycle assessment. The sequence of events in the trial is outlined as follows:

1. Patients received at least two cycles of Lutetium-177 PSMA-I&T without amino acid infusion.
2. Baseline renal function tests and 3D SPECT/CT renal dosimetry post cycle 3, 4 or 5 of Lutetium-177 PSMA-I&T.
3. Patients receive 4th, 5th or 6th cycle of Lutetium-177 PSMA-I&T therapy with amino acid infusion.
4. Post 4th, 5th or 6th cycle renal function tests and 3D SPECT/CT renal dosimetry.
5. Continuous monitoring for adverse events and nephrotoxicity throughout the trial duration.

SCHEMATICS OF THE TRIAL

Castrate resistant Metastatic prostate cancer patients eligible and receiving Lutetium-177 PSMA-I&T

Renal 3D-SPECT Dosimetry

End of study assessment

Received cycle 4, 5 or 6 of Lutetium-177 PSMA-I&T

Renal 3D-SPECT Dosimetry

Eligibility confirmed, consent

Received cycle 3, 4 or 5 of Lutetium-177 PSMA-I&T

## 5.4 Blinding

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## This study will proceed as an unblinded trial. A single qualified medical physicist, Phillip Calais will perform the renal dosimetry, utilizing imaging data from multiple time points and processing results using dedicated MIM software. This physicist will have access to complete patient clinical details necessary for thorough dosimetry analysis.

## Correspondingly, one nuclear medicine physician, Dr Zeyad Al-Ogaili, will review and interpret the imaging results, with an unblinded perspective to the dosimetric data and any alternative imaging modality results. This physician will be provided with the same comprehensive clinical information as noted on the request form by the referring clinician. The unblinded format of the study is deliberately chosen to foster an open evaluation of the dosimetric information alongside the clinical outcomes, ensuring an integrated and accurate analysis of the therapeutic impact.

## 5.5 Maintenance of blinding records

Records will not be blinded as the PSMA-SPECT/CT results will be available on the hospital system, labelled as a research study *not for clinical use.*

## 5.6 Investigational products dosage, regimen, packaging and dispensing

For this trial, patients will receive a single administration of 7.5 GBq ± 10% Lutetium-177 PSMA-I&T intravenously. Infusion time of the Lutetium-177 PSMA-I&T will be 5±1 minute, followed by a 20 mL saline flush over 1 – 2 minutes. Starting 30 – 60 minutes prior to the infusion of Lutetium-177 PSMA-I&T, an infusion of renal-protective amino acids solution, 1000 mL of SYNTHAMIN 17 (Amino acids 10%) without electrolytes solution infusion @Baxter, will be administered intravenously at a rate of 250 mL/h and continued as per the established renal protection protocol that is used for neuroendocrine tumour Lutetium-177 therapy. Serial planar and SPECT/CT renal imaging at 4±1 hour, 24±2 hours, and 120±24 hours post-injection will be conducted, with the inclusion of a 3D SPECT/CT at the 24-hour mark for detailed dosimetry. All radiopharmaceuticals and the amino acid solution will be prepared, packaged, and dispensed in accordance with stringent nuclear medicine regulations to ensure patient safety and treatment integrity.

## 5.7 Study Drug Accountability

An accurate and current account of the dispensing and disposal of Lutetium-177 PSMA-I&T and the associated amino acid solution for each subject will be meticulously documented on the Investigational Drug Accountability Record Form.

## 5.8 Expected duration of the trial and participant participation

Ten men diagnosed with prostate carcinoma referred to our center for PSMA imaging will participate in the study. Each patient will undergo a treatment cycle with Lutetium-177 PSMA-I&T, accompanied by renal protective amino acid infusion, with subsequent renal dosimetry imaging at specified intervals. The participation of each patient in the trial will extend from the commencement of treatment through to the follow-up period, which is anticipated to be around 12 to 14 weeks after treatment, in line with the trial's outlined procedures (as described in section 5.3).

## 5.9 Study termination

The trial will be terminated at completion of the study objectives or earlier if deemed necessary by the investigator.

## 5.10 Data Collection Instruments

The study will conclude upon achievement of the stipulated endpoints or may be terminated earlier at the discretion of the investigators, should circumstances warrant. This could include unforeseen safety concerns or administrative reasons.

