Study Protocol

^{68}Ga-PSMA-PET/CT in addition to mpMRI in men undergoing biopsy during active surveillance for low- to intermediate-risk prostate cancer: study protocol for a prospective cross-sectional study

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Background: In active surveillance there is significant interest in whether imaging modalities such as multiparametric magnetic resonance imaging (mpMRI) or ^{68}Gallium prostate-specific membrane antigen positron emission tomography/computerized tomography (^{68}Ga-PSMA-PET/CT) can improve the detection of progression to clinically significant prostate cancer (csPCa) and thus reduce the frequency of prostate biopsies and associated morbidity. Recent studies have demonstrated the value of mpMRI in active surveillance; however, mpMRI does miss a proportion of disease progression and thus alone cannot replace biopsy. To date, prostate-specific membrane antigen positron emission tomography (PSMA-PET) has shown additive value to mpMRI in its ability to detect prostate cancer (PCa) in the primary diagnostic setting. Our objective is to evaluate the diagnostic utility of PSMA-PET to detect progression to csPCa in active surveillance patients.

Methods: We will perform a prospective, cross-sectional, partially blinded, multicentre clinical trial evaluating the additive value of PSMA-PET with mpMRI against saturation transperineal template prostate biopsy. Two hundred and twenty-five men will be recruited who have newly diagnosed PCa which is suitable for active surveillance. Following enrolment, patients will undergo a PSMA-PET and mpMRI within 3 months of a repeat 12-month confirmatory biopsy. Patients who remain on active surveillance after confirmatory biopsy will then be planned to have a further mpMRI and PSMA-PET prior to a repeat biopsy in 3–4 years. The primary outcome is to assess the ability of PSMA-PET to detect or exclude significant malignancy on repeat biopsy. Secondary outcomes include (I) assess the comparative diagnostic accuracies of mpMRI and PSMA-PET alone [sensitivity/specificity/negative predictive value (NPV)/positive predictive value (PPV)] to detect progression on biopsy based on predefined histologic criteria for progression; (II)

comparison of index lesion identification by template biopsies *vs.* MRI targeted lesions *vs.* PSMA targeted lesions; (III) evaluation of concordance of lesions identified on final histopathology and each imaging modality (PSMA-PET and/or mpMRI) in the subset of patients proceeding to RP.

Discussion: The results of this trial will define the role of PSMA-PET in active surveillance and potentially reduce the number of biopsies needed to detect progression to csPCa.

Trial Registration: The current trial was registered with the ANZCTR on the 3/2/2022 with the trial ID ACTRN12622000188730, it is accessible at https://www.anzctr.org.au/.

Keywords: Prostate cancer (PCa); active surveillance (AS); prostate-specific membrane antigen positron emission tomography (PSMA-PET); protocol; treatment

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Introduction

Active surveillance (AS) has been shown to be an appropriate management strategy for low- to intermediate-risk prostate cancers (PCa) with similar oncological outcomes to immediate radical treatment whilst preserving urinary and sexual function (1). However, there is still significant heterogeneity in AS protocols worldwide. Through a multidisciplinary group the DETECTIVE study aimed to developed consensus statements and recommendations for active surveillance however there was no consensus achieved on inclusion criteria for intermediate-risk PCa and the frequency of repeat biopsy required (2).

Repeat biopsy in patients has been identified as a significant deterrent to remain on AS and causes psychological distress and confers morbidity (3). Thus, one of the current aims in AS protocols is to safely reduce the frequency of or forego biopsy if possible whilst still detecting progression to clinically significant prostate cancer (csPCa) allowing for timely radical treatment without compromising oncological outcomes.

To achieve this there has been an investigation into various imaging tools such as multiparametric magnetic resonance imaging (mpMRI) and biomarkers such as PCA3 and the 4Kscore (4-6). In a recent meta-analysis on the use of MRI in active surveillance, it was shown that the pooled NPV of serial mpMRI was between 0.81 (95% CI: 0.73–0.88) to 0.88 (95% CI: 0.83–0.93). Thus, whilst mpMRI can detect a significant proportion of cancer progression it still does miss some cancers and allows only for a reduction in the frequency of biopsy.

