

**A prospective randomised multi-centre study of the impact of Ga-68 PSMA-PET/CT imaging for staging high risk prostate cancer prior to curative-intent surgery or radiotherapy (proPSMA study): clinical trial protocol**

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## Abstract

### Introduction

Accurate staging of patients with prostate cancer is important for therapeutic decision making. Relapse following surgery or radiotherapy of curative intent is not uncommon and, in part, represents a failure of staging with current diagnostic imaging techniques to detect disease spread. Prostate-specific-membrane-antigen (PSMA) positron emission tomography / computed tomography (PET/CT) is a new whole body scanning technique that enables visualisation of prostate cancer with high contrast. The hypotheses of this study are that (a) PSMA-PET/CT has improved diagnostic performance compared to conventional imaging, (b) PSMA-PET/CT should be used as a first-line diagnostic test for staging, (c) the improved diagnostic performance of PSMA-PET/CT will result in significant management impact and (d) there are economic benefits if PSMA-PET/CT is incorporated into the management algorithm.

**Trial methodology.** This is a prospective, multi-centre study in which patients with untreated high-risk prostate cancer will be randomised to Gallium-68-PSMA11-PET/CT or conventional imaging, consisting of computer tomography of the abdomen/pelvis and bone scintigraphy with SPECT/CT. Inclusion criteria are newly diagnosed prostate cancer patients with select high-risk prostate cancer defined as International Society of Urological Pathology (ISUP) grade group  $\geq 3$  (primary Gleason grade 4, or any Gleason grade 5), PSA  $\geq 20$ ng/mL or clinical stage  $\geq T3$ . Patients with negative, equivocal or oligometastatic disease on first line-imaging will cross-over to receive the other imaging arm. The primary objective is to compare the accuracy of PSMA-PET/CT to conventional imaging for detecting nodal or distant metastatic disease. Histopathologic, imaging and clinical follow-up at six

months will define the primary endpoint according to a pre-defined scoring system. Secondary objectives include comparing management impact, the number of equivocal studies, the incremental value of second-line imaging in patients who cross-over, the cost of each imaging strategy, radiation exposure, inter-observer agreement and safety of PSMA-PET/CT. Longer term follow-up will also assess the prognostic value of a negative PSMA-PET/CT.

**Outcome & Significance.** This trial will provide data to establish whether PSMA-PET/CT should replace conventional imaging in the primary staging of select high-risk localised prostate cancer patients, or whether it should be used to provide incremental diagnostic information in selected cases.

**Trial registration:** The proPSMA study is registered in the Australian and New Zealand Clinical Trial Registry (ANZCTR Trial No. 12617000005358)

**Trial Funding:** This clinical trial is funded by a grant from the The Movember Foundation through Prostate Cancer Foundation of Australia's Research Program

## **Introduction**

Prostate cancer (CaP) is the most commonly diagnosed cancer in Australia, representing a third of all cancers in men, and accounting for approximately 20,000 new cases diagnosed per year. CaP was the second leading cause of cancer deaths in Australian men in 2011, and the fourth leading cause of all deaths[1]. Defining the extent of CaP with accurate imaging is of utmost importance for therapeutic decision-making. Current diagnostic tools are suboptimal for the staging of patients with metastatic disease. Structural imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) have limited sensitivity and specificity to detect small-volume metastatic disease, while a whole-body bone scan (WBBS) can miss early bone marrow metastases. Despite these limitations, CT and WBBS are widely accepted as standard first-line diagnostic imaging workup for staging patients with localised CaP[2]. More recently, positron emission tomography (PET) imaging with  $^{11}\text{C}$ -choline,  $^{18}\text{F}$ -fluorocholine (FCH) or  $^{18}\text{F}$ -fluoride bone PET/CT have demonstrated superior accuracy[3-6] but these techniques remain limited by their inherent non-specificity[7].