# 6. SOURCE AND SELECTION OF PARTICIPANTS

## 6.1 Source of participants and planned recruitment period

Potential participants will be identified from both the Fiona Stanley Hospital Nuclear Medicine and Medical Oncology outpatient department. We aim to recruit 10 patients over a 6-month period. Eligible patients are those with metastatic prostate cancer scheduled for targeted radionuclide therapy with 177Lu-PSMA-I&T as part of their treatment regimen. These patients would have already received two or more cycles of Lutetium-177 PSMA-I&T treatment and have been deemed suitable for ongoing treatment with 177Lu PSMA-I&T by their treating Nuclear Physicians and Medical Oncologists. After the initial nuclear medicine consultation where 177Lu-PSMA therapy is deemed appropriate, suitable patients will be presented with the study information and consent forms by the medical physicist (Phillip Calais). Patients will be given the choice to take the study information with them back home and return the consent form back if they are interested in participating in this trial. Enrolled patients will undergo the necessary imaging procedures as per study protocol upon returning their signed consent forms.

## 6.2 Participant inclusion criteria

1. Male patients aged >18 yrs
2. History of histologically confirmed prostate cancer
3. Metastatic patients who are considered for ongoing treatment with 177Lu–PSMA-617
4. Ability to understand and the willingness to sign a written informed consent

## 6.3 Participant exclusion criteria

1. Life expectancy less than 6 months
2. Unable to give informed consent
3. Unable to comply with required scanning schedule.
4. Other malignant tumors that are likely to express PSMA, such as salivary gland, renal or hepatocellular carcinoma.

## 6.4 Discontinuation/Withdrawal of Subjects

Each Subject has the right to withdraw from the study at any time without giving a reason and without prejudice. In addition, a Subject may be discontinued from the study at any time for any of the following reasons:

1. Ineligibility
2. Significant protocol deviation
3. Significant non-compliance with study requirements
4. Withdrawal of consent
5. Loss to follow up
6. Investigator discretion

Withdrawal from the study prior to its completion will result in exclusion of the data for that Subject from analysis. Subjects who withdraw from the study may be replaced if their data are not complete and suitable for analysis. Subjects who voluntarily withdraw, or are withdrawn, from the study may be offered therapy on an off-trial basis.

# 7. TREATMENT OF PARTICIPANTS

## 7.1 Description and justification for the IMP

This protocol pertains to a controlled study aimed at investigating the renal protective effects of amino acid infusion during cycles 4, 5, or 6 of Lutetium-177 PSMA-I&T therapy for metastatic prostate cancer. This study aims to compare renal dosimetry data using 3D SPECT/CT imaging from treatment cycles with and without amino acid infusion to determine the efficacy of the intervention in renal protection. The IMP under investigation is the amino acid infusion, which is hypothesized to reduce radiation-induced renal damage by minimizing the reabsorption of radiopeptides in the proximal tubular cells, thus protecting renal function. This protective strategy has been indicated in prior research and considered a routine standard of care measure in patients with metastatic neuroendocrine tumours treated with Lutetium-177 Dotatate, but has not yet been systematically evaluated in the context of 177Lu-PSMA-I&T therapy in Australian or international clinical research.

## 7.2 Allowed Medications and Treatments

Participants will continue to receive their standard and approved treatments for metastatic prostate cancer alongside the study protocol. This includes Lutetium-177 PSMA-I&T therapy cycles as per their treatment plan. The amino acid infusion will be introduced prior to the 4th, 5th, or 6th cycle as part of the investigational study.

## 7.3 Procedures for monitoring participant compliance.

Participant compliance with the amino acid infusion protocol will be strictly monitored. The administration of the infusion will be carried out in a controlled clinical environment in the Nuclear Medicine department at Fiona Stanley hospital, ensuring that all participants receive the correct dosage at the appropriate times. Compliance with Lutetium-177 PSMA-I&T therapy will follow standard clinical procedures.

# 8. ASSESSMENT OF EFFICACY

## 8.1 Efficacy parameters

The primary efficacy parameter is the difference in renal dosimetry as measured by 3D SPECT/CT imaging between cycles with amino acid infusion and previous cycles without it. Secondary efficacy parameters include the incidence of renal toxicity, changes in renal function markers, and the occurrence of any side effects following the amino acids infusion.