More recently, ^{68}Gallium prostate-specific membrane antigen positron emission tomography/computerized tomography (^{68}Ga-PSMA-PET/CT) has shown utility in the primary diagnostic setting of PCa. The PRIMARY trial demonstrated that prostate-specific membrane antigen positron emission tomography (PSMA-PET) had an additive value to mpMRI in the diagnosis of PCa with the combination having an improved NPV compared with MRI alone [91% *vs.* 72%, test ratio =1.27 (1.11–1.39), P<0.001] and sensitivity improved (97% *vs.* 83%, P<0.001) (7). Further, a recent retrospective analysis of 1,123 men found that with an SUV_{max} <5 fewer than 10% of patients had PCa upgrading from International Society of Urological Pathology grade group (ISUPGG) 2 to ≥3 on biopsy to radical prostatectomy (8). Thus, initial studies demonstrate that PSMA-PET may have diagnostic utility in active surveillance protocols however this needs to be further investigated in prospective studies which are built to examine this.

As previously stated, the ideal AS protocol would forego any invasive investigations such as biopsy but predict cancer progression within the window of a cure for radical treatments. Current AS protocols including prostate specific antigen (PSA), digital rectal examination (DRE), and mpMRI still require repeat biopsy at regular intervals due to potential missed csPCa. We hypothesize that the addition of PSMA-PET to current AS protocols will allow for a further reduction or elimination of the need for repeat biopsy in AS patients and we look to evaluate this in the PSMA-PET In Active Surveillance (PIAS) trial. We present this article in accordance with the SPIRIT reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-22-708/rc).

Methods

Trial design

This study is designed as a prospective, cross-sectional, partially blinded, multicentre clinical trial. It evaluates the additive value of PSMA-PET to mpMRI to detect or exclude csPCa requiring definitive therapy on repeat biopsy. This study will be conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review boards at St Vincent's Hospital Human Research and Ethics Committee (No. HREC 2021/ETH00169) and was registered in the clinical trial registry (No. ACTRN12622000188730). Written and informed consent will be obtained from all participants.

Participants

Participants will be recruited over 7 sites in Australia. The inclusion criteria for this trial are:

(I) ≥18 years of age;
(II) life expectancy of ≥10 years;
(III) newly diagnosed PCa deemed suitable for AS by treating urologist and not yet had repeat prostate biopsy on AS;
(IV) a diagnosis of PCa meeting the following histopathological criteria:
- ❖ organ-confined PCa:
  - ◆ cT1-2a;
  - ◆ cN0;
  - ◆ cM0/x;
- ❖ Gleason score 3+3 PCa with ANY of the following high-risk features:
  - ◆ >30% maximum cancer core involvement of any single core;
  - ◆ >6 mm cancer in any core;
  - ◆ >4 locations with cancer on biopsy;
  - ◆ PI-RADS V2.1 4 or 5 lesion on baseline mpMRI;
  - ◆ focus on PSMA-PET suspicious for PCa (SUV_{max} >4 in PZ or >5 in TZ);
- ❖ Gleason score 3+4 PCa with:
  - ◆ <20% Gleason pattern 4 overall and in each location;
  - ◆ </=1 mm volume of pattern 4 per location (calculated by length of cancer per location (mm) × % pattern 4 in that location);
- ❖ No evidence of extra-capsular extension (ECE).

(V) no previous PCa treatment;
(VI) able to provide written informed consent to and willing to remain on AS;
(VII) planned for a confirmatory biopsy within the next 12 months following enrolment onto the study;
(VIII) able to give written informed consent to and willing to participate and comply with the study.

The exclusion criteria for the trial are:

(I) inability to provide written informed consent to either AS or study;
(II) unwilling to remain on AS for the duration of study;
(III) has a diagnosis of PCa that does not meet the histological criteria or has cribriform pattern;
(IV) has had prior treatment for PCa;
(V) has a contraindication to mpMRI or PSMA-PET.

Study outline/interventions

The study outline is summarized in *Figure 1*. Participants enrolled will have newly diagnosed PCa and be deemed suitable for AS and consented to the trial by their treating urologists. As part of the standard of care, patients will undergo a repeat mpMRI followed by a confirmatory transperineal saturation +/– targeted biopsy at approximately 12 months (6–18 months) following the initial biopsy. As the intervention for the study, patients will undergo a PSMA-PET within 3 months prior to a repeat biopsy. Any suspicious regions on PSMA-PET or mpMRI will be targeted at time of biopsy. Further urine and blood samples will be collected from the patient at time of PSMA-PET scan for potential future use in biomarker studies.