Prostate-specific membrane antigen (PSMA) is a cell surface transmembrane glycoprotein expressed by the majority of CaP cells and has been established as a target for imaging and also treatment of CaP. PSMA imaging was initially undertaken using the radiolabelled antibody capromab-pendetide (ProstaScint®). This was approved by the Food and Drug Administration (FDA) but the radiotracer targeted the intracellular epitope of PSMA and combined with low resolution of SPECT imaging the technique failed to provide sufficient additional value compared to conventional imaging [8, 9]. Newer generation small molecular ligands that target PSMA have renewed interest in using PSMA targeted imaging of prostate cancer. The most widely adopted to date is <sup>68</sup>Ga-PSMA-11, also known as <sup>68</sup>Ga-HBED-CC or <sup>68</sup>Ga-HBED-PSMA, developed by the Division of Radiopharmaceutical Chemistry at the DKFZ Heidelberg [10, 11]. This is a radioconjugate composed of a small molecule PSMA targeting ligand conjugated to the radioisotope gallium-68. Gallium-68 (<sup>68</sup>Ga) is a positron-emitting isotope that is produced using a small generator device with capacity to have wide clinical availability at relatively low cost. <sup>11</sup>Ga-PSMA-11 binds with affinity to the extracellular domain of PSMA, with rapid uptake and plasma clearance. PET imaging technology also provides superior resolution compared to conventional nuclear medicine imaging [12].

The data in the literature to date are primarily focussed on <sup>68</sup>Ga-PSMA-PET/CT (PSMA-PET/CT) for localisation of CaP in patients with biochemical recurrence (BCR) [13-21], although data of primary staging are also emerging [22-24] and both have been the subject of a recent meta-analysis [25]. The utility of PSMA PET/CT to identify lymph node involvement in the primary staging setting is also encouraging, even for sub-centimetre lymph nodes [26, 27]. Furthermore, the use of radio-guided surgery for lymph nodes identified by PSMA PET/CT is also under investigation [28, 29]. A particular area of note is that of disease localisation in patients with BCR following radical prostatectomy (RP), who are being considered for salvage radiotherapy, a group of patients in whom conventional imaging has particularly poor sensitivity. Van Leeuwen et al reported their experience of PSMA PET/CT in 70 such patients (median PSA 0.2 ng/mL; no patients with PSA > 1.0 ng/mL), and observed positive scans in over 50% of patients [30]. Of particular note, they reported that 28.6% of patients had positive scans outside the prostate bed with significant management impact.

Whilst these data clearly demonstrate the utility of PSMA-PET/CT [31], they are mostly retrospective single centre studies, and do not directly compare PSMA-PET/CT to conventional imaging or address important issues such as the impact of this new imaging test on patient management, patient outcomes or resource use. In particular, the use of PSMA-PET/CT for primary staging is of critical

importance as more accurate staging will potentially have high patient impact by selecting more appropriate management for an individual patient through better selection and planning of definitive treatment strategies. The results of this trial may also inform use of other PSMA targeted PET radiotracers which have similar biodistribution including  $^{68}\text{Ga}$ -PSMA-I&T [32],  $^{18}\text{F}$ -DCFPyL [33, 34],  $^{18}\text{F}$ -PSMA-1007 [35] and THP-PSMA[36].

Current recommendations for imaging patients with newly diagnosed prostate cancer vary in different international guidelines[2]. Generally, imaging is only recommended in high-risk patients as the rate of false positive results may outnumber true positive results if the likelihood of metastatic disease is very low. If the yield of imaging is low, there are also significant health economic implications. This study will incorporate the new five-tier International Society for Urological Pathology (ISUP) grade group system which has been shown to provide superior prognostic stratification compared to the traditional Gleason score[37] [38, 39].

#### **proPSMA - Clinical trial overview:**

This is a multi-centre, prospective, randomised study that compares PSMA-PET/CT to conventional imaging for staging of patients with high-risk localised CaP. The goal of this trial is to provide robust high-level data that will establish whether PSMA-PET/CT should replace conventional imaging in the assessment of such patients or whether it should be used to provide incremental diagnostic information in selected cases. The hypotheses of this study are that (a) PSMA-PET/CT has improved diagnostic accuracy compared to conventional imaging, (b) PSMA-PET/CT should be used as a first-line diagnostic test for staging high-risk localised prostate cancer, (c) the improved diagnostic accuracy of PSMA-PET/CT will result in significant management impact and (d) there are economic benefits if PSMA-PET/CT is incorporated into the management algorithm.

