BMJ Open

PEDAL Protocol: A prospective single arm paired comparison of multiparametric MRI and 18F-DCPFyl PSMA PET/CT to diagnose prostate cancer

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-061815
Article Type:	Protocol
Date Submitted by the Author:	09-Feb-2022
Complete List of Authors:	Tran, Vy; St Vincent's Hospital Melbourne Pty Ltd, Urology; The University of Melbourne, Faculty of Medicine, Dentistry and Health Sciences Hong, Anne; Austin Health, Urology Sutherland, Tom; The University of Melbourne, Department of Medicine; St Vincent's Hospital Melbourne Pty Ltd, Medical Imaging Department Taubman, Kim; St Vincent's Hospital Melbourne Pty Ltd, Nuclear Medicine Lee, Su-Faye; St Vincent's Hospital Melbourne Pty Ltd, Nuclear Medicine Lenaghan, Daniel; St Vincent's Hospital Melbourne Pty Ltd, Urology Sethi, Kapil; St Vincent's Hospital Melbourne Pty Ltd, Urology Corcoran, Niall; The Royal Melbourne Hospital City Campus, Urology Lawrentschuk , Nathan; The University of Melbourne, Surgery; The Royal Melbourne Hospital City Campus, Urology Woo, H; Sydney Adventist Hospital, Urology; The University of Sydney, Surgery Tarlinton, Lisa; Sydney Adventist Hospital, San Radiology and Nuclear Medicine Bolton, Damien ; Austin Hospital; The University of Melbourne, Surgery Spelman, Tim; The University of Melbourne Thomas, Lauren; St Vincent's Hospital Melbourne Pty Ltd, Nuclear Medicine Booth, Russell; St Vincent's Hospital Melbourne Pty Ltd, Nuclear Medicine Hegarty, Justin; Pacific Radiology Christchurch Perry, Elisa; Pacific Radiology Christchurch Wong, Lih-Ming; St Vincent's Hospital Melbourne Pty Ltd, Urology; The University of Melbourne, Surgery
Keywords:	Prostate disease < UROLOGY, Magnetic resonance imaging < RADIOLOGY & IMAGING, Nuclear radiology < RADIOLOGY & IMAGING

Category: Original Research

Title: PEDAL Protocol: A prospective single arm paired comparison of multiparametric MRI and 18F-DCPFyl PSMA PET/CT to diagnose prostate cancer

Authors:

Vy Tran[1,2], Anne Hong[3], Tom Sutherland[4], Kim Taubman[5], Su-Faye Lee[4], Daniel Lenaghan[1], Kapil Sethi[1], Niall Corcoran[6,7], Nathan Lawrentschuk[8,9], Henry Woo[10,11], Lisa Tarlinton[12], Damien Bolton[3,13], Tim Spelman[14], Lauren Thomas[5], Russell Booth[5], Justin Hegarty[15], Elisa Perry[15], Lih-Ming Wong[1,13]*

1. St Vincent's Hospital Melbourne, Department of Urology, VIC, AUS
2. The University of Melbourne, Faculty of Medicine, Dentistry and Health Sciences, Melbourne, VIC, AUS
3. Austin Health, Department of Urology, VIC, AUS
4. St Vincent's Hospital Melbourne, Department of Medical Imaging, VIC, AUS
5. St Vincent's Hospital Melbourne, Department of Nuclear Medicine, VIC, AUS
6. The Royal Melbourne Hospital, Department of Urology, Parkville, VIC, AUS
7. University of Melbourne Victorian Comprehensive Cancer Centre, Parkville, VIC, AUS
8. Peter MacCallum Cancer Centre, Melbourne, VIC, AUS
9. Epworth HealthCare, EJ Whitten Prostate Cancer Research Centre, Melbourne, VIC, AUS
10. Sydney Adventist Hospital, Department of Urology, NSW, AUS
11. The University of Sydney, NSW, AUS
12. Sydney Adventist Hospital, San Radiology and Nuclear Medicine, NSW, AUS
13. Department of Surgery, The University of Melbourne, Melbourne, VIC, AUS
14. The University of Melbourne, Melbourne, VIC, AUS
15. Pacific Radiology Christchurch, Canterbury, NZ

***Corresponding Author**

A/Prof Lih-Ming Wong

Department of Urology, St Vincent's Hospital Melbourne

Department of Surgery, University of Melbourne

Email: lihmingwong@gmail.com

Abstract word count: 288

Manuscript word count: 3035

Number of figures: 1

Number of tables: 2

Abstract

Introduction:

Prostate specific membrane antigen positron emission tomography (PSMA-PET) has emerged as valuable imaging to assessing metastatic disease in prostate malignancy. However, there has been limited studies exploring the utility PSMA-PET as primary imaging assessing for index lesions prior to biopsy. The primary objective of this study is to compare the diagnostic accuracy of 18-fluorine PSMA (18F DCFPyL PSMA) PET scans to multiparametric magnetic resonance imaging (mpMRI) to detect primary prostate cancer at prostate biopsy.

Methods and Analysis:

The PEDAL trial is a multicentre, prospective, single-arm, paired comparison, non-randomised phase III trial in subjects considered for diagnostic prostate biopsy. Subjects who are eligible for a diagnostic mpMRI prostate will undergo additional same-day 18-F DCFPyl PSMA PET/CT of the chest, abdomen and pelvis. Software co-registration of the mpMRI and PSMA-PET/CT images will be performed. The reporting of the mpMRI prostate, PSMA-PET/CT and PSMA PET/MRI co-registration will be performed blinded.

The diagnostic accuracy of PSMA PET/CT alone, and in combination with mpMRI, to detect prostate cancer will be assessed. Histopathology at prostate biopsy will be used as the reference standard. Sample size calculations estimate that 240 subjects will need to be recruited to demonstrate 20% superiority of PSMA-PET/CT.

The sensitivity, specificity, positive predictive value and negative predictive value of the combination of mpMRI prostate and PSMA PET/CT compared to targeted and systematic prostate biopsy will be evaluated. It is hypothesised that PSMA PET/CT combined with mpMRI prostate will have improved diagnostic accuracy compared to mpMRI prostate alone for detection of prostate cancer in biopsy-naïve men, resulting in a significant impact on patient management.

Ethics and Dissemination:

This study was approved by the independent Human Research Ethics Committee and is a registered trial (Trial registration number: ACTRN12620000261910). Participant recruitment commenced in March 2020. Results will be published in peer-reviewed medical journals.

Strengths and Limitations

- This is a multicentre study.
- A strength of this study is its prospective nature of the study design controlled by using patients own biopsy results as comparator, thus limiting confounders.
- This is an adequately powered study with objective primary and secondary outcome measures.
- Potential limitations pertain to generalisability of results given use of DCFPYL tracer for PSMA-PET/CT. There are currently limited studies directly comparing different PSMA-PET tracers.

Keywords:

prostate cancer, diagnosis, PSMA PET, multiparametric MRI, PSMA, imaging

Introduction

Prostate cancer (PCa) is very common, with one in six men being diagnosed before the age of 85 years[1]. The age-standardised incidence rate has increased from 80 cases per 100,000 males to 141 cases per 100,000 males since 1982, likely driven by the implementation of prostate-specific antigen (PSA) screening. With the growing incidence of disease, prostate imaging has become increasingly important in the diagnostic evaluation of prostate cancer to detect clinically significant prostate cancer (csPCa, Grade group ≥2) and assess tumour burden.

In Australia, multiparametric magnetic resonance imaging (mpMRI) of the prostate gland has also become available under Australian government funded rebate for diagnostic evaluation of suspected prostate cancer and active surveillance of low-risk prostate cancer with economic analysis suggesting significant savings to the health system[2,3]. mpMRI offers reliable visualisation and characterisation of csPCa compared to the traditional transrectal ultrasound (TRUS), and is seen to have greater sensitivity of detection for lesions greater than 1cm, Gleason score of ≥7 and index lesions compared to satellite lesions, thus enabling better selection of patients for prostate biopsy[4]. In a meta-analysis of 42 studies, the pooled negative predictive value of mpMRI was reported to be 90.8 – 97%[5]. mpMRI-targeted prostate biopsy has been reported to detect more csPCa than systematic TRUS-guided biopsy (38% versus 26%)[6]. Nevertheless, mpMRI is not without limitations. Variable imaging quality, interreader variability, low specificity and missed or underestimated tumours remain an issue[7,8]. The PAIREDCAP trial reported 15% of patients with negative mpMRI findings were found to have csPCa on systematic prostate biopsy[9].

Along with mpMRI, prostate-specific membrane antigen positron emission tomography (PSMA-PET) is one of the key advancements to emerge in prostate cancer assessment over the last two decades[10,11]. Prostate specific membrane antigen (PSMA) is a type II transmembrane protein that is overexpressed on PCa cell membranes in all but 5 – 10% of cases, showing high specificity and

sensitivity relating to tumour aggressiveness and metastatic potential[12,13]. 18F-Choline PET scans have been shown to improve risk stratification when used in conjunction with mpMRI[14] . This in conjunction with the prostate specific tracer of PSMA leads to strong support using PSMA-targeted PET imaging for staging of high-risk disease and biochemical recurrence [15-18]. In the proPSMA trial, PSMA PET/CT was demonstrated to have 27% greater accuracy than conventional staging (92% versus 65%) for pelvic or distant metastases, providing superior accuracy with fewer equivocal results and lower radiation exposure[15].

The use of PSMA PET/CT as a first line diagnostic tool for suspected prostate cancer is under investigation[19,20]. The PRIMARY study[19] recently reported the additive value of pelvic-only 68Ga-PSMA PET/CT to a "triaged" mpMRI population to detect csPCa in men with suspicious for prostate cancer. The trial showed combined PSMA-PET/CT and MRI compared to MRI alone improved the negative predictive value (91% vs 72%, p<0.001) and sensitivity (97% vs. 83%, p<0.001). However, specificity was reduced (40% vs. 53%, p=0.01). Several other studies demonstrated similar results of improved sensitivity[10,21]. Additionally, for equivocal lesions on mpMRI (i.e. PIRADS 3), PSMA-PET/CT may add to stratification of these lesions, with csPCa was more often detected when any focal PSMA uptake was detected 3/6 (50%), compared to those with no appreciable PSMA uptake 2/11 (18%) [22]. Finally, PSMA-PET/CT in addition to mpMRI showed increased sensitivity when detecting extraprostatic extension and seminal vesical invasion[23], although specificity reduced slightly[23], as seen in the PRIMARY trial. Hybrid PET/MRI scanners utilizing the 68Ga-PSMA ligand have also provided compelling evidence that it may be superior to prostate mpMRI alone to detect csPCa, however use of these machines will be limited by cost and poor accessibility[24,25].

Given the morbidity and mortality associated with prostate biopsy and prostate cancer treatment, the potential for improved diagnostic accuracy using PSMA PET/CT to localize prostate cancer in biopsy-naïve men warrants further investigation. The PEDAL trial is a prospective, single-arm paired

comparison trial that aims to provide high quality evidence regarding the diagnostic accuracy of 18F-DCFPyl-PSMA PET/CT in conjunction with mpMRI prostate for primary diagnosis of prostate cancer.

Methods and Design:

Ethics

This clinical trial has been approved by the St Vincent's Hospital, Melbourne Human Research Ethics Committee (HREC 230/19) and is registered on the Australian New Zealand Clinical trials registry (ACTRN12620000261910). It will be conducted in accordance with the International Conference on Harmonisation protocols and Good Clinical Practice. In addition, the trial will be conducted in compliance with all applicable laws and regulatory requirements relevant to the use of new therapeutic agents in Australia and any other participating country. Funding will be acquired through Cyclotek (manufacturer of DCFPYL), General Electrical Healthcare, and philanthropic grants.

The trial schema is outlined in Figure 1.

Patient and public involvement

No formal patient advisory committee was set up and there was no patient or public involvement in the design and planning of the study. The study was so designed as the mpMRI, PSMA-PET and prostate biopsy procedures used are not novel concepts or techniques, and are widely available in Australia as part of the Medicare system for which consumer and stakeholder comment is sought prior to inclusion of these interventions. Nevertheless, the patients are invited to provide feedback at each point of contact with the healthcare system. In addition, the results are intended for publication in peer reviewed medical journals.

Study design

This is a prospective single arm paired comparison diagnostic phase III trial in patients who are being considered for diagnostic prostate biopsy to detect prostate cancer. We aim to evaluate the role of PSMA-PET/CT in those with high clinical suspicion of prostate cancer. The PSMA-PET/CT, by identifying a suspicious lesion, is likely to impact the decision for prostate biopsy and the target location. The diagnostic accuracy of the imaging studies will be assessed by comparison of imaging results to prostate biopsy results.

Patient screening, eligibility, and enrolment

Patients with features suspicious for PCa based on an abnormal PSA or DRE will be screened by a urologist for trial eligibility in the study according to the inclusion and exclusion criteria listed below in Table 1[26]. A target of 240 subjects will be recruited from multiple sites.