Patients who progress to csPCa at 12-month biopsy will be reviewed by their treating urologist and decision to proceed to radical treatment will be discussed with the patient. Patients who do not progress to csPCa will continue on AS and the trial following discussion with treating urologists. At the 3–4-year timepoint, patients will undergo a further repeat PSMA-PET, MRI, and prostate biopsy as per the protocol below:

- ❖ If Gleason 3+3 with a high concern or any Gleason 3+4, repeat mpMRI/PSMA-PET at 30 months then biopsy within 3–6 months of MRI (i.e., biopsy at 33–36 months);
- ❖ If Gleason 3+3 with low to intermediate concern, repeat MRI at 42 months then biopsy within 3–6 months of MRI/PSMA-PET (i.e., biopsy at 45–48 months).

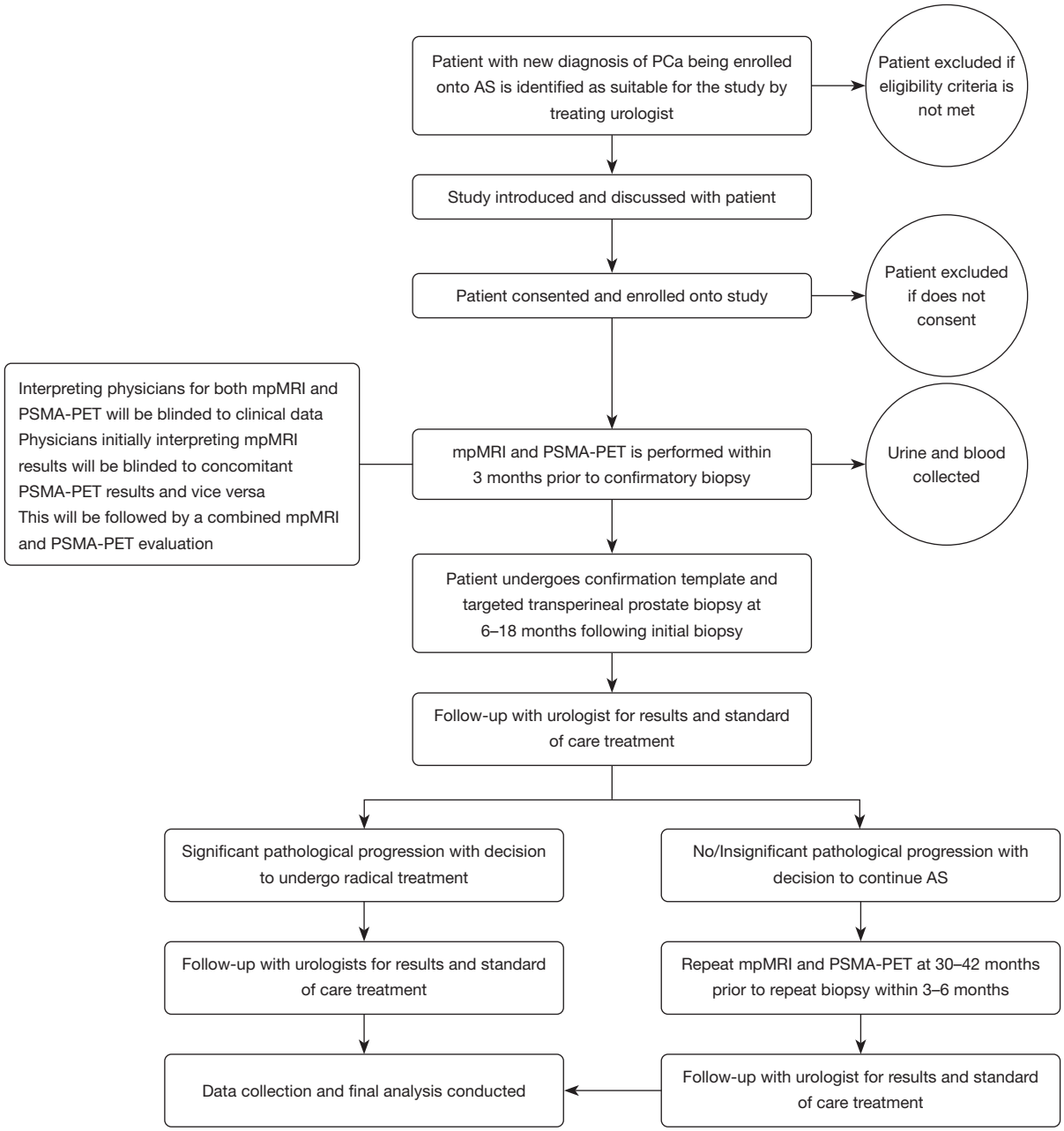

Figure 1 Study outline. PCa, prostate cancer; AS, active surveillance; mpMRI, multiparametric magnetic resonance imaging; PSMA-PET, prostate-specific membrane antigen positron emission tomography.

mpMRI

Patients will undergo a mpMRI as per standardized protocols in keeping with PI-RADS V2 (9). This will include:

- 1.5 or 3-Tesla magnet field strength;
- 32-channel system with 14-channel spine coil and 18-channel pelvic phased array coil arrangement or other high-resolution small field of view coil;
- T1-weighted whole pelvis field of view to identify biopsy haemorrhage artifact and bone marrow signal;
- T2-weighted, high spatial resolution, anatomical imaging to identify and precisely localise areas of

suspicion, and direct MRI-guided biopsy where performed;
- T2-weighted imaging in 3 planes with sagittal, coronal, axial and TSE images;
- diffusion-weighted imaging with software derived apparent diffusion co-efficient (ADC) quantitative analysis maps, and multiple B-values (0, 400, 800, 1,400);
- dynamic contrast enhanced imaging (DCEI) with automatically delivered IV gadolinium DTPA bolus 10 mL at 3 mL/second followed by rapid sequences with temporal resolution of between 4–7 seconds between scans;
- analysis of DCEI according to PIRADS DCEI analytic guidelines;
- post-contrast whole pelvis fat saturation T1 weighted sequence.

mpMRI will be reported by local radiologists according to PI-RADS V2 using a scale from 1 to 5.

PSMA-PET