The primary objective of this study is to compare diagnostic accuracy of PSMA-PET/CT to that of conventional imaging (CI) for detecting nodal or distant metastatic disease. The secondary objectives are:

- a. To compare the first-line management impact of PSMA-PET/CT to that of CI
- b. To compare the number of equivocal study results using PSMA-PET/CT to the number using CI
- c. To assess incremental accuracy of PSMA-PET/CT or CI as a second-line imaging modality by their ability to detect additional metastases in a subset of patients who cross-over and have both tests
- d. To assess the incremental management impact of PSMA-PET/CT or CI as a second-line imaging

- modality in the subset of patients who cross-over and have both tests
- e. To evaluate the prognostic value of PSMA-PET/CT with regards to disease-free status (3 years from accrual of the last patient)
  - f. To compare the cost of each imaging staging strategy
  - g. To compare patient radiation exposure between imaging strategies
  - h. To assess inter-reporter agreement of PSMA-PET/CT by comparing blinded central imaging laboratory interpretations to on-site clinical care interpretations
  - i. To report the acute adverse events for PSMA-PET/CT

A tertiary objective is to investigate the diagnostic accuracy of whole body MRI compared to PSMA PET/CT in a non-randomised exploratory endpoint.

### **Patients and Methods**

We aim to evaluate the role of PSMA-PET/CT in a patient population with a significant risk of metastatic disease but a relatively low pre-test likelihood of positive conventional imaging results. This will be defined by ISUP grade group  $\geq 3$  (primary Gleason grade 4, or any Gleason grade 5), PSA  $\geq 20$ ng/mL or clinical stage  $\geq T3$ . A total of 200 patients will be recruited in up to 10 centres. Follow-up for the study will stop three years after randomisation of the last patient.

The study is approved by the Peter MacCallum Cancer Centre Human Research Ethics Committee, sponsored by the Peter MacCallum Cancer Centre and prospectively registered in the Australian and New Zealand Clinical Trial Registry (ANZCTR Trial No. 12617000005358). This clinical trial is funded by a grant from the The Movember Foundation through Prostate Cancer Foundation of Australia's Research Program. This study will be conducted according to local regulations and laws, the ethical principles that have their origin in the Declaration of Helsinki and the principles of Good Clinical Practice.

The inclusion and exclusion criteria are listed in Table 1. The trial schema is outlined in Figure 1, and an abbreviated Schedule of Events in Table 2.

**First-line Diagnostic Imaging (DI).** The participant will undergo the first-line DI within 21 days following randomisation:

- Arm A (Experimental): The experimental arm will undergo PET/CT following injection of  $^{68}\text{Ga}$ -

PSMA-11, a human (PSMA) targeting ligand, Glu-urea-Lys(Ahx) (Glu-NH-CO-NH-Lys(Ahx)), conjugated, via the chelator N,N'-bis [2-hydroxy-5-(carboxyethyl)benzyl] ethylenediamine-N,N'-diacetic acid (HBED-CC), to the radioisotope gallium-68.

- Arm B (Control): Contrast enhanced CT (abdomen and pelvis) and whole body bone scan with SPECT/CT encompassing thorax, abdomen and pelvis.

**Second-line DI.** Patients will cross-over to the other arm (second-line DI) unless greater or equal to 3 sites of unequivocal *distant* metastases were demonstrated. Following second-line imaging, at the discretion of the treating doctor as per routine clinical care, additional confirmatory studies may be performed to further evaluate findings from first-line or second-line DI. These may include biopsy, x-ray, CT, MRI, Choline PET/CT, FDG PET/CT and other investigations. For patients with distant metastases, where feasible, biopsy confirmation of disease is strongly encouraged.

**Six month follow-up imaging.** Repeat imaging as per randomised arm with crossover will be performed at six months ( $\pm$  30 days) after randomisation in patients with (1) initial staging of N1 or M1 or (2) biochemical or clinical suspicion of residual / recurrent disease for patients with initial stage N0 M0. Temporal changes identified on imaging will assist in defining the primary endpoint.