Table 1. Study inclusion and exclusion criteria

[Adapted from New Medicare Benefits Scheme (MBS) for mpMRI of the prostate][20]

Inclusion criteria
• Men (≥18 years) with an elevated PSA who are suitable for an eligible MBS mpMRI prostate: (MBS items 63541 and 63542) AND who have NOT had recent (≤3 years) prostate biopsy or mpMRI prostate. For MBS items 63541 and 63542 (NK) the patient must be suspected of having prostate cancer based on (*): a) DRE which is suspicious for prostate cancer; or b) in a person aged less than 70 years, at least prostate specific antigen (PSA) tests performed within an interval of 1- 3 months are greater than 3.0 ng/ml, and the free/total PSA ratio is less than 25% or the repeat PSA exceeds 5.5 ng/ml; or c) in a person aged less than 70 years, whose risk of developing prostate cancer based on family history is at least double the average risk, at least two PSA tests performed within an interval of 1- 3 months are greater than 2.0ng/ml, and the free/total PSA ratio is less than 25%; or d) in a person aged 70 years or older, at least two PSA tests performed within an interval of 1- 3 months are greater than 5.5ng/ml and the free/total PSA ratio is less than 25%. *NB: Relevant family history is a first degree relative with prostate cancer or suspected of carrying a BRCA 1, BRCA 2 mutation.*
• Patient has provided written informed consent for participation in trial
• In the opinion of the investigator, willing and able to comply with required study procedures
Exclusion criteria
• Known diagnosis of prostate cancer.
• Previous prostate biopsy within 3 years of randomization. A transurethral resection of the prostate performed for primary purpose of alleviating lower urinary tract symptoms is considered acceptable.
• Previous mpMRI prostate within 3 years of randomization.
• History of other active malignancy within the last 3 years, with the exception of non-melanoma skin cancer or melanoma in-situ.
• Any absolute contra-indication to 3T mpMRI prostate, or previous history of total hip joint replacement.
• Significant intercurrent morbidity that, in the judgement of the investigator, would limit compliance with study protocols.
DRE= digital rectal examination; mpMRI = multiparametric magnetic resonance imaging; PSA= prostate specific antigen

Follow-up

Participants will be followed-up by their referring urologist to discuss results and ongoing management of either PSA surveillance, active surveillance, radical treatment or non-curative treatment.

Funding

Subjects will be informed of the costs of participation as part of the informed consent. For those eligible, the mpMRI will be funded through the Australian Government Department of Health Medicare Benefits Scheme (i.e. free of charge to the patient). The PSMA PET/CT will be funded through the clinical trial. The prostate biopsy will be funded as standard practice through the Medicare Benefits Scheme, private health insurance and subject. Subjects will not be paid for their participation and no participating clinical or researcher will be paid outside of their normal salary.

Diagnostic Imaging Procedures

All participants will undergo both the PSMA-PET/CT and mpMRI within four weeks of enrolment into this study and both scans performed on the same day to minimise disruption to participants' personal schedules. To standardize parameters of acquisition and image quality, these will be performed at an approved study centre.

Multiparametric MRI

All subjects will undergo 3-Tesla mpMRI prostate according to standard protocols (Appendix 1). The images will be reported by a single experienced Radiologist using the Prostate Imaging–Reporting and Data System (PI-RADS) version 2.1 on a scale of 1 to 5 (Appendix 2). Any suspicious intraprostatic

lesion described as PI-RADS 3 or greater will be considered a positive lesion with a targeted prostate biopsy recommended. The presence of extracapsular extension, seminal vesicle invasion, locoregional disease and subjective likelihood of csPCa will be recorded. The initial report of the mpMRI prostate will be blinded to the PSMA-PET/CT result.

PSMA-PET/CT

All participants will undergo PSMA-PET/CT imaging with18F-DCFPyL according to standard protocol (Appendix 3) at the participating site, on the same day as the mpMRI. The 18F-DCFPyL radiotracer will be produced in Australia and New Zealand by Cyclotek Pty Ltd, who will provide the local site with a Quality Control Release notification form. A single, intravenous bolus dose of 18F-DCFPyL PSMA (250MBq +/-50 MBq) will be administered with an uptake time of 120 minutes post 18F-DCFPyL injection. 18F-PSMA PET with CT chest, abdomen and pelvis will be performed for anatomic localisation and attenuation correction

PSMA-PET/CT images will be reported at a per-patient and per-lesion level by an experienced reader at each site. The initial report of PSMA-PET/CT will be blinded to the mpMRI prostate result. To standardise lesion imaging reporting, the intraprostatic lesions will be described according to the sector map specified in PI-RADS version 2.1 for mpMRI prostate. The PSMA intensity score (SUVmax), focality and ratio to background will be assessed. The reader will report disease location and extent, as well as assign a subjective likelihood for the presence of csPCa. All lesions with SUVmax scores of 4.0 or higher are deemed appropriate for targeted biopsy. While results of the PRIMARY trial were disseminated after our protocol was designed, it also uses a SUVmax of 4.0 as at this stage the sensitivity for csPCa was 92%[19]. This may be adjusted following quantitative analysis of thresholds, (liver and background prostate in particular), for the presence of malignancy, although the PRIMARY trial would suggest that adjustments will not be required[19].

Co-registration of the PSMA-PET/CT with mpMRI prostate

After both diagnostic imaging arms have been independently reported, co-registration of the two modalities will be performed using the GE Advantage Workstation® (General Electric, Boston, Massachusetts, United States) software Reporting of co-registered PSMA-PET/CT with mpMRI images will be performed by an experienced dual-trained radiologist with PET accreditation and experience of reporting prostate mpMRI. A synoptic report will describe lesions seen on the mpMRI alone, PSMA-PET/CT alone, followed by the result of the co-registration process to determine concordance between 18F-DCFPyL PSMA-PET and mpMRI and the reader's subjective likelihood of the presence of csPCa will be reported. Lesions will be numbered to enable accurate cataloguing at time of prostate biopsy, and visually represented on the PI-RADS version 2.1 prostate map.

Prostate Biopsy

Prostate biopsy procedure

The referring urologist will have access to reports and images for both diagnostic imaging modalities and PSMA-PET/MRI co-registration results in order to make a clinical decision regarding prostate biopsy. Subjects with any positive and/or equivocal findings in either diagnostic imaging arm are recommended to undergo a targeted biopsy of all lesions and a systematic biopsy for histopathological analysis. Targeting is accomplished via cognitive fusion at time of biopsy. The study recommends a standardised transperineal ultrasound guided template biopsy format perfumed under general anaesthesia. A minimum of four cores of any targeted lesion and minimum 24 systematic cores to be taken. Subjects with no abnormalities on mpMRI and PSMA PET/CT are recommended to have a systematic biopsy (24 cores). All biopsies are performed by surgeons

already trained in and practicing the transperineal biopsy route, thus minimising variability and possible confounders.

Histopathology

Biopsy specimens will be labelled based on location and whether obtained through targeted or systematic prostate biopsy. Reporting of the prostate biopsy will be performed by genito-urinary histopathologists at each site using standardized proformas, detailing the number of cores taken, location (including the index lesion), histological subtype, and International Society of Urological Pathology (ISUP) grade group, number of positive cores per site, percentage and longest length of cancer in one core and perineural invasion[27].

Study assessment

Study objective and endpoints

The endpoints of this study are summarised in Table 2. The primary objective is to assess for diagnostic superiority of PSMA-PET/CT in combination with mpMRI in detection of lesions with any ISUP grade prostate cancer. Specifically, cancer detection rates, sensitivity, specificity, negative predictive values, positive predictive values and AUC are explored. The secondary outcomes involve detection of csPCa.

Table 2. PEDAL Study endpoints

Primary endpoint
• Comparison of diagnostic accuracy of mpMRI prostate to PSMA-PET/CT alone and in combination with mpMR in the detection of prostate cancer (any ISUP) per patient and per lesion.
Secondary endpoints
• Detection of clinically significant (ISUP Grade Group ≥2) primary prostate cancer at prostate biopsy • Detection of radiologically significant lesions in the prostate at PSMA-PET/CT and MRI co-registration. • Detection of radiological evidence of metastatic lesions on PSMA-PET/CT and/or mpMRI Prostate. • Number of adverse events reported during and post-administration of radiotracer for PSMA PET/CT.
ISUP= International Society of urological Pathology; mpMRI= multiparametric magnetic resonance imaging; PSMA=prostate specific membrane antigen; PET/CT=positron emission tomography / computed tomography,

Sample size and Power Calculation

The trial will proceed to recruit to an ideally powered sample size of 240 subjects to achieve a power of 0.80. Sample size calculations were based on the primary endpoint of detection of all ISUP grade prostate cancer detection. Area under the receiver operator characteristic (ROC) curve (the AUC), sensitivity and specificity for mpMRI and PSMA-PET/CT are 0.84, 0.603 and 0.89[28], and 0.91, 0.88 and 0.93[29] respectively. The following assumptions were made for sample size calculations: 50% of men who undergo prostate biopsy will be diagnosed with prostate cancer, , the proportion of cases (PSMA PET/CT as opposed to mpMRI) is 20% higher, the absolute margin of improvement is 7% (0.35 to 0.42) to declare PSMA-PET/CT is superior, the estimated correlation between the two tests is 80% and a two-sided type I error of 5%. In addition, this sample size makes allowance for a dropout rate of 10%.

Blinding

Blinding occurs at the level of the clinician reviewing the imaging and biopsy specimens. Separate clinicians review the mpMRI, PSMA-PET/CT and co-registered PMSA-PET/CT and mpMRI images, with each clinician blinded to the results of the other two imaging assessment modalities. The uropathologist will receive tissue samples labelled as a systematic or targeted biopsy and its position, however is blinded to the results of PI-RADS score or PSMA-PET/CT positivity.

Results and Outcomes

Summary tables will be prepared giving numbers of participants by arm, disease assessment compliance, eligibility infringements and losses to follow-up. Baseline characteristics by treatment arm will be summarized in frequency tables by the use of descriptive statistics for variables. Ninety-five percent confidence intervals (95% CI) for differences between arms of all important endpoints will be calculated, and p-values will be two-sided. Exact tests will be performed with binary outcome data.

Diagnostic Accuracy

To determine diagnostic accuracy of PSMA PET/CT compared to mpMRI prostate in the detection of csPCa, findings of imaging will be compared to prostate biopsy histopathology to determine presence or absence of cancer. Clinically significant prostate cancer at prostate biopsy is defined as ISUP Grade Group ≥2. For the primary objective, positivity will be defined by histological confirmation of cancer at prostate biopsy.

Accuracy of each diagnostic imaging arm will be assessed by the AUC. mpMRI accuracy will be compared to PSMA PET/CT alone, and in combination with mpMRI. Point estimates of the sensitivity and specificity of each modality alone will be determined, and approximations to their distributions will be estimated using the normal approximation to the binomial distribution. Using independence of the sensitivity and specificity, the AUC will be calculated as the mean of the estimated sensitivity and specificity, and its variance as the sum of the variances of the sensitivity and specificity. Equivocal lesions will be considered negative for clinical purposes, however these lesions will be targeted during biopsy and a sensitivity analysis will be performed in which lesions rated as equivocal will be considered positive for malignancy. The difference between the AUCs will be used to characterise the true underlying difference between AUC's of the two modalities and to apply a hypothesis test for the existence of a clinically important difference between them (the null hypothesis will be a 7% difference).

Risks of PSMA-PET/CT

Several preclinical and clinical studies have shown the safety of 18F-PSMA. The critical dose-organs are the kidneys (0.0945 mSv/MBq) and urinary bladder (0.085 mSv/MBq) and were calculated from human biodistribution data using OLINDA/EXM (Organ Level Internal Dose Assessment/Exponential Modelling) software. Based on the FDA, a single-organ dose of 0.05 Sv is allowable. This corresponds to an activity of 400 MBq (10.8 mCi) of 18F-PSMA for a 70-100 kg male subject with a prostate cancer, well above the doses used in this study. Accordingly, the effective dose expected to the whole body is 0.0066 Sv, which is below the 0.03 Sv upper limit recommended by the Food and Drug Administration (FDA).

Adverse events and contraindications

No adverse effects due to intravenous administration of 18 F-PSMA for imaging have been reported in the published literature. There are no known contraindications for 18F-PSMA. Overall,18F-PSMA PET scan may be used in clinical research with no risk to subjects with PCa.

Acute adverse events, defined as those experienced by the subject at the time of radiotracer administration and during the two hours following injection will be recorded. Any toxicity will be graded by NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0[30].

Discussion

The drive to accurately detect intraprostatic and extraprostatic disease at the time of prostate cancer diagnosis has led to the intense interest in PSMA-PET/CT as an adjunct to mpMRI prostate. PSMA PET/CT has shown to be highly useful in the setting of high-risk disease and biochemical failure post-radical treatment[31,32], however its utility as a diagnostic tool for prostate cancer evaluation until recently[19], there has had minimal high-quality prospective data. Our hypothesis is that PSMA-PET/CT will be superior in diagnostic accuracy to mpMRI prostate at identifying cancer within the prostate. As mpMRI prostate is established in its ability to successfully identify prostate cancer, this is a high standard to achieve. Even if PSMA-PET/CT does not supersede mpMRI prostate in diagnostic accuracy, establishing comparable diagnostic accuracy may result in a viable alternative for men who have contraindications to mpMRI.

The trial may also demonstrate (i) a synergistic effect in cancer diagnosis by the combination of the two imaging techniques, (ii) a benefit for PSMA-PET/CT in men with equivocal mpMRI prostate findings; (iii) benefit for men with concerning clinical features but negative/equivocal mpMRI prostate; and (iv) provide an all-encompassing diagnostic and staging scan for men who have high risk features for metastatic disease at diagnosis. Unlike the PRIMARY trial, our PSMA-PET/CT

protocol encompasses chest, abdomen and pelvis, so will be able to add valuable information to this outcome.

Proprietary software from the GE Advantage® Workstation will perform co-registration between mpMRI prostate and PSMA-PET/CT images will be utilised in this trial. Co-registration has potential to improve targeting of prostate biopsy techniques, and help provide an alternative to expensive, difficult to access hybrid PET/MRI machines.