PSMA-PET will be performed at 3 centres across Australia. All PET cameras will be harmonized for dose calibration and intensity score assessment. ^{68}Ga-PSMA will be produced on site compliant with Good Laboratory Practice guidelines. A limited field of view PSMA-PET of the pelvis will be undertaken around 60 minutes (±10 minutes) post-injection with a non-contrast-enhanced CT scan (pelvis) performed around 60 minutes (±10 minutes) post tracer injection.

PSMA-PET images will be clinically reported at a per patient and per lesional level. All abnormalities will be classified as 'definitely positive', 'equivocal probably positive', 'equivocal probably negative' and 'definitely negative'. Size and location of lesions will be documented. The corresponding mpMRI report will not be available to the reporting clinician, partially blinding the reporter to avoid bias.

An additional quantitative analysis of the PSMA-PET will also be undertaken determining SUV_{max} and metabolic volume of prostatic lesions to determine cut-offs for malignancy and repeat PSMA-PET scans will be compared to initial PSMA-PET scans.

Biopsy

Transperineal prostate biopsy will be performed as a saturation template +/– targeted biopsy at baseline, 12 months and 3–4 years. Template biopsies will involve a minimum of 20 cores dependent on prostate volume. Targeted biopsies of PSMA-PET and mpMRI lesions will be performed using cognitive or software assisted fusion with each lesion having a minimum of 3 cores taken.

Histopathology

Biopsies will be reported as per the ISUP guidelines. The preferred provider of each site will report histopathology.

Progression to csPCa will be predefined as:
- ISUP grade group progression to 3–5;
- Progression to ISUP grade group 2 with percentage pattern 4 ≥20% in one or more locations and volume of pattern 4 (>1 mm length) in one or more locations (calculated by length of cancer per location (mm) × % pattern 4 in that location);
- Development of suspected ECE on biopsy.

Follow-up

Patients will follow-up with their treating urologists after repeat biopsies for discussion of results. For the subset of patients proceeding to radical prostatectomy, histopathological concordance with identified lesions on each of the imaging modalities will be analysed. The proportion of men with change in Gleason grade group following radical prostatectomy will also be recorded.