**Six, 18, 30 and up to 42 and 54 months follow-up.** For patients who underwent PSMA-PET/CT for first- or second-line imaging and the results of this study did not demonstrate *distant* metastatic disease (*i.e.*, N0 M0, N1 M0), the following data will be collected:

- PSA
- new pelvic nodal or distant metastases defined by histopathology or imaging
- commencement of salvage therapy
- patient death

**PSMA PET/CT Quality Control (QC).** The production, QC and release of  $^{68}\text{Ga}$ -PSMA must meet minimum study specifications. The production method may be automated or manual and must pass full quality control with a minimum of three consecutive validation runs before enrolling patients (see Table 3). The minimum quality control requirements for each  $^{68}\text{Ga}$ -PSMA-11 synthesis prior to release for patient administration will consist of: (1) Appearance (visual inspection), (2) Label inspection, (3) pH, (4) Radiochemical identity (half-life), (5) Radiochemical purity (HPLC and TLC) and (6) Measurement of total radioactivity at reference time (by dose calibrator).

**PET/CT Quality Assurance.** Prior to beginning enrolment, all PET imaging sites will be certified by an

independent review of equipment provided by Australasian Radiopharmaceutical Trials Network (ARTnet). This will be carried out using the ARTnet phantom (NEMA NU2 IEC Body Phantom) filled with  $^{68}\text{Ga}$  and performing PET acquisition with clinical protocols. The DICOM data will be analysed by the ARTnet core laboratory to ensure minimum specifications are met. By analysing the average SUV against the injected activity, the process will also provide validation of the dose calibrator for  $^{68}\text{Ga}$ .

During the study, further quality assurance will be performed by a central core imaging laboratory (CIL). The PSMA PET/CT images in DICOM format for first-line and second-line imaging will be sent to the CIL in an anonymised format. Two experienced readers will review the study at the CIL with any disagreement resolved by consensus. The results from the CIL will be sent back to the local reader within three business days of the scan acquisition. Any discrepancy of the scan findings between the local reader and central review will be resolved by discussion in order to reach a consensus. If a consensus cannot be reached, this will be recorded, and the patient will be managed according to results of the local reader.

**PET/CT Acquisition.** PSMA PET/CT will be performed following administration of 1.8 - 2.2 MBq  $^{68}\text{Ga}$ -PSMA-11 per kilogram bodyweight, subject to variation that may be required owing to variable elution efficiencies obtained during the lifetime of the  $^{68}\text{Ge}/^{68}\text{Ga}$  generator. The CT and PET imaging session will begin 45 to 75 minutes after  $^{68}\text{Ga}$ -PSMA-11 administration. The patient should be well hydrated and void immediately before commencement of the scan. The CT will be performed contrast. PET image acquisition should be from pelvis towards head, with a minimum bed step acquisition time of 120 seconds.

**MRI.** A subset of up to 50 patients will participate in this exploratory non-randomised endpoint. These patients will undergo whole body MRI (WB-MRI) using a standardised comprehensive protocol targeted for evaluation of pelvic nodal and distant metastatic disease. MRI will be performed after first and second-line and clinical reports will not be issued. MRI scans for research purposes will be centrally read to ascertain reporter agreement with local reading. A total of 50 WB-MRI will be performed.

**Clinical management:**

Clinical management of patients within this study is at the discretion of individual clinicians working within a multidisciplinary framework. The study protocol does not determine how patients are managed, however, the management impact of each imaging modality is recorded by the treating

clinician after each scan. As these patients are being considered for localised treatment at the time of inclusion, it is expected that the majority of patients within the study will proceed to radical prostatectomy with or without lymph node dissection, or radiotherapy (external beam or high-dose rate brachytherapy). Pathological findings at surgery will be compared with imaging.

**Sample size and power calculation for the primary endpoint.** Sample size was estimated to test the hypothesis that PSMA PET/CT achieves an AUC at least 10% better (absolute) than conventional imaging. Simulation was used to estimate that a sample size of 180 (90 patients per arm) will achieve a power of 0.8 using the following pragmatic assumptions:

- 1) Conventional imaging (CI) has a true underlying AUC of 0.65, consisting of a sensitivity of 0.65 and a specificity of 0.65.
- 2) PSMA-PET/CT has a true underlying AUC of 0.9, consisting of a sensitivity of 0.9 and a specificity of 0.9.
- 3) The proportion of cases (as opposed to controls) is 40%.
- 4) Two-sided type I error of 10%.

To allow for a patient drop-out rate of up to 10%, 200 patients will be accrued to the study.

## **Results**

The study endpoints are summarised in Table 4.