After diagnostic accuracy of PSMA-PET/CT is established, its potential for significant economic impact as a diagnostic test can be thoroughly investigated. Reductions in prostate biopsy, efficiencies in consolidation of diagnostic and staging imaging tests, and using software co-registration as an alternative to hybrid PET/MRI all represent potential economic benefits to our health system.

The PEDAL trial commenced in March 2020, and although recruitment has been delayed due to Covid 19 related adjustments in health care delivery the current aim is to complete recruitment in 36 months. This innovative study will add valuable evidence to demonstrate the diagnostic accuracy of PSMA-PET/CT. It has potential to significantly impact how prostate cancer is diagnosed.

Funding statement

This clinical trial is supported by Cyclotek (Aust) Pty Ltd and their key partners, the Australian Government as part of its CRC Projects Program, General Electrical Healthcare, Macquarie University and the EJ Whitten Prostate Cancer Research Centre at Epworth Healthcare. We are also grateful for philanthropic donations from Reese Limited, the Pitcher and Cicutto families via the St Vincent's Foundation.

Participating Centres

- St Vincent's Hospital, Melbourne VIC

- St Vincent's Private Hospital, Melbourne VIC
- The Royal Melbourne Hospital, VIC
- Epworth Healthcare, VIC
- Sydney Adventist Hospital, NSW
- Pacific Radiology Canterbury, Christchurch NZ

Declaration of Interests

The authors confirm that there are no relevant financial or non-financial competing interests to report.

CONTRIBUTORSHIP STATEMENT

- Dr. Vy Tran: protocol design, ethical submission, procurement of funding, data collection, statistical analysis, manuscript preparation, patient care, supervision
- Dr Anne Hong: manuscript preparation, statistical analysis
- A/Prof. Tom Sutherland: protocol design, ethical submission, procurement of funding, data collection, statistical analysis, manuscript preparation, patient care, supervision
- Dr. Kim Taubman: protocol design, ethical submission, procurement of funding, data collection, statistical analysis, manuscript preparation, patient care, supervision
- Dr. Su-Faye Lee: protocol design, ethical submission, procurement of funding, data collection, statistical analysis, manuscript preparation, patient care, supervision
- Dr. Daniel Lenaghan: patient care, supervision
- Dr. Kapil Sethi: patient care, supervision
- A/Prof. Niall Corcoran: patient care, supervision
- A/Prof. Nathan Lawrentschuk: patient care, supervision
- Prof. Henry Woo: patient care, supervision
- Dr. Lisa Tarlinton: patient care, supervision
- Prof. Damien Bolton: manuscript preparation, supervision
- Dr. Tim Spelman: patient care, data collection, statistical analysis, supervision
- Ms. Lauren Thomas: patient care, data collection
- Mr. Russell Booth: patient care, data collection
- Dr. Justin Hegarty: patient care, data collection
- Dr. Elisa Perry: patient care, data collection
- A/Prof. Lih-Ming Wong: protocol design, ethical submission, procurement of funding, data collection, statistical analysis, manuscript preparation, patient care, supervision

References

1 Australian Institute of Health and Welfare Canberra. *Cancer in Australian 2019*, <https://www.aihw.gov.au/reports/cancer/cancer-in-australia-2019/data> (2021).

2 Mottet N, Bellmunt J, Bolla M *et al.* EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *Eur Urol* 2017; **71**: 618-629.

3 Whish-Wilson T, Costello D, Finch S, Sutherland T & Wong L M Funding of prostate magnetic resonance imaging leads to fewer biopsies and potential savings to health systems in the management of prostate cancer. *BJU Int* 2021; **127 Suppl 1**: 6-12.

4 Ahmed H U, El-Shater Bosaily A, Brown L C *et al.* Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. *Lancet* 2017; **389**: 815-822.

5 Sathianathen N J, Omer A, Harriss E *et al.* Negative Predictive Value of Multiparametric Magnetic Resonance Imaging in the Detection of Clinically Significant Prostate Cancer in the Prostate Imaging Reporting and Data System Era: A Systematic Review and Meta-analysis. *Eur Urol* 2020; **78**: 402-414.

6 Kasivisvanathan V, Rannikko A S, Borghi M *et al.* MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. *N Engl J Med* 2018; **378**: 1767-1777.

7 Sonn G A, Fan R E, Ghanouni P *et al.* Prostate Magnetic Resonance Imaging Interpretation Varies Substantially Across Radiologists. *Eur Urol Focus* 2019; **5**: 592-599.

8 Borofsky S, George A K, Gaur S *et al.* What Are We Missing? False-Negative Cancers at Multiparametric MR Imaging of the Prostate. *Radiology* 2018; **286**: 186-195.

9 Elkhoury F F, Felker E R, Kwan L *et al.* Comparison of Targeted vs Systematic Prostate Biopsy in Men Who Are Biopsy Naive: The Prospective Assessment of Image Registration in the Diagnosis of Prostate Cancer (PAIREDCAP) Study. *JAMA Surg* 2019; **154**: 811-818.

10 Hicks R M, Simko J P, Westphalen A C *et al.* Diagnostic Accuracy of (68)Ga-PSMA-11 PET/MRI Compared with Multiparametric MRI in the Detection of Prostate Cancer. *Radiology* 2018; **289**: 730-737.

11 Margel D, Bernstine H, Groshar D *et al.* Diagnostic Performance of (68)Ga Prostate-specific Membrane Antigen PET/MRI Compared with Multiparametric MRI for Detecting Clinically Significant Prostate Cancer. *Radiology* 2021; **301**: 379-386.

12 Chang S S Overview of prostate-specific membrane antigen. *Rev Urol* 2004; **6 Suppl 10**: S13-18.

13 Perner S, Hofer M D, Kim R *et al.* Prostate-specific membrane antigen expression as a predictor of prostate cancer progression. *Hum Pathol* 2007; **38**: 696-701.

14 Davenport M S, Montgomery J S, Kunju L P *et al.* (18)F-Choline PET/mpMRI for Detection of Clinically Significant Prostate Cancer: Part 1. Improved Risk Stratification for MRI-Guided Transrectal Prostate Biopsies. *J Nucl Med* 2020; **61**: 337-343.

15 Hofman M S, Lawrentschuk N, Francis R J *et al.* Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. *Lancet* 2020; **395**: 1208-1216.

16 Afshar-Oromieh A, Zechmann C M, Malcher A *et al.* Comparison of PET imaging with a (68)Ga-labelled PSMA ligand and (18)F-choline-based PET/CT for the diagnosis of recurrent prostate cancer. *Eur J Nucl Med Mol Imaging* 2014; **41**: 11-20.

17 Koschel S, Murphy D G, Hofman M S & Wong L M The role of prostate-specific membrane antigen PET/computed tomography in primary staging of prostate cancer. *Curr Opin Urol* 2019; **29**: 569-577.

18 Perera M, Papa N, Roberts M *et al.* Gallium-68 Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer-Updated Diagnostic Utility, Sensitivity, Specificity, and Distribution of Prostate-specific Membrane Antigen-avid Lesions: A Systematic Review and Meta-analysis. *Eur Urol* 2020; **77**: 403-417.

19 Emmett L, Buteau J, Papa N *et al.* The Additive Diagnostic Value of Prostate-specific Membrane Antigen Positron Emission Tomography Computed Tomography to Multiparametric Magnetic Resonance Imaging Triage in the Diagnosis of Prostate Cancer (PRIMARY): A Prospective Multicentre Study. *Eur Urol* 2021; **80**: 682-689.

20 Gaur S, Mena E, Harmon S A *et al.* Prospective Evaluation of (18)F-DCFPyL PET/CT in Detection of High-Risk Localized Prostate Cancer: Comparison With mpMRI. *AJR Am J Roentgenol* 2020; **215**: 652-659.

21 Lee M S, Cho J Y, Kim S Y *et al.* Diagnostic value of integrated PET/MRI for detection and localization of prostate cancer: Comparative study of multiparametric MRI and PET/CT. *J Magn Reson Imaging* 2017; **45**: 597-609.

22 Anconina R, Hawsawy A, Ortega C, Veit-Haibach P, Ghai S & Metser U Detection of clinically significant prostate cancer with ¹⁸F-DCFPyL (PSMA) PET/MR compared to mpMR alone: preliminary results of a prospective trial. *Journal of Nuclear Medicine* 2019; **60**: 1574-1574.

23 Muehlematter U J, Burger I A, Becker A S *et al.* Diagnostic Accuracy of Multiparametric MRI versus (68)Ga-PSMA-11 PET/MRI for Extracapsular Extension and Seminal Vesicle Invasion in Patients with Prostate Cancer. *Radiology* 2019; **293**: 350-358.

24 Afshar-Oromieh A, Haberkorn U, Schlemmer H P *et al.* Comparison of PET/CT and PET/MRI hybrid systems using a 68Ga-labelled PSMA ligand for the diagnosis of recurrent prostate cancer: initial experience. *Eur J Nucl Med Mol Imaging* 2014; **41**: 887-897.

25 Grubmüller B, Baltzer P, Hartenbach S *et al.* PSMA Ligand PET/MRI for Primary Prostate Cancer: Staging Performance and Clinical Impact. *Clin Cancer Res* 2018; **24**: 6300-6307.

26 Australian Government Department of Health. *New Medicare Benefits Scheme (MBS) Items for multiparametric magnetic resonance imaging (mpMRI) of the prostate 2018*, <http://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/Factsheet-MRIProstate> (2018).

27 van Leenders G J L H, van der Kwast T H, Grignon D J *et al.* The 2019 International Society of Urological Pathology (ISUP) Consensus Conference on Grading of Prostatic Carcinoma. *The American Journal of Surgical Pathology* 2020; **44**.

28 Li M, Huang Z, Yu H, Wang Y, Zhang Y & Song B Comparison of PET/MRI with multiparametric MRI in diagnosis of primary prostate cancer: A meta-analysis. *Eur J Radiol* 2019; **113**: 225-231.

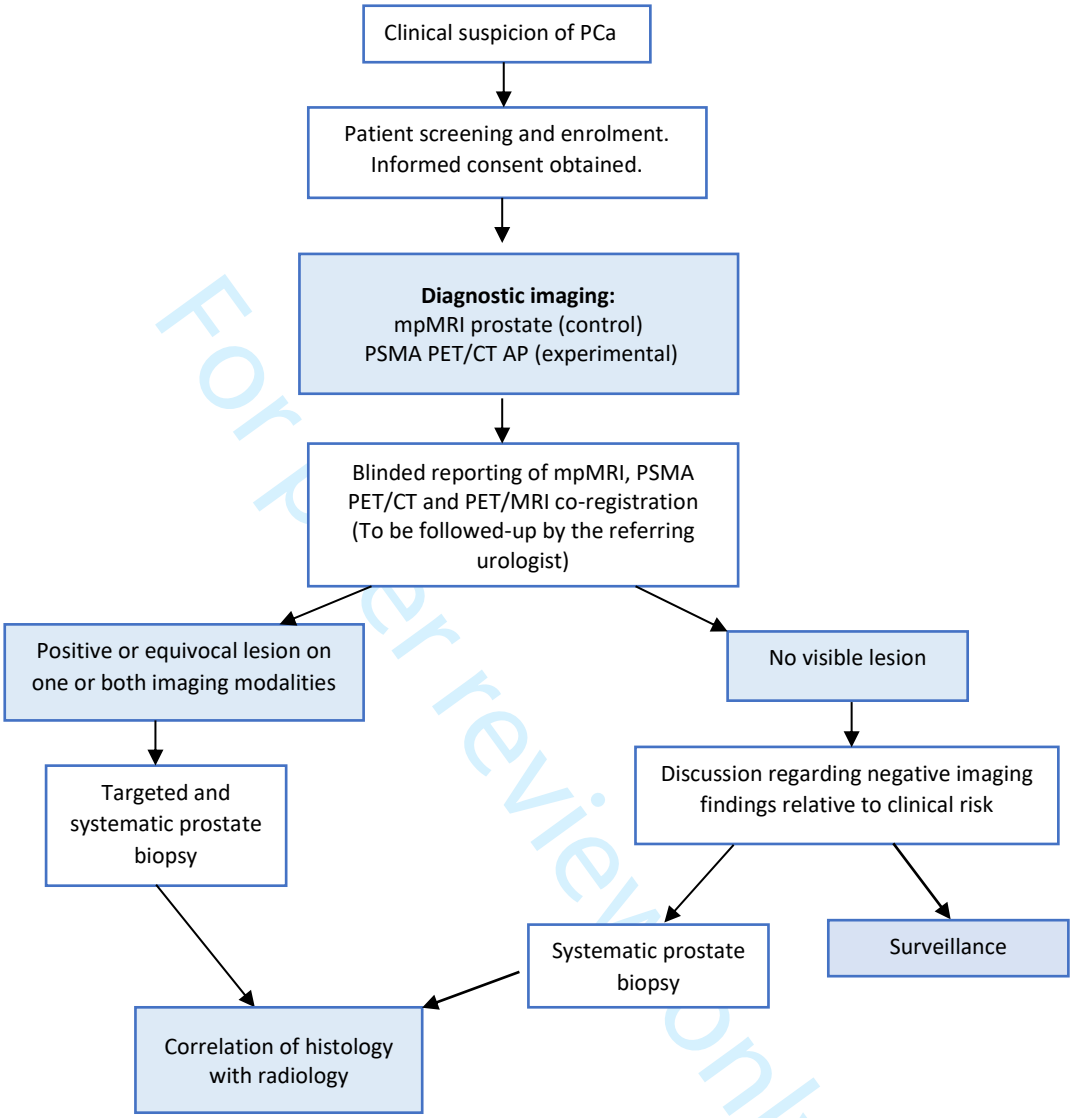
29 Scheltema M J, Chang J I, Stricker P D *et al.* Diagnostic accuracy of (68) Ga-prostate-specific membrane antigen (PSMA) positron-emission tomography (PET) and multiparametric (mp)MRI to detect intermediate-grade intra-prostatic prostate cancer using whole-mount pathology: impact of the addition of (68) Ga-PSMA PET to mpMRI. *BJU Int* 2019; **124 Suppl 1**: 42-49.