Endpoints

Primary objective
- Assess the ability of PSMA-PET to detect significant malignancy requiring definitive therapy on 12-month confirmatory and repeat 3–4 years biopsy in men on AS.

Secondary objectives
- Assess the accuracy (NPV/PPV/sensitivity/specificity) of PSMA-PET to detect biopsy-proven progression for men on AS using the following pre-defined histological progression criteria:
  - ISUP Grade Group progression to ISUP Grade Group 3–5;
  - ISUP Grade Group 2 with:
    - percentage of pattern 4 to ≥20% in one or more locations;
    - volume of pattern 4 (>1 mm length) in one or

more locations (calculated by length of cancer per location (mm) × % pattern 4 in that location);
- the development of suspected ECE.

- Assess the combined and comparative accuracy (NPV/PPV/sensitivity/specificity) of mpMRI and/or PSMA-PET in the detection of disease progression as above with stratification of favourable intermediate-risk disease and low-risk disease;
- Comparison of index lesion identification by template biopsies *vs.* targeted lesions identified on mpMRI and PSMA-PET;
- Comparison of the accuracy of targeted *vs.* template biopsy to see if template biopsy can be avoided;
- Evaluation of concordance of lesions identified on final histopathology and each imaging modality (PSMA-PET and/or mpMRI) in the subset of patients proceeding to RP;
- Collection of blood and urine samples to enable future assessment and comparison of the accuracy (NPV/PPV/sensitivity/specificity) of blood/urine-based biomarkers in comparison to and in combination with PSMA/MRI to detect progression on biopsy for men on AS using pre-defined histological inclusion and progression criteria;
- Develop a multi-variate nomogram evaluating age, PSA and kinetics, DRE, prostate volume, family history, mpMRI, PSMA-PET and biopsy factors to predict the likelihood of pathologic/clinical progression at 12-month confirmatory and 3–4 years repeat biopsy in patients on AS;
- Cost-effectiveness analysis;
- Quantitative analysis on PSMA-PET changes and the likelihood of pathological progression.

Analysis

Case report forms, only identifiable by the unique enrolment number for demographics, mpMRI, PSMA-PET, histopathology and follow-up will be stored in a secure REDCap database and used for analysis.

Sample size calculation

Based on pilot data, it is estimated that a sample size of 225 will be required to detect a NPV ratio of 1.3 comparing PSMA-PET in addition to mpMRI verse mpMRI alone, under a paired study design, with 80% power and at a two-sided significance level of 0.05 (10).

Statistical analysis

Diagnostic accuracy including sensitivity, specificity, PPV, NPV and the area under the receiver operating characteristic (ROC) curve (AUC) will be calculated with 95% CI for both PSMA-PET with mpMRI and mpMRI alone.

The McNemar's test of two correlated proportions will be used to compare the paired data of PSMA-PET with mpMRI, and mpMRI alone in sensitivity and specificity. A permutation test procedure will be used to compare paired data AUCs (11). The comparison in PPV and NPV between the two diagnostic approaches will be based on the relative ratio and involves multinomial-poisson transformation (10). The generalised linear regression model approach will also be used to compare PPVs and NPVs, with control for patients' characteristics (12).

Procedure funding

Funding for this project will be provided by St. Vincent's Prostate Cancer Research Centre to support the participating sites. mpMRI will be funded through the Medicare rebate scheme and patients if ineligible for rebate. PSMA-PET will be funded through the trial. Biopsy will be funded through the Medicare rebate scheme, private health insurance and patient as per standard practice.

Patients will not be paid for participating and no clinicians and researchers will be paid by the trial.

Blinding

The reporting radiologist and nuclear medicine physician will be blinded to participant clinical data. Upon initial mpMRI evaluation, the interpreting radiologist will be blinded to the compatriot PSMA-PET study and vice versa. This will be followed by a combined evaluation of both studies. All available information including imaging reports will be available to the treating urologist to guide optimal ongoing clinical management of the participant.