**Accuracy.** The diagnostic accuracy of PSMA-PET/CT and CI for determining the presence or absence of pelvic nodal or distant metastases will be evaluated as the primary endpoint. To define accuracy, diagnostic findings will be compared to the ground truth which will be established using all data available to the six-month follow-up time-point ( $\pm 30$  days). Where feasible, biopsy confirmation of disease is strongly encouraged. Criteria adapted from a prior RCT designed to assess  $^{18}\text{F}$ -PET in prostate cancer (NCT00882609) were modified. Cases will be considered positive by ground truth if

they satisfy at least 1 hard criterion or at least 3 soft criteria amongst the criteria as listed in Table 5. This criteria will be applied for pelvic nodal (N) and distant metastatic (M).

Accuracy will be assessed by the area under the receiver operator characteristic (ROC) curve (the AUC). The ROC for a diagnostic instrument is the curve of sensitivity against  $1 - \text{specificity}$  as the threshold for rating an assessment as 'positive' changes. When the diagnostic instrument produces a dichotomous (T/F) decision, as is the case in this study, the AUC is simply equal to the mean of the sensitivity and specificity. For the purposes of estimating sensitivity, specificity and AUC, lesions rated as equivocal will be considered negative for metastatic disease. The primary analysis will be a patient level analysis with any pelvic nodal (N) or distant metastatic (M) disease considered positive. We will report the difference in AUC between the arms, its 95% CI, and the p-value for the null hypothesis that the AUC for the PSMA arm is 10% greater (absolutely) than the AUC in the conventional imaging arm.

**Management impact.** The treating clinician will record the intended management plan at baseline, following first- and second-line imaging. Management impact will be classified as per Table 6. The proportion of patients requiring a change of management will be compared between arms using an exact test for comparing two independent binary variables (either Fisher's exact test or Barnard's test).

**Equivocal studies.** An equivocal imaging finding may result in further investigations, delays in undertaking definitive intervention and/or increased patient anxiety. For CI, the combined findings of both CT and bone scan are considered. In patients with multiple lesions, the finding is only considered to be an equivocal study if there are no positive sites, e.g. if there are two bone metastases, one classified as positive for metastatic disease and another classified as equivocal, the study is **not** deemed equivocal. The frequency of equivocal findings for *pelvic nodal* and *distant metastases* will be reported separately.

**Incremental accuracy of second-line imaging.** The incremental accuracy of a second-line DI is a measure of its ability to uncover disease that was not diagnosed by a first-line DI modality. All patients who crossed over will be included in the assessment of this endpoint. For each arm considered separately, the proportion of M0 patients who were upstaged to M1 by second-line imaging (with any number of metastases) will be estimated, together with its 95% CI, using an exact method. In addition, the proportion of N0 patients who were upstaged to N1 by second-line imaging

will be estimated using the same method. Amongst M1 patients with oligometastatic disease, the extent of upstaging elicited by second-line imaging will be separately estimated.

**Incremental Management Impact of second-line imaging.** The incremental management impact of a second-line DI is a measure of its ability to result in a management change compared to the post first-line management plan. Amongst patients who crossed over to second-line imaging, the proportion of patients experiencing a change in management as a result of second-line imaging will be estimated together with its 95% CI, estimated using an exact method.

**Prognostic value.** The prognostic value of PSMA PET/CT is the ability of a negative PSMA PET/CT for distant metastatic disease at baseline (1<sup>st</sup> or second-line diagnostic imaging) to predict time until clinical treatment failure. Results will be stratified by staging of baseline PSMA PET/CT into 2 groups: (a) N0 M0, and (b) N1 M0. Each of the following 3 kinds of clinical treatment failure will be considered separately and collectively:

1. Biochemical failure: For patients treated with radiotherapy this will be defined as a rise by 2 ng/mL or more above the nadir PSA greater than six weeks after completion of radiotherapy. For patients treated with surgery, this will be defined as a PSA of >0.2ng/ml and rising on at least two consecutive measures at least three weeks apart after surgical therapy.
2. Regional or distant metastatic disease. This will be defined by biopsy confirming recurrent prostate carcinoma or unequivocal development of abnormalities on imaging.
3. Salvage therapy. This will be defined by receipt of additional prostate cancer therapy following initial prostate surgery or radiotherapy.

Kaplan-Meier curves will be plotted for time until the first of i) biochemical failure or ii) metastatic disease or iii) salvage therapy.