30 National Cancer Institute. *NCI Common Terminology Criteria for Adverse Events*, <https://evs.nci.nih.gov/ftp1/CTCAE/About.html> (2017).

31 Koschel S, Taubman K, Sutherland T *et al.* Patterns of disease detection using [(18)F]DCFPyL PET/CT imaging in patients with detectable PSA post prostatectomy being considered for salvage radiotherapy: a prospective trial. *Eur J Nucl Med Mol Imaging* 2021; **48**: 3712-3722.

32 Perry E, Talwar A, Taubman K *et al.* [(18)F]DCFPyL PET/CT in detection and localization of recurrent prostate cancer following prostatectomy including low PSA < 0.5 ng/mL. *Eur J Nucl Med Mol Imaging* 2021; **48**: 2038-2046.

Figure 1: PEDAL Trial Schema



Appendix 1: Multiparametric Magnetic Resonance Imaging Protocol

IMAGING ACQUSITION:

MRI prostate imaging is acquired as per international guidelines specified by Prostate Imaging-Reporting and Data System, version 2.1 (PIRADS V2.1).

A multi-parametric MRI scan will be performed according to the following technical protocol, consistent with the highest standards of prostate MRI after appropriate bowel preparation (suggest Microlax suppository morning of diagnostic imaging) and buscopan or glucagon injection (where not contraindicated):

- 3-Tesla magnet field strength
- 32-channel cardiac coil, anteriorly and spinal coil posteriorly
- T2 sequences to show pathology, aid localisation of the lesion, and to fuse with ultrasound for those Urologists using co-registration biopsy method.
    - High resolution T2 FSE in 3 planes: axial, coronal and sagittal
    - 3D T2 sequence

Diffusion-Weighted Imaging (DWI) with software derived Apparent Diffusion Co-efficient (ADC) quantitative analysis maps, and multiple b-values (acquired b50, acquired b1400, calculated b2000);

Dynamic Contrast Enhanced imaging (DCE) 3D imaging, with IV gadolinium DTPA bolus determined by body weight, at 2.5ml/second followed by T1 DCE TRICKS (Time-Resolved Imaging of Contrast KineticS).

Analysis of DCEI according to PI-RADS DCEI analytic guidelines using PROCAD software

· No use of Endo-rectal coils or MR Spectroscopy as per current guidelines

· Approximate scan time 30 to 40 minutes

CONTRAINDICATIONS TO MRI

Patient with any contraindication to MRI will not undergo MRI. This includes, but not restricted, to pacemaker or other electronic implants, total hip joint replacement, known metal in the orbit, MR incompatible surgical or cerebral aneurysm clips, shrapnel, non-removable body piercings.

REPORTING OF MPMRI PROSTATE

The mpMRI will be reported by experienced subspecialist Radiologists according to the Prostate Imaging-Reporting and Data System, version 2.1, with each lesion categorised on a scale from 1 to 5.

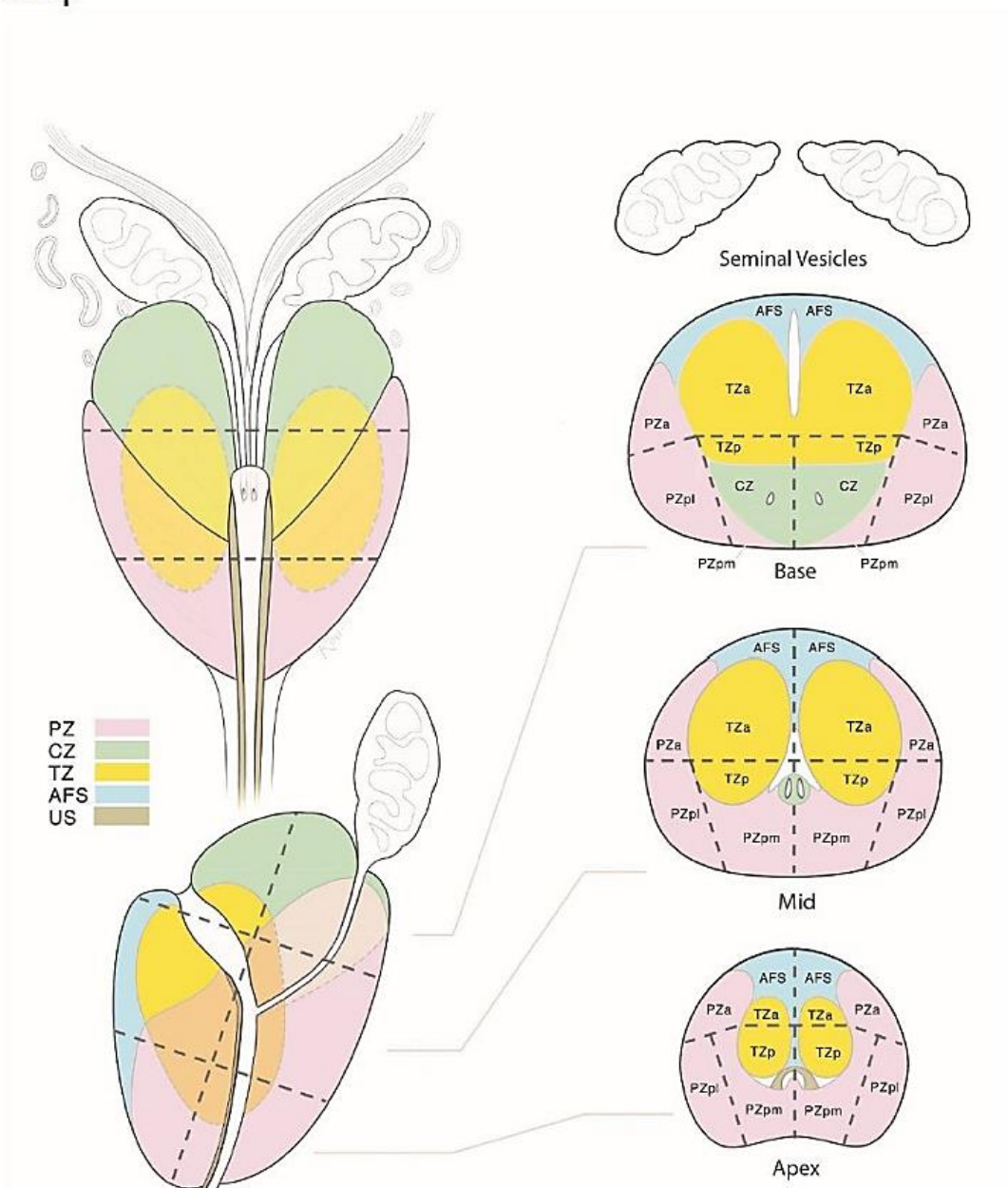
OPTIMIZATION OF CO-REGISTRATION BETWEEN MPMRI PROSTATE AND PSMA-PET/CT

To enable better co-registration of mpMRI to PSMA-PET/CT:

- option to use of suppositories to help eliminate gas/faeces from rectum
- ensure flat pelvis
- Use of structured knee bolster and strapping of feet to aid pelvic alignment

Appendix 2: Prostate Imaging-Reporting and Data System (version 2.1) Sector Map

Sector Map



American College of Radiology® 2019 31 PI-RADSv2.1

Appendix 3: 18F-DCFPyL PSMA administration and PET/CT Imaging Protocol

RADIOPHARMACEUTICAL

18F DCFPyL will be produced at Cyclotek (Aust) Pty Ltd under GMP Licence Number MI-12092005-LI-000904-2 and (parametric) release after certain quality control tests are performed and transported to the imaging site under regulatory criteria for dangerous goods. Cyclotek will provide the imaging site with a Quality Control Release notification form. Patients will complete the radiopharmaceutical consent form at their local site prior to injection.

18F-DCFPYL PSMA INJECTION DOSING AND ADMINISTRATION

Patients will be administered a single, intravenous 250MBq bolus dose of 18F-DCFPyL PSMA (acceptable: 200-300MBq depending on patient weight and activity provided on day of scan). The administered activity of 18F-DCFPyL PSMA is approximately 3MBq per kilogram body weight up to 350 maximum dose.

18F-PSR PET/CT imaging protocol for initial diagnosis/staging of Prostate Ca Imaging Protocol

Patient Preparation:

● No fasting required. (*Must be well hydrated, approximately 1-2 litres of plain water in the 2 hours before appointment.)

● The activity is administered intravenously through a cannula either utilising the automatic injector and a 100ml Saline bag or via hand injection through the cannula utilising the 5ml syringe shield and 2x10mls saline flushes.

● The dose pre and post syringe activities and times must be recorded to work out the exact administered activity for the injection time.

● Uptake Time: 120 minutes post 18F-DCFPyL injection. The patient is free to leave the department if they wish during this waiting time.

● Patient to void before the scan

SCANNER

Patients will be imaged on a GE Discovery 690 or 710 PET/CT (General Electric Medical Systems, Milwaukee, WI) combining a 64 slice multidetector CT scanner with a dedicated, full ring PET scanner with lutetium-based crystals.

Scan:

Scan range: Mid/Upper thighs to Lung Apices. Patient position supine, arms up and feet first to ensure bladder is in its emptiest state. CT scan acquired using a low-dose protocol (120/140 kVp and automatic exposure control ('Smart mA', max 200mA). Low-dose attenuation correction CT images were acquired and reconstructed to a 3.75mm slice thickness with an increment of 3.27mm using iterative reconstruction (50% ASiR). PET images were acquired at 3.5min/bed through the pelvis and 3.0min/bed to the lung apices. PET images were reconstructed from time of flight emission data using VUE Point FX and Q-Clear™ iterative technique with β value of 400. Q-Clear™ is a fully convergent reconstruction method which incorporates point spread function corrections, scatter correction and ULD-CT attenuation corrections. Sharp IR function was applied with no Z-axis filter. PET images were reconstructed on a 256 matrix.

PET/CT 18F-PSR <90kg 120min post injection

kV 120, Smart mA 200, noise index 30

3.5min over pelvis (2)

3.0min for rest of body (4)

Total: 6 beds ~ 19min

PET/CT 18F-PSR >90kg 120min post injection

kV 140, Smart mA 200, noise index 32

4.0min over pelvis (2)

3.5min for rest of body (4)

Total: 6 beds ~ 22min

Image Reconstruction: Images are reconstructed using the Q.Clear GE reconstruction method with a β value of 400.

Workstation used for scan interpretation: GE AW Server 3.2 Ext 1.0 or Inteleviewer.

BMJ Open

PEDAL Protocol: A prospective single arm paired comparison of multiparametric MRI and 18F-DCPFyl PSMA PET/CT to diagnose prostate cancer

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-061815.R1
Article Type:	Protocol
Date Submitted by the Author:	10-Jul-2022

Complete List of Authors:	Tran, Vy; St Vincent's Hospital Melbourne Pty Ltd, Urology; The University of Melbourne, Faculty of Medicine, Dentistry and Health Sciences Hong, Anne; Austin Health, Urology Sutherland, Tom; The University of Melbourne, Department of Medicine; St Vincent's Hospital Melbourne Pty Ltd, Medical Imaging Department Taubman, Kim; St Vincent's Hospital Melbourne Pty Ltd, Nuclear Medicine Lee, Su-Faye; St Vincent's Hospital Melbourne Pty Ltd, Nuclear Medicine Lenaghan, Daniel; St Vincent's Hospital Melbourne Pty Ltd, Urology Sethi, Kapil; St Vincent's Hospital Melbourne Pty Ltd, Urology Corcoran, Niall; The Royal Melbourne Hospital City Campus, Urology Lawrentschuk , Nathan; The University of Melbourne, Surgery; The Royal Melbourne Hospital City Campus, Urology Woo, H; Sydney Adventist Hospital, Urology; The University of Sydney, Surgery Tarlinton, Lisa; Sydney Adventist Hospital, San Radiology and Nuclear Medicine Bolton, Damien ; Austin Hospital; The University of Melbourne, Surgery Spelman, Tim; The University of Melbourne Thomas, Lauren; St Vincent's Hospital Melbourne Pty Ltd, Nuclear Medicine Booth, Russell; St Vincent's Hospital Melbourne Pty Ltd, Nuclear Medicine Hegarty, Justin; Pacific Radiology Christchurch Perry, Elisa; Pacific Radiology Christchurch Wong, Lih-Ming; St Vincent's Hospital Melbourne Pty Ltd, Urology; The University of Melbourne, Surgery
Primary Subject Heading:	Urology
Secondary Subject Heading:	Surgery, Research methods
Keywords:	Prostate disease < UROLOGY, Magnetic resonance imaging < RADIOLOGY & IMAGING, Nuclear radiology < RADIOLOGY & IMAGING

Category: Original Research

Title: PEDAL Protocol: A prospective single arm paired comparison of multiparametric MRI and 18F-DCPFyl PSMA PET/CT to diagnose prostate cancer

Authors:

Vy Tran[1,2], Anne Hong[3], Tom Sutherland[4], Kim Taubman[5], Su-Faye Lee[4], Daniel Lenaghan[1], Kapil Sethi[1], Niall Corcoran[6,7], Nathan Lawrentschuk[8,9], Henry Woo[10,11], Lisa Tarlinton[12], Damien Bolton[3,13], Tim Spelman[14], Lauren Thomas[5], Russell Booth[5], Justin Hegarty[15], Elisa Perry[15], Lih-Ming Wong[1,13]*

1. St Vincent's Hospital Melbourne, Department of Urology, VIC, AUS
2. ` University of Melbourne, Faculty of Medicine, Dentistry and Health Sciences, Melbourne, VIC, AUS
3. Austin Health, Department of Urology, VIC, AUS
4. St Vincent's Hospital Melbourne, Department of Medical Imaging, VIC, AUS
5. St Vincent's Hospital Melbourne, Department of Nuclear Medicine, VIC, AUS
6. The Royal Melbourne Hospital, Department of Urology, Parkville, VIC, AUS
7. University of Melbourne Victorian Comprehensive Cancer Centre, Parkville, VIC, AUS
8. Peter MacCallum Cancer Centre, Melbourne, VIC, AUS
9. Epworth HealthCare, EJ Whitten Prostate Cancer Research Centre, Melbourne, VIC, AUS
10. Sydney Adventist Hospital, Department of Urology, NSW, AUS
11. The University of Sydney, NSW, AUS
12. Sydney Adventist Hospital, San Radiology and Nuclear Medicine, NSW, AUS
13. Department of Surgery, The University of Melbourne, Melbourne, VIC, AUS
14. The University of Melbourne, Melbourne, VIC, AUS
15. Pacific Radiology Christchurch, Canterbury, NZ

***Corresponding Author**

A/Prof Lih-Ming Wong

Department of Urology, St Vincent's Hospital Melbourne

Department of Surgery, University of Melbourne

Email: lihmingwong@gmail.com

Abstract word count: 298

Manuscript word count: 3801

Number of figures: 1

Number of tables: 2

Abstract

Introduction:

Prostate specific membrane antigen positron emission tomography (PSMA-PET) has emerged as valuable imaging to assessing metastatic disease in prostate malignancy. However, there has been limited studies exploring the utility PSMA-PET as primary imaging assessing for index lesions prior to biopsy. The primary objective of this study is to compare the diagnostic accuracy of 18-fluorine PSMA (18F DCFPyL PSMA) PET scans to multiparametric magnetic resonance imaging (mpMRI) to detect primary prostate cancer at prostate biopsy.

Methods and Analysis:

The PEDAL trial is a multicentre, prospective, single-arm, paired comparison, non-randomised phase III trial in subjects considered for diagnostic prostate biopsy. Subjects who are eligible for a diagnostic mpMRI prostate will undergo additional same-day 18-F DCFPyl PSMA PET/CT of the chest, abdomen and pelvis. Software co-registration of the mpMRI and PSMA-PET/CT images will be performed. The reporting of the mpMRI prostate, PSMA-PET/CT and PSMA PET/MRI co-registration will be performed blinded.

The diagnostic accuracy of PSMA PET/CT alone, and in combination with mpMRI, to detect prostate cancer will be assessed. Histopathology at prostate biopsy will be used as the reference standard. Sample size calculations estimate that 240 subjects will need to be recruited to demonstrate 20% superiority of PSMA-PET/CT.

The sensitivity, specificity, positive predictive value and negative predictive value of the combination of mpMRI prostate and PSMA PET/CT compared to targeted and systematic prostate biopsy will be evaluated. It is hypothesised that PSMA PET/CT combined with mpMRI prostate will have improved diagnostic accuracy compared to mpMRI prostate alone for detection of prostate cancer in biopsy-naïve men, resulting in a significant impact on patient management.

Ethics and Dissemination:

This study was approved by the independent Human Research Ethics Committee and is a registered trial (Trial registration number: ACTRN12620000261910). Results will be published in peer-reviewed medical journals with eligible investigators will significantly contribute.

Strengths and Limitations

- This is a multicentre study.
- A strength of this study is its prospective nature of the study design controlled by using patients own biopsy results as comparator, thus limiting confounders.
- This is an adequately powered study with objective primary and secondary outcome measures.
- Potential limitations pertain to generalisability of results given use of DCFPYL tracer for PSMA-PET/CT. There are currently limited studies directly comparing different PSMA-PET tracers.

Keywords:

prostate cancer, diagnosis, PSMA PET, multiparametric MRI, PSMA, imaging

Introduction

Prostate cancer (PCa) is very common, with one in six men being diagnosed before the age of 85 years[1]. The age-standardised incidence rate has increased from 80 cases per 100,000 males to 141 cases per 100,000 males since 1982, likely driven by the implementation of prostate-specific antigen (PSA) screening. With the growing incidence of disease, prostate imaging and biomarkers[2, 3] has become increasingly important in the diagnostic evaluation of prostate cancer to detect clinically significant prostate cancer (csPCa, Grade group ≥2) and assess tumour burden.

In Australia, multiparametric magnetic resonance imaging (mpMRI) of the prostate gland has also become available under Australian government funded rebate for diagnostic evaluation of suspected prostate cancer and active surveillance of low-risk prostate cancer with economic analysis suggesting significant savings to the health system[4, 5]. mpMRI offers reliable visualisation and characterisation of csPCa compared to the traditional transrectal ultrasound (TRUS), and is seen to have greater sensitivity of detection for lesions greater than 1cm, Gleason score of ≥7 and index lesions compared to satellite lesions, thus enabling better selection of patients for prostate biopsy[6]. In a meta-analysis of 42 studies, the pooled negative predictive value of mpMRI was reported to be 90.8 – 97%[7]. mpMRI-targeted prostate biopsy has been reported to detect more csPCa than systematic TRUS-guided biopsy (38% versus 26%)[8]. Nevertheless, mpMRI is not without limitations. Variable imaging quality, interreader variability, low specificity and missed or underestimated tumours remain an issue[9, 10]. The PAIREDCAP trial reported 15% of patients with negative mpMRI findings were found to have csPCa on systematic prostate biopsy[11].

Along with mpMRI, prostate-specific membrane antigen positron emission tomography (PSMA-PET) is one of the key advancements to emerge in prostate cancer assessment over the last two decades[12, 13]. Prostate specific membrane antigen (PSMA) is a type II transmembrane protein that is overexpressed on PCa cell membranes in all but 5 – 10% of cases, showing high specificity and

sensitivity relating to tumour aggressiveness and metastatic potential[14, 15]. 18F-Choline PET scans have been shown to improve risk stratification when used in conjunction with mpMRI[16] . This in conjunction with the prostate specific tracer of PSMA leads to strong support using PSMA-targeted PET imaging for staging of high-risk disease and biochemical recurrence [17-20]. In the proPSMA trial, PSMA PET/CT was demonstrated to have 27% greater accuracy than conventional staging (92% versus 65%) for pelvic or distant metastases, providing superior accuracy with fewer equivocal results and lower radiation exposure[17]. Moreover, recent evidence demonstrate that Ga-PSMA-11 intensity on PET/CT imaging is associated with Gleason score, and is more intense in those patients who underwent upgrading of their Gleason score at biopsy to Gleason score at radical prostatectomy[21], and could develop to be a new biomarker for prognosis in prostate cancer.

The use of PSMA PET/CT as a first line diagnostic tool for suspected prostate cancer is under investigation[22, 23]. The PRIMARY study[22] recently reported the additive value of pelvic-only 68Ga-PSMA PET/CT to a "triaged" mpMRI population to detect csPCa in men with suspicious for prostate cancer. The trial showed combined PSMA-PET/CT and MRI compared to MRI alone improved the negative predictive value (91% vs 72%, p<0.001) and sensitivity (97% vs. 83%, p<0.001). However, specificity was reduced (40% vs. 53%, p=0.01). Several other studies demonstrated similar results of improved sensitivity[12, 24]. Additionally, for equivocal lesions on mpMRI (i.e. PIRADS 3), PSMA-PET/CT may add to stratification of these lesions, with csPCa was more often detected when any focal PSMA uptake was detected 3/6 (50%), compared to those with no appreciable PSMA uptake 2/11 (18%) [25]. Finally, PSMA-PET/CT in addition to mpMRI showed increased sensitivity when detecting extraprostatic extension and seminal vesical invasion[26], although specificity reduced slightly[26], as seen in the PRIMARY trial. Hybrid PET/MRI scanners utilizing the 68Ga-PSMA ligand have also provided compelling evidence that it may be superior to

prostate mpMRI alone to detect csPCa, however use of these machines will be limited by cost and poor accessibility[27, 28].

Given the morbidity and mortality associated with prostate biopsy and prostate cancer treatment, the potential for improved diagnostic accuracy using PSMA PET/CT to localize prostate cancer in biopsy-naïve men warrants further investigation. The PEDAL trial is a prospective, single-arm paired comparison trial that aims to provide high quality evidence regarding the diagnostic accuracy of 18F-DCFPyl-PSMA PET/CT in conjunction with mpMRI prostate for primary diagnosis of prostate cancer.

Methods and Design:

Ethics

This clinical trial has been approved by the St Vincent's Hospital, Melbourne Human Research Ethics Committee (HREC 230/19) and is registered on the Australian New Zealand Clinical trials registry (ACTRN12620000261910). The current protocol is version 3, dated June 2019. It will be conducted in accordance with the International Conference on Harmonisation protocols and Good Clinical Practice. In addition, the trial will be conducted in compliance with all applicable laws and regulatory requirements relevant to the use of new therapeutic agents in Australia and any other participating country. Funding will be acquired through Cyclotek (manufacturer of DCFPYL), General Electrical Healthcare, and philanthropic grants. These parties will not be involved in study design; data processing and interpretation; writing of the report; and the decision to submit the report for publication.

The trial schema is outlined in Figure 1.

Patient and public involvement

No formal patient advisory committee was set up and there was no patient or public involvement in the design and planning of the study. The study was so designed as the mpMRI, PSMA-PET and prostate biopsy procedures used are not novel concepts or techniques, and are widely available in Australia as part of the Medicare system for which consumer and stakeholder comment is sought prior to inclusion of these interventions. Nevertheless, the patients are invited to provide feedback at each point of contact with the healthcare system. In addition, the results are intended for publication in peer reviewed medical journals.

Study design

This is a prospective single arm paired comparison diagnostic phase III trial in patients who are being considered for diagnostic prostate biopsy to detect prostate cancer. We aim to evaluate the role of PSMA-PET/CT in those with high clinical suspicion of prostate cancer. The PSMA-PET/CT, by identifying a suspicious lesion, is likely to impact the decision for prostate biopsy and the target location. The diagnostic accuracy of the imaging studies will be assessed by comparison of imaging results to prostate biopsy results. Any modifications and updates to study protocol will be communicated to the relevant parties via e-mail.

Patient screening, eligibility, and enrolment

Patients with features suspicious for PCa based on an abnormal PSA or DRE will be screened by a urologist for trial eligibility in the study according to the inclusion and exclusion criteria listed below in Table 1[29], and will be consented by the urologist (including for any ancillary studies). Where a substitute decision make is required, the legal next of kin or the power of attorney may consent in

the patient's stead. A target of 240 subjects will be recruited from multiple sites. Aside from the addition of PSMA PET/CT, all patients will follow routine care for prostate cancer and there are no specific interventions that are prohibited or permitted.

Table 1. Study inclusion and exclusion criteria

[Adapted from New Medicare Benefits Scheme (MBS) for mpMRI of the prostate][20]

Inclusion criteria
• Men (≥18 years) with an elevated PSA who are suitable for an eligible MBS mpMRI prostate: (MBS items 63541 and 63542) AND who have NOT had recent (≤3 years) prostate biopsy or mpMRI prostate. For MBS items 63541 and 63542 (NK) the patient must be suspected of having prostate cancer based on (*): a) DRE which is suspicious for prostate cancer; or b) in a person aged less than 70 years, at least prostate specific antigen (PSA) tests performed within an interval of 1- 3 months are greater than 3.0 ng/ml, and the free/total PSA ratio is less than 25% or the repeat PSA exceeds 5.5 ng/ml; or c) in a person aged less than 70 years, whose risk of developing prostate cancer based on family history is at least double the average risk, at least two PSA tests performed within an interval of 1- 3 months are greater than 2.0ng/ml, and the free/total PSA ratio is less than 25%; or d) in a person aged 70 years or older, at least two PSA tests performed within an interval of 1- 3 months are greater than 5.5ng/ml and the free/total PSA ratio is less than 25%. *NB: Relevant family history is a first degree relative with prostate cancer or suspected of carrying a BRCA 1, BRCA 2 mutation.*
• Patient has provided written informed consent for participation in trial
• In the opinion of the investigator, willing and able to comply with required study procedures
Exclusion criteria
• Known diagnosis of prostate cancer.
• Previous prostate biopsy within 3 years of recruitment. A transurethral resection of the prostate performed for primary purpose of alleviating lower urinary tract symptoms is considered acceptable.
• Previous mpMRI prostate within 3 years of recruitment.
• History of other active malignancy within the last 3 years, with the exception of non-melanoma skin cancer or melanoma in-situ.
• Any absolute contra-indication to 3T mpMRI prostate, or previous history of total hip joint replacement.
• Significant intercurrent morbidity that, in the judgement of the investigator, would limit compliance with study protocols.
DRE= digital rectal examination; mpMRI = multiparametric magnetic resonance imaging; PSA= prostate specific antigen

Follow-up

Participants will be followed-up by their referring urologist to discuss results and ongoing management of either PSA surveillance, active surveillance, radical treatment or non-curative treatment. Patient retention and follow-up is anticipated to be complete as the study patients require further testing (eg. Biopsy) to complete management of their prostate cancer.