Quantitative and Qualitative Image Analysis: Images will be first analysed by a qualified medical physicist using a dedicated MIM software, and then interpreted by nuclear physicians, following the quantitative and qualitative interpretation protocol adapted for this study. The interpretation will focus on the assessment of renal dosimetry from 3D SPECT/CT imaging, comparing the images from cycles with amino acid infusion to those from cycles without it. The quantitative results will include a renal absorbed radiation dose as measured by 3D SPECT/CT and renal radiation dose in mSV per GBq of injected activity.

## 8.2 Methods and timing for assessing, recording, and analyzing efficacy parameters.

Renal dosimetry will be assessed using 3D SPECT/CT imaging performed prior to and following the administration of the amino acid infusion. Clinical assessments, including monitoring for signs of allergic reaction or renal toxicity and basic vital signs, will be conducted at baseline, prior to each therapy cycle, and at follow-up visits in accordance with the standard of care. Additional assessments, including laboratory tests for renal function markers and evaluations for TMA, will be carried out at specified intervals to correlate imaging findings with clinical and laboratory parameters.

# 9. SAFETY ASSESSMENT

## 9.1 Potential risks and benefits for study participants

The primary risks to patients involve the administration of amino acids and the subsequent radiation exposure from Lutetium-177 PSMA-I&T therapy, compounded by radiation exposure from 3D SPECT/CT imaging. Prior to the commencement of the study, the safety of the radiation exposure will be validated by Medical Physicists at the institution.

Patients with a history of hypersensitivity to any amino acids or components within the infusion solution will be excluded from the study. Similarly, individuals who are unable to remain still for the duration required for SPECT/CT imaging due to restlessness or claustrophobia will also be excluded. Consideration may be given to the administration of a mild sedative before the scan to alleviate discomfort or anxiety.

**Risks Associated with Radiation Exposure:**

While the dosimetry parameters for 177Lu-PSMA-I&T therapy are well-established, our study includes an additional safety layer through post-therapeutic dosimetry using 3D SPECT/CT imaging to ensure individualized patient safety. The radiation dose associated with Lu-PSMA-I&T is within accepted therapeutic ranges for the patient cohort in question and is considered justified given the substantial expected benefit related to the mitigation of serious disease.

**Radiation Exposure from 3D SPECT/CT Imaging:**

Post-Lutetium-177 therapy SPECT/CT is routinely requested by nuclear physicians as part of standard of care imaging. The SPECT component of the SPECT/CT imaging does not result in any additional radiation dose to the subject. The CT component contributes about 1 – 2 % of the total whole body effective dose in addition to the radiation dose from the Lutetium-177 PSMA therapy itself. The effective dose from 3D SPECT/CT imaging will be monitored and recorded. The total effective dose from the imaging and 177Lu-PSMA-I&T therapy combined must be accounted for, ensuring that the cumulative radiation exposure does not exceed safety thresholds as established by international guidelines.

The potential benefits to patients include close monitoring of renal function, access to standard-of-care imaging for prostate cancer, and the potential mitigative effects of the amino acid infusion on renal toxicity, which is of particular interest in this study.

## 9.2 Safety monitoring

Safety monitoring and adverse event reporting will be carried out in accordance with guidelines provided by the National Health and Medical Research Council (NHMRC).

**Adverse Events (AEs):**

AEs related to the amino acid infusion, 177Lu-PSMA-I&T therapy must be diligently recorded. Any hypersensitivity reactions will be managed in line with the department's emergency response protocols, and the relevant treatment cycle or imaging may need to be modified or discontinued accordingly. Investigators will engage in regular dialogue with participants to identify and document any AEs, noting their onset, duration, severity, management, and resolution, as well as their potential relation to the study interventions.

All AEs will be thoroughly documented and assessed for their relation to the amino acid infusion, radioligand therapy, or the imaging procedures. In compliance with the local Human Research Ethics Committee (HREC) policies, the principal investigator will report all AEs—expected or unexpected—to the HREC in a timely and transparent manner.

# 10. DATA MANAGEMENT, STATISTICAL ANALYSIS AND RECORD KEEPING

## 10.1 Statistical Methods and Considerations

This study will employ paired comparative analysis methods. A paired t-test (or non-parametric equivalent, such as the Wilcoxon signed-rank test for non-normally distributed variables) will be used to analyze the difference in renal dosimetry as measured by 3D SPECT/CT imaging between intervention (with amino acid infusion) and control (previous cycle without amino acid infusion) measurements. The primary endpoint will be the difference in renal dosimetry between these paired cycles. Secondary endpoints will include the incidence of renal toxicity and occurrence of TMA, which will be analyzed using appropriate statistical tests based on the data distribution.