#### **Health Economic Analysis.**

*Service Delivery.* Costs for the delivery of diagnostic imaging (DI) services will consider the equipment, personnel and time resources involved for the development and preparation of scanning services. For PSMA-PET/CT consideration will be given to whether production occurs at the site. For on-site production, the time required by personnel for production and quality assurance of a batch of <sup>68</sup>Ga-PSMA-11 will be required. The consumable and equipment items required including

cartridges, kits, chemicals or reagents, disposable equipment, gallium generator, automated synthesis unit and HPLC system will be recorded.

Cost per activity required for DI preparation will be estimated by applying prices to each resource type used to deliver imaging services, and aggregating over the specific components of DI preparation. This will compare PSMA PET/CT to the conventional imaging (cost of both CT and bone scanning). Resources will be valued for costing purposes using publicly available, such as those published online via the Medicare Benefits Schedule for publicly funded services in Australia.

*Patient Impact.* The two modes of DI administration are anticipated to have different impacts on patient time and activity. For example, PSMA PET is administered over one day and requires approximately one hour between the administration of the radiotracer and initiation of PET. Patients undergoing CT and bone-scans will have two scans (often on separate days), with the bone-scan requiring up-to four hours between administration of radiotracer and initiation of the scan. To assess the impact on patient time and activity associated with complying with DI, the patient waiting time (assessed as the difference between time of the radiotracer administration and the time the scan commenced) and duration of the procedure (difference between the time the patient commences the scan and the time the scan is completed and patient leaves) will be assessed.

**Radiation Exposure to Patients.** Cumulative radiation exposure will be defined as the sum of the effective doses from first-line DI, second-line DI and any confirmatory DI. The radiation dose from CT examinations including CT component of PET/CT and SPECT/CT will be calculated from the dose-length product (DLP) using conversion factors [40], with the results reported in millisieverts. When the DLP is not available, the average radiation dose on the basis of trial data will be used. For nuclear medicine imaging, the effective dose will be calculated from the administered activity of radioisotope injected. For other types of imaging performed for confirmatory imaging, the effective dose will be estimated based on the type of examination performed.

Radiation exposure will be compared between the randomised groups with the use of Student's unpaired t-test if its assumption of normality within each arm is not breached. Otherwise, the Wilcoxon rank-sum test will be used.

**Reporter agreement.** All PSMA-PET/CT performed as first- or second-line imaging will be centrally read. Levels of agreement between the central rater and the local raters for pelvic nodal and distant disease will be estimated using the stratified Cohen's weighted kappa[41], with stratification by site.

**Adverse Events.** Acute adverse events associated with PSMA-PET/CT will be recorded, defined as those experienced by the patient at the time of radiotracer administration and during the two hours following injection. Any toxicity will be graded by NCI Common Terminology Criteria for Adverse Events (CTCAE) version v4.03 and its relationship to the diagnostic imaging will be described as unrelated, unlikely, possible, probable or definite. The worst grade of each toxicity type for each patient within the toxicity assessment window will be tabulated.

## **Discussion**

Although there has been a surge in publications regarding the use of  $^{68}\text{Ga}$ -PSMA-PET/CT in CaP[42], most of these have been retrospective, single centre studies. Furthermore, the majority of publications to date have focussed on BCR, with less evidence for the role of PSMA PET/CT in primary staging. Despite these limitations, results from the literature suggest superior sensitivity and specificity of  $^{68}\text{Ga}$ -PSMA-PET/CT over other modalities, as illustrated in a meta-analysis by Perera et al [43]. Conducting a well-designed, prospective, multicentre randomised clinical trial will provide robust data on the utility of PSMA PET compared to conventional imaging in the primary staging setting of patients with high-risk localised prostate cancer. In the short to medium term, the improved detection of metastatic disease in the primary staging of high-risk prostate cancer is likely to have high impact for patient management, by directing more appropriate treatment.

The cost of diagnostic imaging is increasingly recognised as a major component of health expenditure. Diagnostic imaging accounts for approximately 15% of Australia's government funded system (Medicare) outlay, with estimated costs of \$3.1 billion per annum [44]. The utilisation of diagnostic imaging is showing rapid growth world-wide. By incorporating a health economic analysis into the clinical trial, this study should inform health care providers of the costs of PSMA-PET/CT compared to conventional imaging in the management of CaP. Given the high incidence of CaP in Australia, this may have significant implications for the long term.