Funding

Subjects will be informed of the costs of participation as part of the informed consent. For those eligible, the mpMRI will be funded through the Australian Government Department of Health Medicare Benefits Scheme (i.e. free of charge to the patient). The PSMA PET/CT will be funded through the clinical trial. The prostate biopsy will be funded as standard practice through the Medicare Benefits Scheme, private health insurance and subject. Subjects will not be paid for their participation and no participating clinical or researcher will be paid outside of their normal salary.

Diagnostic Imaging Procedures

All participants will undergo both the PSMA-PET/CT and mpMRI within four weeks of enrolment into this study and both scans performed on the same day to minimise disruption to participants' personal schedules. To standardize parameters of acquisition and image quality, these will be performed at an approved study centre.

Multiparametric MRI

All subjects will undergo 3-Tesla mpMRI prostate according to standard protocols (Appendix 1). The images will be reported by a single experienced Radiologist using the Prostate Imaging–Reporting

and Data System (PI-RADS) version 2.1 on a scale of 1 to 5 (Appendix 2). Any suspicious intraprostatic lesion described as PI-RADS 3 or greater will be considered a positive lesion with a targeted prostate biopsy recommended. The presence of extracapsular extension, seminal vesicle invasion, locoregional disease and subjective likelihood of csPCa will be recorded. The initial report of the mpMRI prostate will be blinded to the PSMA-PET/CT result.

PSMA-PET/CT

All participants will undergo PSMA-PET/CT imaging with18F-DCFPyL according to standard protocol (Appendix 3) at the participating site, on the same day as the mpMRI. The 18F-DCFPyL radiotracer will be produced in Australia and New Zealand by Cyclotek Pty Ltd, who will provide the local site with a Quality Control Release notification form. A single, intravenous bolus dose of 18F-DCFPyL PSMA (250MBq +/-50 MBq) will be administered with an uptake time of 120 minutes post 18F-DCFPyL injection. 18F-PSMA PET with CT chest, abdomen and pelvis will be performed for anatomic localisation and attenuation correction

PSMA-PET/CT images will be reported at a per-patient and per-lesion level by an experienced reader at each site. The initial report of PSMA-PET/CT will be blinded to the mpMRI prostate result. To standardise lesion imaging reporting, the intraprostatic lesions will be described according to the sector map specified in PI-RADS version 2.1 for mpMRI prostate. The PSMA intensity score (SUVmax), focality and ratio to background will be assessed. The reader will report disease location and extent, as well as assign a subjective likelihood for the presence of csPCa. All lesions with SUVmax scores of 4.0 or higher are deemed appropriate for targeted biopsy. While results of the PRIMARY trial were disseminated after our protocol was designed, it also uses a SUVmax of 4.0 as at this stage the sensitivity for csPCa was 92%[22]. This may be adjusted following quantitative analysis

of thresholds, (liver and background prostate in particular), for the presence of malignancy, although the PRIMARY trial would suggest that adjustments will not be required[22].

Co-registration of the PSMA-PET/CT with mpMRI prostate

After both diagnostic imaging arms have been independently reported, co-registration of the two modalities will be performed using the GE Advantage Workstation® (General Electric, Boston, Massachusetts, United States) software. Reporting of co-registered PSMA-PET/CT with mpMRI images will be performed by an experienced dual-trained radiologist with PET accreditation and experience of reporting prostate mpMRI. A synoptic report will describe lesions seen on the mpMRI alone, PSMA-PET/CT alone, followed by the result of the co-registration process to determine concordance between 18F-DCFPyL PSMA-PET and mpMRI and the reader's subjective likelihood of the presence of csPCa will be reported. Lesions will be numbered to enable accurate cataloguing at time of prostate biopsy, and visually represented on the PI-RADS version 2.1 prostate map.

Prostate Biopsy

Prostate biopsy procedure

The referring urologist will have access to reports and images for both diagnostic imaging modalities and PSMA-PET/MRI co-registration results in order to make a clinical decision regarding prostate biopsy. Subjects with any positive and/or equivocal findings in either diagnostic imaging arm are recommended to undergo a targeted biopsy of all lesions and a systematic biopsy for histopathological analysis. Targeting is accomplished via cognitive fusion at time of biopsy. The study recommends a standardised transperineal ultrasound guided template biopsy format perfumed under general anaesthesia. A minimum of four cores of any targeted lesion and minimum 24 systematic cores to be taken. Subjects with no abnormalities on mpMRI and PSMA PET/CT are

recommended to have a systematic biopsy (24 cores). All biopsies are performed by surgeons already trained in and practicing the transperineal biopsy route, thus minimising variability and possible confounders.

Histopathology

Biopsy specimens will be labelled based on location and whether obtained through targeted or systematic prostate biopsy. Reporting of the prostate biopsy will be performed by genito-urinary histopathologists at each site using standardized proformas, detailing the number of cores taken, location (including the index lesion), histological subtype, and International Society of Urological Pathology (ISUP) grade group, number of positive cores per site, percentage and longest length of cancer in one core and perineural invasion[30].

Study assessment

Study objective and endpoints

The endpoints of this study are summarised in Table 2. The primary objective is to assess for diagnostic superiority of PSMA-PET/CT in combination with mpMRI in detection of lesions with any ISUP grade prostate cancer. Specifically, cancer detection rates, sensitivity, specificity, negative predictive values, positive predictive values and AUC are explored. The secondary outcomes involve detection of csPCa as well as a cost evaluation using a decision curve analysis.

Table 2. PEDAL Study endpoints

Primary endpoint
• Comparison of diagnostic accuracy of mpMRI prostate to PSMA-PET/CT alone and in combination with mpMR in the detection of prostate cancer (any ISUP) per patient and per lesion.
Secondary endpoints
• Detection of clinically significant (ISUP Grade Group ≥2) primary prostate cancer at prostate biopsy • Detection of radiologically significant lesions in the prostate at PSMA-PET/CT and MRI co-registration. • Detection of radiological evidence of metastatic lesions on PSMA-PET/CT and/or mpMRI Prostate. • Number of adverse events reported during and post-administration of radiotracer for PSMA PET/CT. • Decision curve analysis
ISUP= International Society of urological Pathology; mpMRI= multiparametric magnetic resonance imaging; PSMA=prostate specific membrane antigen; PET/CT=positron emission tomography / computed tomography,

Sample size and Power Calculation

The trial will proceed to recruit to an ideally powered sample size of 240 subjects to achieve a power of 0.80. Sample size calculations were based on the primary endpoint of detection of all ISUP grade prostate cancer detection. Area under the receiver operator characteristic (ROC) curve (the AUC), sensitivity and specificity for mpMRI and PSMA-PET/CT are 0.84, 0.603 and 0.89[31], and 0.91, 0.88 and 0.93[32] respectively. The following assumptions were made for sample size calculations: 50% of men who undergo prostate biopsy will be diagnosed with prostate cancer, the proportion of cases (PSMA PET/CT as opposed to mpMRI) is 20% higher, the absolute margin of improvement is 7% (0.35 to 0.42) to declare PSMA-PET/CT is superior, the estimated correlation between the two tests is 80% and a two-sided type I error of 5%. In addition, this sample size makes allowance for a dropout rate of 10%.

Data management

Data will be collected onto a password protected files located on the institutional computer, also password protected. Access is given only relevant researchers of this study. The institutional computer is situated in a locked office with only the relevant investigators having access. Data collection is performed by investigators not directly involved in patient care with one investigator collecting data and a second reviewing data independent to ensure completeness. Given the prospective nature of this study, identifiable information is collected for enrolled patients with security measures as detailed above. Range checks will be carried out to promote quality. Data will be audited on a monthly basis to ensure quality. Auditors are investigators independent from sponsors. There is no input from any sponsors to data management. The final trial dataset will be deidentified prior to statistical analysis. The lead investigator as well as those involved in data analysis will have access to the final trial dataset

Blinding

Blinding occurs at the level of the clinician reviewing the imaging and biopsy specimens. Separate clinicians review the mpMRI, PSMA-PET/CT and co-registered PMSA-PET/CT and mpMRI images, with each clinician blinded to the results of the other two imaging assessment modalities. The uropathologist will receive tissue samples labelled as a systematic or targeted biopsy and its position, however is blinded to the results of PI-RADS score or PSMA-PET/CT positivity. There is no anticipated need for unblinding of investigator clinicians, as the complete results for each study patient will be viewed by a treating clinicians after all reporting is completed.

Results and Outcomes

Summary tables will be prepared giving numbers of participants by arm, disease assessment compliance, eligibility infringements and losses to follow-up. Baseline characteristics by treatment arm will be summarized in frequency tables by the use of descriptive statistics for variables. Ninety-five percent confidence intervals (95% CI) for differences between arms of all important endpoints will be calculated, and p-values will be two-sided. Exact tests will be performed with binary outcome data. Data collection forms can be made available upon request.

Diagnostic Accuracy

To determine diagnostic accuracy of PSMA PET/CT compared to mpMRI prostate in the detection of csPCa, findings of imaging will be compared to prostate biopsy histopathology to determine presence or absence of cancer. Clinically significant prostate cancer at prostate biopsy is defined as ISUP Grade Group ≥2. For the primary objective, positivity will be defined by histological confirmation of cancer at prostate biopsy.

Accuracy of each diagnostic imaging arm will be assessed by the AUC. mpMRI accuracy will be compared to PSMA PET/CT alone, and in combination with mpMRI. Point estimates of the sensitivity and specificity of each modality alone will be determined, and approximations to their distributions will be estimated using the normal approximation to the binomial distribution. Using independence of the sensitivity and specificity, the AUC will be calculated as the mean of the estimated sensitivity and specificity, and its variance as the sum of the variances of the sensitivity and specificity. Equivocal lesions will be considered negative for clinical purposes, however these lesions will be targeted during biopsy and a sensitivity analysis will be performed in which lesions rated as equivocal will be considered positive for malignancy. The difference between the AUCs will be used to characterise the true underlying difference between AUC's of the two modalities and to apply a hypothesis test for the existence of a clinically important difference between them (the null hypothesis will be a 7% difference).

Cost evaluations

The potential for cost savings will be evaluated. Considerations included in our analysis are: reductions in prostate biopsy (and efficiencies in consolidation of diagnostic and staging imaging tests) and using software co-registration as an alternative to hybrid PET/MRI machines. Cost evaluations using tools such as a decision curve analysis will be conducted as a secondary outcome. This is preferred as traditional decision-analytical methodologies does not assess clinical consequences and provide results in a continuous form rather than binary[33]. Decision curve analysis will be conducted according to Vickers *et al.*[33] of PSMA PET/CT compared to prostate biopsy results for clinically significant prostate cancer.

Risks of PSMA-PET/CT

Several preclinical and clinical studies have shown the safety of 18F-PSMA. The critical dose-organs are the kidneys (0.0945 mSv/MBq) and urinary bladder (0.085 mSv/MBq) and were calculated from human biodistribution data using OLINDA/EXM (Organ Level Internal Dose Assessment/Exponential Modelling) software. Based on the FDA, a single-organ dose of 0.05 Sv is allowable. This corresponds to an activity of 400 MBq (10.8 mCi) of 18F-PSMA for a 70-100 kg male subject with a prostate cancer, well above the doses used in this study. Accordingly, the effective dose expected to the whole body is 0.0066 Sv, which is below the 0.03 Sv upper limit recommended by the Food and Drug Administration (FDA).

Adverse events and contraindications

No adverse effects due to intravenous administration of 18 F-PSMA for imaging have been reported in the published literature. There are no known contraindications for 18F-PSMA. Overall,18F-PSMA

PET scan may be used in clinical research with no risk to subjects with PCa. As such, there is no anticipated additional adverse events from PSMA PET/CT imaging.

Acute adverse events, defined as those experienced by the subject at the time of radiotracer administration and during the two hours following injection will be recorded. Any toxicity will be graded by NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0[34].

Discussion

The drive to accurately detect intraprostatic and extraprostatic disease at the time of prostate cancer diagnosis has led to the intense interest in PSMA-PET/CT as an adjunct to mpMRI prostate. PSMA PET/CT has shown to be highly useful in the setting of high-risk disease and biochemical failure post-radical treatment[35, 36], however its utility as a diagnostic tool for prostate cancer evaluation until recently[22], there has had minimal high-quality prospective data. Our hypothesis is that PSMA-PET/CT will be superior in diagnostic accuracy to mpMRI prostate at identifying cancer within the prostate. As mpMRI prostate is established in its ability to successfully identify prostate cancer, this is a high standard to achieve. Even if PSMA-PET/CT does not supersede mpMRI prostate in diagnostic accuracy, establishing comparable diagnostic accuracy may result in a viable alternative for men who have contraindications to mpMRI.

The use of PSMA intensity as a biomarker shows potential. Roberts *et al*. demonstrated association between 68Ga-PSMA-11 intensity and Gleason score, in addition to upgrading of Gleason score between biopsy and radical prostatectomy results. Specifically, 9 of 14 upgraded patients from biopsy were from Gleason 3+4 to 4+3 on radical prostatectomy histology. This has strong implications for those Gleason 3+4 patients who were initially planned for active surveillance, with the authors suggesting SUVmax of > 8 in Gleason 3+4 malignancy could be a potential prognostic

biological marker of more aggressive disease[21]. While our study utilizes 18F-DCPFyl PSMA, we expect to achieve similar results. Furthermore, several other biomarkers such as the prostate health index have emerged as promising diagnostic implement[3]. The prostate health index showed high accuracy in predicting positive biopsy results[2]. As such, inclusion of biomarkers as part of our study is not ruled out and development of a diagnostic algorithm including biomarkers could improve detection of clinically significant prostate cancer.