Safety

An adverse event to PSMA-PET scan will be considered as any unfavourable and unintended sign, symptom, or disease temporarily associated with the use, whether it is or is not directly related to the PSMA-PET scan. Should an adverse event occur, it will be reported to the trial investigators, as

well as documented in the participant's medical records. The trial investigators will then decide, dependent on the severity and possible causal relationship of the event, to refer events to the institutional review board.

Confidentiality

Each participating site will be responsible for the safe and appropriate management of identifiable and re-identifiable study data. All electronic identifiable/re-identifiable study data will be stored in a password protected database on a secure, internal server at each site. Physical data will be stored in filing cabinets or folders within the relevant departments accessible to study staff in locked units or swipe card accessible departments. Only principal investigators or delegated study staff will be permitted to access the data. All source documentation will be held confidentially in line with current legislation governing health information and will not be made publicly available.

Discussion

Emerging trends in AS involve the increasing use of non-invasive diagnostic tests such as biomarkers and imaging modalities to limit the need for invasive prostate biopsy to detect progression to csPCa. Repeat prostate biopsy has been shown to be a deterrent for patients to choose active surveillance and confers associated morbidity and increases healthcare system costs (13,14).

mpMRI has demonstrated significant value in the primary diagnostic setting for detecting csPCa whilst avoiding detection of insignificant cancers (15-17). Thus, its effectiveness in AS protocols has been of interest and evaluated by several studies. Amin *et al.* demonstrated that mpMRI used annually over a three-year period in AS patients to detect pathological progression had a PPV, NPV, sensitivity and specificity of 45%, 89%, 61% and 80% respectively (18). Similarly, other studies have demonstrated that the use of PSA and mpMRI in AS may detect most cases of progression to csPCa however repeat biopsy is still necessary to detect cases missed by non-invasive diagnostic tools (19-22).

PSMA-PET is an evolving imaging modality in PCa. It was first demonstrated as an excellent tool for detecting sites of recurrent disease in post radical treatment such as lymph nodes and bony metastases (23). More recently it has demonstrated additive value to mpMRI in the primary cancer diagnosis setting for intraprostatic lesions. In analysis of 56 patients undergoing radical prostatectomy, Scheltema et al demonstrated that the combination of PSMA-PET and mpMRI for detecting ISUP grade group 2–3 PCa had a sensitivity, specificity, NPV and PPV of 92%, 90%, 96% and 81%, respectively (24). Similarly, Emmett *et al.* demonstrated in a prospective multicentre trial that the combination of PSMA-PET and mpMRI significantly improved sensitivity to 97% against 83% for mpMRI alone and NPV to 91% against 72% for mpMRI alone (7).

In the current prospective trial, we will provide participating surgeons with PSMA-PET/CT images to allow for more accurate targeting of potential PCa lesions. This may further improve the detection of cancer progression in AS patients as seen with MRI targeted biopsy. However, as with all studies where biopsy is the reference test the accuracy of biopsy may significantly impact the results.

Given the diagnostic utility PSMA-PET has demonstrated in PCa diagnosis it follows that it may have a role in an AS protocol and when potentially used in combination with mpMRI and biomarkers may reduce or eliminate the need for repeat biopsy in patients. Further, it is important to consider the cost-effectiveness of PSMA-PET/CT in AS protocols. The addition of PSMA-PET/CT may incur significant costs to patients and healthcare systems and the benefit must outweigh this cost.

The current prospective study is the first that we are aware of looking to evaluate this. The PIAS trial began recruitment in September 2021 with the aim to complete recruitment within 18 months. We believe it will contribute significantly to global literature and has the potential to direct AS protocols of the future.

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Footnote

Reporting Checklist: The authors have completed the SPIRIT

reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-22-708/rc

Peer Review File: Available at https://tau.amegroups.com/article/view/10.21037/tau-22-708/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-22-708/coif). MJR reports the consulting fees (proctoring, prostate biopsy technique) from BXTAccelyon, and the participation on DSMB (PSMA-PET related) in Peter MacCallum Cancer Centre, Melbourne. DW and RS report the employment with I-MED Radiology. WD reports the employment with Douglass Hanly Moir pathology. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study will be conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review boards at St Vincent's Hospital Human Research and Ethics Committee (No. HREC 2021/ETH00169) and was registered in the clinical trial registry (No. ACTRN12622000188730). Written and informed consent will be obtained from all participants.

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