The proPSMA Study has commenced with all 11 participating sites now activated and actively recruiting. The first patient was randomised in March 2017 and recruitment is proceeding on target. As part of multi-centre site validation, it was identified on  $^{68}\text{Ga}$  phantom validation studies that 10 of the 14 PET systems underestimated the standardised uptake value (SUV) by 15% on average. We

identified an incorrect factory-shipped dose calibrator setting as the cause. This was corrected at each site prior to site activation[45]. This experience emphasizes that pre-qualifying site assessment testing of the entire chain of measurements and calibration required for PET imaging is an important aspect of quality assurance.

The proPSMA randomised study design is innovative because it assesses the impact of PSMA-PET/CT as either a first or second-line investigation. This will enable us to establish whether PSMA-PET/CT should replace conventional imaging in the primary staging of high risk patients or whether it should be used to provide incremental diagnostic information in selected cases. The integration of the trial into real-world practice with a practical clinical endpoint [46] will contribute significantly to the global literature and may provide a strong case for changing the conventional investigation paradigm of CaP.

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**Participating Centres:**

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**Table 1: Study inclusion and exclusion criteria**

**Inclusion Criteria:**

1. Untreated, biopsy-proven adenocarcinoma of the prostate
2. Patient is being considered for curative-intent treatment with radical prostatectomy or radiotherapy
3. Patients must have high-risk features including at least one of the following features:
  - PSA  $\geq$  20.0 ng/ml within 12 weeks prior to randomisation
  - Gleason grade group 3, 4 or 5
  - Clinical stage  $\geq$  T3
4. Age  $\geq$  18 years
5. Patient has provided written informed consent for participation in this trial
6. In the opinion of investigator, willing and able to comply with required study procedures

**Exclusion Criteria:**

1. Patient has had any prior therapy for prostate cancer
2. Patient has undergone, within 8 weeks prior to randomisation, imaging for the primary purpose of staging pelvic nodal or distant metastatic disease of prostate cancer (MRI performed for primary purpose of assessing T-stage or to guide biopsy is acceptable)
3. A history of other active malignancy within the last 2 years, with exception of non-melanoma skin cancer or melanoma in-situ
4. Prostate cancer with significant sarcomatoid or spindle cell or neuroendocrine small cell components
5. Significant intercurrent morbidity that, in the judgment of the investigator, would limit compliance with study protocols

**Table 2: Schedule of Events**

	Diagnostic Period			6 months follow-up (180 ± 30 days from randomisation)	18, 30, and up to 42, 54 months (± 60 days from randomisation)
	Pre-randomisation / Screening Period (12 weeks)	First-line DI (within 21 days from randomisation)	Second-line DI (within 14 days from First-line DI)		
Written informed consent	x				
Demographics	x				
Disease Specific Medical History	x				
Diagnostic Imaging		x	x	x	
Additional confirmatory studies				x	
Adverse events		x	x		
Central imaging laboratory review <sup>6</sup>		x	x		
Health Service Utilisation		x	x		
Management Plan	x	x	x	x	
Clinical treatment failure				x	x

**Table 3: Minimum quality control specifications for <sup>68</sup>Ga-PSMA11 production**

Test	Specification
Visual inspection	Clear, colourless, particulate free
Product mass	≤ 30 micrograms PSMA-11
Radiochemical purity HPLC	>91% <sup>68</sup> Ga-PSMA-11 <2% <sup>68</sup> Ga (III) ion
pH	4-8
Radionuclide identity	T1/2 68 mins (62-74mins) 511keV energy peak
Radiochemical purity (TLC)	<3% colloidal form
Radiochemical purity (HPLC)	>91% <sup>68</sup> Ga-PSMA-11 purity <2% <sup>68</sup> Ga (III)ion
Ge-68 contamination	<0.001% <sup>68</sup> Ge
Residual solvent analysis	Ethanol <100,000ppm
Filter integrity	Meets filter manufacturers testing specification
Sterility test	Pass
Endotoxin test	<175 EU/dose