## 10.2 Sample size calculation

For this pilot study, a total of 10 patients will be enrolled. The sample size is based on the expectation that it will provide enough data to assess the primary endpoint of renal dosimetry using 3D SPECT imaging effectively. As renal dosimetry is a quantitative measure and the comparison is within-subject between cycles, the number is deemed sufficient to detect a clinically meaningful difference in radiation dose to the kidneys, though statistical power has not been formally calculated.

## 10.3 Participants to be included in the analyses

All patients who receive the amino acid infusion prior to their 4th, 5th, or 6th cycle of 177Lu-PSMA-I&T therapy and have complete renal dosimetry data from the 3D SPECT imaging for both the intervention and the corresponding control cycle will be included in the analysis.

## 10.4 Data Collection and Retention

Patient data will be collated and stored in a secure, password-protected electronic excel sheet database at WA health server in a de-identified form. Data retention will be in accordance with institutional guidelines, maintained for a minimum of 15 years following publication. The data, stripped of identifying information, will be made available for future research and scrutiny by other researchers within the scientific community.

Missing data will be addressed by analyzing the patterns of missingness and its potential impact on the study's results. In the case of data anomalies, the data in question will be assessed by the principal investigator and re-evaluated against the source documents for verification. Spurious data, if confirmed, will either be corrected or excluded from the analysis based on a predefined protocol and in consultation with the study's statistician.

For the purpose of publication, only de-identified data will be used, ensuring participant confidentiality. All study-related documents will be stored securely and will only be accessible to authorized personnel.

# 11. MONITORING / AUDIT

## 11.1Audit Trials by Regulatory Bodies

The trial investigators will facilitate trial-related monitoring, audits, and regulatory inspections, allowing access to source data/documents as required. This includes compliance with audits conducted by the Human Research Ethics Committees, Institutional Governance Review Bodies, and other relevant regulatory entities. Such oversight is vital to uphold ethical standards and regulatory compliance.

**11.2 Intra and Interdepartmental Monitoring**

In lieu of external monitoring, this trial will implement intra and interdepartmental monitoring processes involving the Medical Oncology and Nuclear Medicine departments at Fiona Stanley Hospital. This internal monitoring will be conducted to ensure the reliability and accuracy of the trial data. After two months from the commencement of the study, an internal audit will be undertaken by these departments to assess data integrity and protocol compliance. This approach is designed to promptly identify and address any significant issues without the need for external monitoring agencies.

# 12. QUALITY CONTROL AND QUALITY ASSURANCE

## 12.1 GCP Compliance, QA

Conducting the trial in strict accordance with the protocol, Good Clinical Practice, and all regulatory obligations is essential to safeguard the safety, rights, and well-being of the participants, ensuring that the trial data are robust and credible.

## 12.2 Quality Control

Renal dosimetry data acquired from PSMA-SPECT/CT imaging will be independently reviewed by an experienced medical physicist, Mr Phillip Calais, and then cross checked by an experienced nuclear medicine specialist, Dr. Zeyad Al-Ogaili. This structure is designed to mitigate inter-reporter variability and validate the consistency and accuracy of the dosimetry data.

# 13. ETHICS

Patients will be invited to participate by their treating team, which includes medical oncologists, and nuclear physicians. It will be emphasized during recruitment that their choice to participate is voluntary and will not influence their current or future care. Medical physicist, Mr Phillip Calais, who is not involved in patient clinical consultations will present the patients with the participants information sheet and consent form. Informed consent will be sought after thoroughly communicating the potential for additional radiation exposure which is normally considered part of the patients standard clinical care and any other study-related risks, alongside the detailed explanation in the participant information and consent documents.

# 14. BUDGET, FINANCING, INDEMNITY AND INSURANCE

Budgetary considerations, financing, indemnity, and insurance pertaining to the trial will be outlined in a detailed and separate agreement to ensure transparency and proper handling of trial-related expenses.

# 15. PUBLICATION

In line with the Declaration of Helsinki and local regulatory requirements, the trial will be registered on the Australian New Zealand Clinical Trials Registry (ANZCTR) before patient recruitment begins. This registration will foster transparency and allow public access to trial information.

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