The trial may also demonstrate (i) a synergistic effect in cancer diagnosis by the combination of the two imaging techniques, (ii) a benefit for PSMA-PET/CT in men with equivocal mpMRI prostate findings; (iii) benefit for men with concerning clinical features but negative/equivocal mpMRI prostate; and (iv) provide an all-encompassing diagnostic and staging scan for men who have high risk features for metastatic disease at diagnosis. Unlike the PRIMARY trial, our PSMA-PET/CT protocol encompasses chest, abdomen and pelvis, so will be able to add valuable information to this outcome.

Proprietary software from the GE Advantage® Workstation will perform co-registration between mpMRI prostate and PSMA-PET/CT images will be utilised in this trial. Co-registration has potential to improve targeting of prostate biopsy techniques, and help provide an alternative to expensive, difficult to access hybrid PET/MRI machines.

After diagnostic accuracy of PSMA-PET/CT is established, its potential for significant economic impact as a diagnostic test can be thoroughly investigated. Reductions in prostate biopsy, efficiencies in consolidation of diagnostic and staging imaging tests, and using software co-

registration as an alternative to hybrid PET/MRI all represent potential economic benefits to our health system.[2, 3]

The PEDAL trial commenced in March 2020, and although recruitment has been delayed due to Covid 19 related adjustments in health care delivery the current aim is to complete recruitment in 36 months. This innovative study will add valuable evidence to demonstrate the diagnostic accuracy of PSMA-PET/CT. It has potential to significantly impact how prostate cancer is diagnosed.

Funding statement

This clinical trial is supported by Cyclotek (Aust) Pty Ltd and their key partners, the Australian Government as part of its CRC Projects Program, General Electrical Healthcare, Macquarie University and the EJ Whitten Prostate Cancer Research Centre at Epworth Healthcare. We are also grateful for philanthropic donations from Reese Limited, the Pitcher and Cicutto families via the St Vincent's Foundation.

Participating Centres

- St Vincent's Hospital, Melbourne VIC
- St Vincent's Private Hospital, Melbourne VIC
- The Royal Melbourne Hospital, VIC
- Epworth Healthcare, VIC
- Sydney Adventist Hospital, NSW
- Pacific Radiology Canterbury, Christchurch NZ

Declaration of Interests

The authors confirm that there are no relevant financial or non-financial competing interests to report.

CONTRIBUTORSHIP STATEMENT

- Dr. Vy Tran: protocol design, ethical submission, procurement of funding, data collection, statistical analysis, manuscript preparation, patient care, supervision
- Dr Anne Hong: manuscript preparation, statistical analysis
- A/Prof. Tom Sutherland: protocol design, ethical submission, procurement of funding, data collection, statistical analysis, manuscript preparation, patient care, supervision
- Dr. Kim Taubman: protocol design, ethical submission, procurement of funding, data collection, statistical analysis, manuscript preparation, patient care, supervision
- Dr. Su-Faye Lee: protocol design, ethical submission, procurement of funding, data collection, statistical analysis, manuscript preparation, patient care, supervision
- Dr. Daniel Lenaghan: patient care, supervision
- Dr. Kapil Sethi: patient care, supervision
- A/Prof. Niall Corcoran: patient care, supervision
- A/Prof. Nathan Lawrentschuk: patient care, supervision
- Prof. Henry Woo: patient care, supervision
- Dr. Lisa Tarlinton: patient care, supervision
- Prof. Damien Bolton: manuscript preparation, supervision
- Dr. Tim Spelman: patient care, data collection, statistical analysis, supervision
- Ms. Lauren Thomas: patient care, data collection
- Mr. Russell Booth: patient care, data collection
- Dr. Justin Hegarty: patient care, data collection
- Dr. Elisa Perry: patient care, data collection
- A/Prof. Lih-Ming Wong: protocol design, ethical submission, procurement of funding, data collection, statistical analysis, manuscript preparation, patient care, supervision

References

1. Australian Institute of Health and Welfare Canberra. *Cancer in Australian 2019*. 2021 [cited 2021 24/03/2021]; Available from: https://www.aihw.gov.au/reports/cancer/cancer-in-australia-2019/data.
2. Ferro, M., et al., *Prostate Health Index and Multiparametric MRI: Partners in Crime Fighting Overdiagnosis and Overtreatment in Prostate Cancer.* Cancers (Basel), 2021. **13**(18).
3. Ferro, M., et al., *The emerging landscape of tumor marker panels for the identification of aggressive prostate cancer: the perspective through bibliometric analysis of an Italian translational working group in uro-oncology.* Minerva Urol Nephrol, 2021. **73**(4): p. 442-451.
4. Mottet, N., et al., *EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent.* Eur Urol, 2017. **71**(4): p. 618-629.
5. Whish-Wilson, T., et al., *Funding of prostate magnetic resonance imaging leads to fewer biopsies and potential savings to health systems in the management of prostate cancer.* BJU Int, 2021. **127 Suppl 1**: p. 6-12.
6. Ahmed, H.U., et al., *Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study.* Lancet, 2017. **389**(10071): p. 815-822.
7. Sathianathen, N.J., et al., *Negative Predictive Value of Multiparametric Magnetic Resonance Imaging in the Detection of Clinically Significant Prostate Cancer in the Prostate Imaging Reporting and Data System Era: A Systematic Review and Meta-analysis.* Eur Urol, 2020. **78**(3): p. 402-414.
8. Kasivisvanathan, V., et al., *MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis.* N Engl J Med, 2018. **378**(19): p. 1767-1777.
9. Sonn, G.A., et al., *Prostate Magnetic Resonance Imaging Interpretation Varies Substantially Across Radiologists.* Eur Urol Focus, 2019. **5**(4): p. 592-599.
10. Borofsky, S., et al., *What Are We Missing? False-Negative Cancers at Multiparametric MR Imaging of the Prostate.* Radiology, 2018. **286**(1): p. 186-195.
11. Elkhoury, F.F., et al., *Comparison of Targeted vs Systematic Prostate Biopsy in Men Who Are Biopsy Naive: The Prospective Assessment of Image Registration in the Diagnosis of Prostate Cancer (PAIREDCAP) Study.* JAMA Surg, 2019. **154**(9): p. 811-818.
12. Hicks, R.M., et al., *Diagnostic Accuracy of (68)Ga-PSMA-11 PET/MRI Compared with Multiparametric MRI in the Detection of Prostate Cancer.* Radiology, 2018. **289**(3): p. 730-737.
13. Margel, D., et al., *Diagnostic Performance of (68)Ga Prostate-specific Membrane Antigen PET/MRI Compared with Multiparametric MRI for Detecting Clinically Significant Prostate Cancer.* Radiology, 2021. **301**(2): p. 379-386.
14. Chang, S.S., *Overview of prostate-specific membrane antigen.* Rev Urol, 2004. **6 Suppl 10**(Suppl 10): p. S13-8.
15. Perner, S., et al., *Prostate-specific membrane antigen expression as a predictor of prostate cancer progression.* Hum Pathol, 2007. **38**(5): p. 696-701.
16. Davenport, M.S., et al., *(18)F-Choline PET/mpMRI for Detection of Clinically Significant Prostate Cancer: Part 1. Improved Risk Stratification for MRI-Guided Transrectal Prostate Biopsies.* J Nucl Med, 2020. **61**(3): p. 337-343.
17. Hofman, M.S., et al., *Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study.* Lancet, 2020. **395**(10231): p. 1208-1216.
18. Afshar-Oromieh, A., et al., *Comparison of PET imaging with a (68)Ga-labelled PSMA ligand and (18)F-choline-based PET/CT for the diagnosis of recurrent prostate cancer.* Eur J Nucl Med Mol Imaging, 2014. **41**(1): p. 11-20.

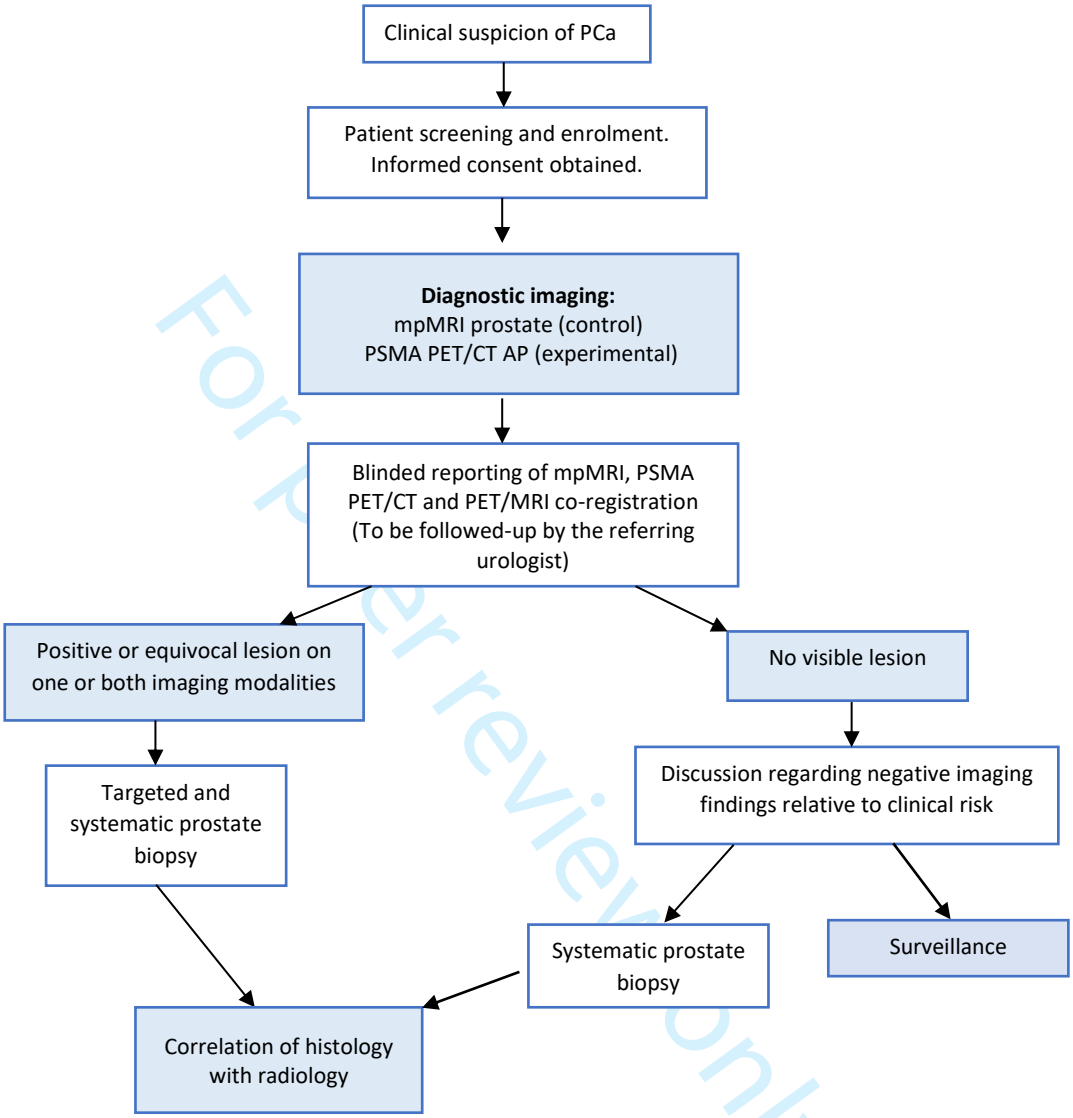
19. Koschel, S., et al., *The role of prostate-specific membrane antigen PET/computed tomography in primary staging of prostate cancer.* Curr Opin Urol, 2019. **29**(6): p. 569-577.
20. Perera, M., et al., *Gallium-68 Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer-Updated Diagnostic Utility, Sensitivity, Specificity, and Distribution of Prostate-specific Membrane Antigen-avid Lesions: A Systematic Review and Meta-analysis.* Eur Urol, 2020. **77**(4): p. 403-417.
21. Roberts, M.J., et al., *(68)Ga-PSMA PET/CT tumour intensity pre-operatively predicts adverse pathological outcomes and progression-free survival in localised prostate cancer.* Eur J Nucl Med Mol Imaging, 2021. **48**(2): p. 477-482.
22. Emmett, L., et al., *The Additive Diagnostic Value of Prostate-specific Membrane Antigen Positron Emission Tomography Computed Tomography to Multiparametric Magnetic Resonance Imaging Triage in the Diagnosis of Prostate Cancer (PRIMARY): A Prospective Multicentre Study.* Eur Urol, 2021. **80**(6): p. 682-689.
23. Gaur, S., et al., *Prospective Evaluation of (18)F-DCFPyL PET/CT in Detection of High-Risk Localized Prostate Cancer: Comparison With mpMRI.* AJR Am J Roentgenol, 2020. **215**(3): p. 652-659.
24. Lee, M.S., et al., *Diagnostic value of integrated PET/MRI for detection and localization of prostate cancer: Comparative study of multiparametric MRI and PET/CT.* J Magn Reson Imaging, 2017. **45**(2): p. 597-609.
25. Anconina, R., et al., *Detection of clinically significant prostate cancer with ¹⁸F-DCFPyL (PSMA) PET/MR compared to mpMR alone: preliminary results of a prospective trial.* Journal of Nuclear Medicine, 2019. **60**(supplement 1): p. 1574-1574.
26. Muehlematter, U.J., et al., *Diagnostic Accuracy of Multiparametric MRI versus (68)Ga-PSMA-11 PET/MRI for Extracapsular Extension and Seminal Vesicle Invasion in Patients with Prostate Cancer.* Radiology, 2019. **293**(2): p. 350-358.
27. Afshar-Oromieh, A., et al., *Comparison of PET/CT and PET/MRI hybrid systems using a 68Ga-labelled PSMA ligand for the diagnosis of recurrent prostate cancer: initial experience.* Eur J Nucl Med Mol Imaging, 2014. **41**(5): p. 887-97.
28. Grubmüller, B., et al., *PSMA Ligand PET/MRI for Primary Prostate Cancer: Staging Performance and Clinical Impact.* Clin Cancer Res, 2018. **24**(24): p. 6300-6307.
29. Australian Government Department of Health. *New Medicare Benefits Scheme (MBS) Items for multiparametric magnetic resonance imaging (mpMRI) of the prostate 2018*. 2018 [cited 2019 20/6/2019]; Available from: http://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/Factsheet-MRIProstate.
30. van Leenders, G.J.L.H., et al., *The 2019 International Society of Urological Pathology (ISUP) Consensus Conference on Grading of Prostatic Carcinoma.* The American Journal of Surgical Pathology, 2020. **44**(8).
31. Li, M., et al., *Comparison of PET/MRI with multiparametric MRI in diagnosis of primary prostate cancer: A meta-analysis.* Eur J Radiol, 2019. **113**: p. 225-231.
32. Scheltema, M.J., et al., *Diagnostic accuracy of (68) Ga-prostate-specific membrane antigen (PSMA) positron-emission tomography (PET) and multiparametric (mp)MRI to detect intermediate-grade intra-prostatic prostate cancer using whole-mount pathology: impact of the addition of (68) Ga-PSMA PET to mpMRI.* BJU Int, 2019. **124 Suppl 1**: p. 42-49.
33. Vickers, A.J. and E.B. Elkin, *Decision curve analysis: a novel method for evaluating prediction models.* Med Decis Making, 2006. **26**(6): p. 565-74.
34. National Cancer Institute. *NCI Common Terminology Criteria for Adverse Events*. 2017 [cited 2021 24/3/2021]; Available from: https://evs.nci.nih.gov/ftp1/CTCAE/About.html.