**Table 4: Study endpoints**

<p><b>Primary endpoint</b></p> <ol style="list-style-type: none"><li>1. Detection of metastatic disease on first-line imaging, being either pelvic nodal (N) or distant metastatic (M) disease</li></ol>
<p><b>Secondary endpoints</b></p> <ol style="list-style-type: none"><li>1. Impact of first -line DI on choice of therapy, defined as a decision to alter the original (pre-first-line diagnostic imaging) plan of treatment after considering the result of the first-line DI (Impact is categorised as high, medium, low or potential impact ignored)</li><li>2. Occurrence of equivocal study results</li><li>3. Occurrence of patients who were upstaged by second-line DI, ie. N0 to N1, M0 or M1, or detection of additional metastases amongst patients with oligometastatic disease</li><li>4. Impact of second-line DI on choice of therapy, defined as decision to alter the post first-line DI plan of treatment after considering the result of second-line DI</li><li>5. Time to clinical treatment failure defined by biochemical failure, development of metastatic disease or commencement of salvage therapy in patients without distant metastatic disease on PSMA PET/CT</li><li>6. Total cost of diagnostic work-up</li><li>7. Total patient radiation exposure (mSv)</li><li>8. Reporter agreement in interpretation of on-site readers providing clinical care and those of the central imaging laboratory readers</li><li>9. Number of adverse events reported during and post-administration of radiotracer for PSMA PET/CT</li></ol>

**Table 5:** Ground truth criteria using all information available up until 6 months post randomization.

A minimum of one hard criteria or three soft criteria must be met.

<b>For staging of distant metastatic disease</b>
<p><b>Hard criteria:</b></p> <ul style="list-style-type: none"><li>• Histopathology demonstrating prostate adenocarcinoma</li><li>• Change of bone lesion to sclerotic/blastic on follow-up imaging assessment</li></ul> <p><b>Soft criteria:</b></p> <ul style="list-style-type: none"><li>• Typical appearance of multi-focal metastatic disease</li><li>• Typical appearance of a metastatic lesion on an imaging modality other than the one performed as the index scan</li><li>• Increase in the number or size of bone lesion(s) or soft tissue lesion(s) from one imaging exam to the next, over time following the index scan</li><li>• Decrease in the number or size of bone lesion(s) or soft tissue lesion(s) following disease-appropriate treatment from one imaging exam to the next, over time following the index scan</li><li>• Presence of a lesion on an initial imaging examination with associated clinical symptoms suggesting malignancy</li><li>• Increasing alkaline phosphatase (ALP) or prostate specific antigen (PSA) in keeping with clinical scenario of progression, or decreasing levels in response to treatment, or PSA &gt;0.2 ng/ml at least three weeks following prostatectomy</li><li>• Patient received localised treatment for metastasis (e.g. radiotherapy)</li><li>• Unequivocal persistence of positive finding present on the baseline scan on repeat imaging at 6 months, in setting of PSA &gt;0.2 ng/ml at least three weeks following prostatectomy</li></ul>
<b>For <u>staging of pelvic nodal disease</u></b>
<p><b>Hard criteria:</b></p> <ul style="list-style-type: none"><li>• Histopathology demonstrating prostate adenocarcinoma</li></ul> <p><b>Soft criteria:</b></p> <ul style="list-style-type: none"><li>• Typical appearance of multi-focal metastatic disease</li><li>• Appearance of a metastatic lesion on an imaging modality other than the one performed as the index scan</li><li>• Increase in the number or size of soft tissue lesion(s) from one imaging exam to the next,</li></ul>

over time following the index scan

- Decrease in the number or size of soft tissue lesion(s) following disease-appropriate treatment from one imaging exam to the next, over time following the index scan
- Presence of a lesion on an initial imaging examination with associated clinical symptoms suggesting malignancy
- Increasing prostate specific antigen (PSA) in keeping with clinical scenario of progression, decreasing levels in response to treatment, or PSA >0.2 ng/ml at least three weeks following prostatectomy
- Patient received localised treatment for metastasis (e.g. radiotherapy)
- Unequivocal persistence of positive finding present on the baseline scan on repeat imaging at 6 months, in setting of PSA >0.2 ng/ml at least three weeks following prostatectomy

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**Table 6: Management impact classification**

<b>Impact</b>	<b>Definition</b>
High impact	Change in management intent or modality
Medium impact	Change in delivery of modality, but not intent
Low impact	Management plan was not altered
Potential impact ignored	Management plan not altered despite imaging findings demonstrating distant metastatic disease

Figure 1: Trial Schema