35. Koschel, S., et al., *Patterns of disease detection using [(18)F]DCFPyL PET/CT imaging in patients with detectable PSA post prostatectomy being considered for salvage radiotherapy: a prospective trial.* Eur J Nucl Med Mol Imaging, 2021. **48**(11): p. 3712-3722.
36. Perry, E., et al., *[(18)F]DCFPyL PET/CT in detection and localization of recurrent prostate cancer following prostatectomy including low PSA < 0.5 ng/mL.* Eur J Nucl Med Mol Imaging, 2021. **48**(6): p. 2038-2046.

FIGURE LEGEND

Figure 1: trial schema.

Figure 1: PEDAL Trial Schema



Appendix 1: Multiparametric Magnetic Resonance Imaging Protocol

IMAGING ACQUSITION:

MRI prostate imaging is acquired as per international guidelines specified by Prostate Imaging-Reporting and Data System, version 2.1 (PIRADS V2.1).

A multi-parametric MRI scan will be performed according to the following technical protocol, consistent with the highest standards of prostate MRI after appropriate bowel preparation (suggest Microlax suppository morning of diagnostic imaging) and buscopan or glucagon injection (where not contraindicated):

- 3-Tesla magnet field strength
- 32-channel cardiac coil, anteriorly and spinal coil posteriorly
- T2 sequences to show pathology, aid localisation of the lesion, and to fuse with ultrasound for those Urologists using co-registration biopsy method.
    - High resolution T2 FSE in 3 planes: axial, coronal and sagittal
    - 3D T2 sequence

Diffusion-Weighted Imaging (DWI) with software derived Apparent Diffusion Co-efficient (ADC) quantitative analysis maps, and multiple b-values (acquired b50, acquired b1400, calculated b2000);

Dynamic Contrast Enhanced imaging (DCE) 3D imaging, with IV gadolinium DTPA bolus determined by body weight, at 2.5ml/second followed by T1 DCE TRICKS (Time-Resolved Imaging of Contrast KineticS).

Analysis of DCEI according to PI-RADS DCEI analytic guidelines using PROCAD software

· No use of Endo-rectal coils or MR Spectroscopy as per current guidelines

· Approximate scan time 30 to 40 minutes

CONTRAINDICATIONS TO MRI

Patient with any contraindication to MRI will not undergo MRI. This includes, but not restricted, to pacemaker or other electronic implants, total hip joint replacement, known metal in the orbit, MR incompatible surgical or cerebral aneurysm clips, shrapnel, non-removable body piercings.

REPORTING OF MPMRI PROSTATE

The mpMRI will be reported by experienced subspecialist Radiologists according to the Prostate Imaging-Reporting and Data System, version 2.1, with each lesion categorised on a scale from 1 to 5.

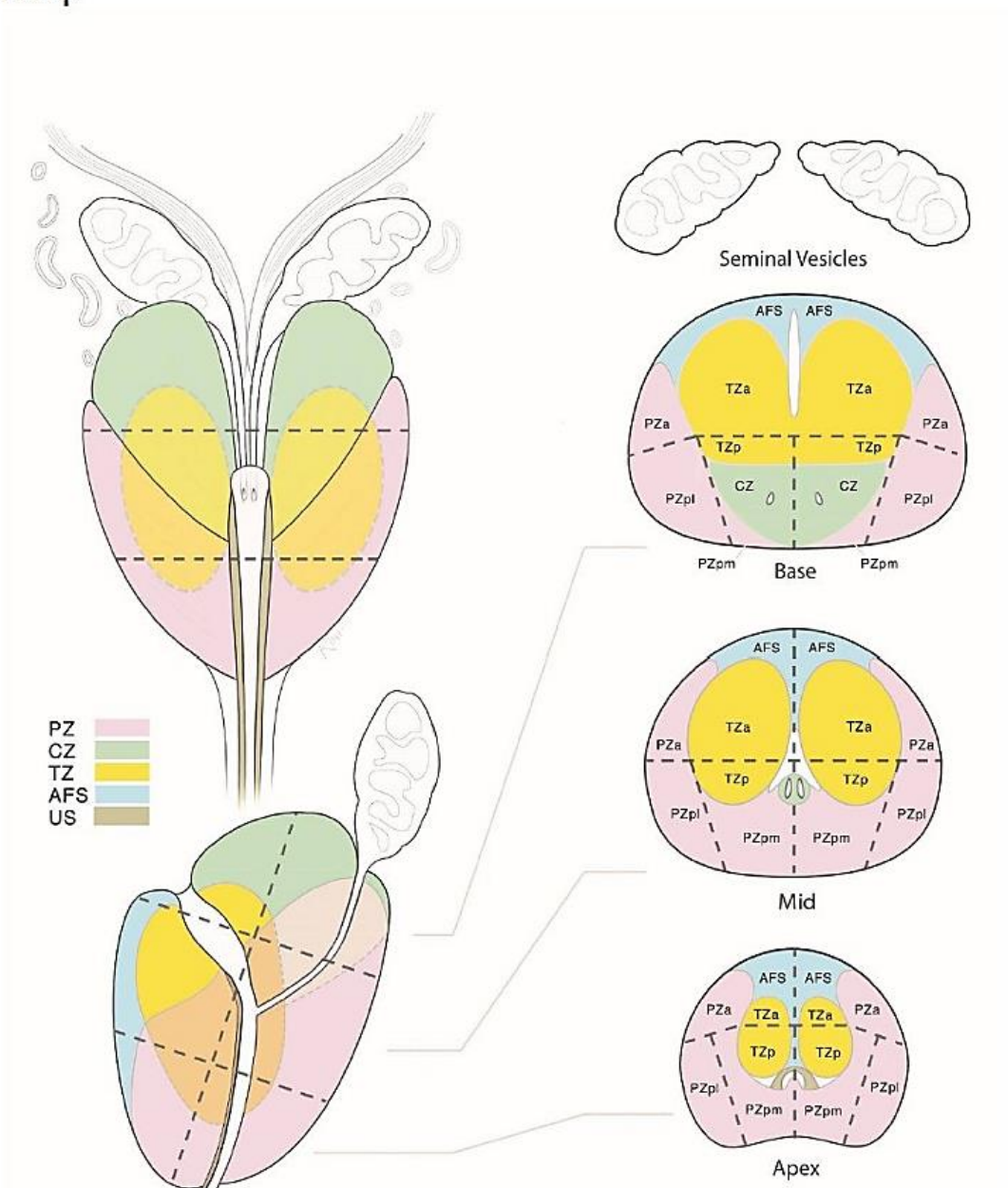
OPTIMIZATION OF CO-REGISTRATION BETWEEN MPMRI PROSTATE AND PSMA-PET/CT

To enable better co-registration of mpMRI to PSMA-PET/CT:

- option to use of suppositories to help eliminate gas/faeces from rectum
- ensure flat pelvis
- Use of structured knee bolster and strapping of feet to aid pelvic alignment

Appendix 2: Prostate Imaging-Reporting and Data System (version 2.1) Sector Map

Sector Map



American College of Radiology® 2019 31 PI-RADSv2.1

Appendix 3: 18F-DCFPyL PSMA administration and PET/CT Imaging Protocol

RADIOPHARMACEUTICAL

18F DCFPyL will be produced at Cyclotek (Aust) Pty Ltd under GMP Licence Number MI-12092005-LI-000904-2 and (parametric) release after certain quality control tests are performed and transported to the imaging site under regulatory criteria for dangerous goods. Cyclotek will provide the imaging site with a Quality Control Release notification form. Patients will complete the radiopharmaceutical consent form at their local site prior to injection.

18F-DCFPYL PSMA INJECTION DOSING AND ADMINISTRATION

Patients will be administered a single, intravenous 250MBq bolus dose of 18F-DCFPyL PSMA (acceptable: 200-300MBq depending on patient weight and activity provided on day of scan). The administered activity of 18F-DCFPyL PSMA is approximately 3MBq per kilogram body weight up to 350 maximum dose.

18F-PSR PET/CT imaging protocol for initial diagnosis/staging of Prostate Ca Imaging Protocol

Patient Preparation:

● No fasting required. (*Must be well hydrated, approximately 1-2 litres of plain water in the 2 hours before appointment.)

● The activity is administered intravenously through a cannula either utilising the automatic injector and a 100ml Saline bag or via hand injection through the cannula utilising the 5ml syringe shield and 2x10mls saline flushes.

● The dose pre and post syringe activities and times must be recorded to work out the exact administered activity for the injection time.

● Uptake Time: 120 minutes post 18F-DCFPyL injection. The patient is free to leave the department if they wish during this waiting time.

● Patient to void before the scan

SCANNER

Patients will be imaged on a GE Discovery 690 or 710 PET/CT (General Electric Medical Systems, Milwaukee, WI) combining a 64 slice multidetector CT scanner with a dedicated, full ring PET scanner with lutetium-based crystals.

Scan:

Scan range: Mid/Upper thighs to Lung Apices. Patient position supine, arms up and feet first to ensure bladder is in its emptiest state. CT scan acquired using a low-dose protocol (120/140 kVp and automatic exposure control ('Smart mA', max 200mA). Low-dose attenuation correction CT images were acquired and reconstructed to a 3.75mm slice thickness with an increment of 3.27mm using iterative reconstruction (50% ASiR). PET images were acquired at 3.5min/bed through the pelvis and 3.0min/bed to the lung apices. PET images were reconstructed from time of flight emission data using VUE Point FX and Q-Clear™ iterative technique with β value of 400. Q-Clear™ is a fully convergent reconstruction method which incorporates point spread function corrections, scatter correction and ULD-CT attenuation corrections. Sharp IR function was applied with no Z-axis filter. PET images were reconstructed on a 256 matrix.

PET/CT 18F-PSR <90kg 120min post injection

kV 120, Smart mA 200, noise index 30

3.5min over pelvis (2)

3.0min for rest of body (4)

Total: 6 beds ~ 19min

PET/CT 18F-PSR >90kg 120min post injection

kV 140, Smart mA 200, noise index 32

4.0min over pelvis (2)

3.5min for rest of body (4)

Total: 6 beds ~ 22min

Image Reconstruction: Images are reconstructed using the Q.Clear GE reconstruction method with a β value of 400.

Workstation used for scan interpretation: GE AW Server 3.2 Ext 1.0 or Inteleviewer.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	143-145
	2b	All items from the World Health Organization Trial Registration Data Set	145
Protocol version	3	Date and version identifier	145
Funding	4	Sources and types of financial, material, and other support	192-198, 419-424
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	5-24, 437-460
	5b	Name and contact information for the trial sponsor	420-425
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	151-153
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Not applicable

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	129-139
	6b	Explanation for choice of comparators	165-171
Objectives	7	Specific objectives or hypotheses	269-275
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	165-172
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	427-433
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	183
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	165-172
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Not applicable
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Not applicable
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	179-181
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	277
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	154

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	280-290
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	289-290
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Not applicable
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Not applicable
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Not applicable
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	305-312
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	310-312
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	292-303
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	189-190

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	287-291
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	314-320
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	314-320
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	289-290
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	291
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Not applicable
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	362-369
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	300-301
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	144-146
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	171-172

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	175-177
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	175-177
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	292-303
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	434-436
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	301-303
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	362-366
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	64-68
	31b	Authorship eligibility guidelines and any intended use of professional writers	67-68
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Protocol submitted for publication
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	See attached___
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable__

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.