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# **BMJ Open**

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

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1 2		
3 4 5	1	Category: Original Research
6 7	2	Title: PEDAL Protocol: A prospective single arm paired comparison of multiparametric MRI and 18F-
8 9	3	DCPFyl PSMA PET/CT to diagnose prostate cancer
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36	Number of tables: 2
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3	38	Abstract	
4 5			
6	39	Introduction:	
7	55		
8 9	40	Prostate specific membrane antigen positron emission tomography (PSMA-PET) has emerged as	
10	40	rostate specific memorane antigen position emission tomography (FSMA FET) has emerged as	
11	41	valuable imaging to assessing metastatic disease in prostate malignancy. However, there has been	
12 13			
14	42	limited studies exploring the utility PSMA-PET as primary imaging assessing for index lesions prior to	
15	43	biopsy. The primary objective of this study is to compare the diagnostic accuracy of 18-fluorine	
16 17			
18	44	PSMA (18F DCFPyL PSMA) PET scans to multiparametric magnetic resonance imaging (mpMRI) to	
19 20			
20 21	45	detect primary prostate cancer at prostate biopsy.	
22	46		
23 24			
24	47	Methods and Analysis:	
26			
27 28	48	The PEDAL trial is a multicentre, prospective, single-arm, paired comparison, non-randomised phase	
29			
30	49	III trial in subjects considered for diagnostic prostate biopsy. Subjects who are eligible for a	
31 32	50	diagnostic mpMRI prostate will undergo additional same-day 18-F DCFPyl PSMA PET/CT of the chest,	
33	50		
34 25	51	abdomen and pelvis. Software co-registration of the mpMRI and PSMA-PET/CT images will be	
35 36		performed The reporting of the mpMRI prostate DSMA_DET/CT and DSMA_DET/MRI co-registration	
37	52	performed. The reporting of the mpMRI prostate, PSMA-PET/CT and PSMA PET/MRI co-registration	
38 39	53	will be performed blinded.	
39 40			
41	54	The diagnostic accuracy of PSMA PET/CT alone, and in combination with mpMRI, to detect prostate	
42 43	54	The diagnostic accuracy of FSWATET/eF alone, and in combination with inplaint, to detect prostate	
44	55	cancer will be assessed. Histopathology at prostate biopsy will be used as the reference standard.	
45			
46 47	56	Sample size calculations estimate that 240 subjects will need to be recruited to demonstrate 20%	
48	57	superiority of PSMA-PET/CT.	
49	57		
50 51	58	The sensitivity, specificity, positive predictive value and negative predictive value of the combination	
52	20	The sensitivity, specificity, positive predictive value and negative predictive value of the combination	
53 54	59	of mpMRI prostate and PSMA PET/CT compared to targeted and systematic prostate biopsy will be	
54 55			
56	60	evaluated. It is hypothesised that PSMA PET/CT combined with mpMRI prostate will have improved	
57 58	61	diagnostic accuracy compared to mpMRI prostate alone for detection of prostate cancer in biopsy-	
58 59	91	anglissie decidely compared to inplain prostate done for detection of prostate cancer in blopsy-	
60	62	naïve men, resulting in a significant impact on patient management.	

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5 6 7	64	Ethics and Dissemination:
8 9 10	65	This study was approved by the independent Human Research Ethics Committee and is a registered
11 12	66	trial (Trial registration number: ACTRN12620000261910). Participant recruitment commenced in
13 14 15	67	March 2020. Results will be published in peer-reviewed medical journals.
16 17	68	
18		
19 20 21	69	Strengths and Limitations
22 23	70	This is a multicentre study.
24 25 26	71	A strength of this study is its prospective nature of the study design controlled by using
27 28	72	patients own biopsy results as comparator, thus limiting confounders.
29 30	73	This is an adequately powered study with objective primary and secondary outcome
31 32 33	74	measures.
34 35	75	Potential limitations pertain to generalisability of results given use of DCFPYL tracer for
36 37	76	PSMA-PET/CT. There are currently limited studies directly comparing different PSMA-PET
38 39 40	77	tracers.
41 42	78	Keywords:
43 44 45	79	Keywords:
46 47	80	prostate cancer, diagnosis, PSMA PET, multiparametric MRI, PSMA, imaging
48 49 50	81	
50 51 52 53 54 55 56 57 58 59 60		

Introduction

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Prostate cancer (PCa) is very common, with one in six men being diagnosed before the age of 85

years<sup>1</sup>. 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

In Australia, multiparametric magnetic resonance imaging (mpMRI) of the prostate gland has also

prostate cancer and active surveillance of low-risk prostate cancer with economic analysis

suggesting significant savings to the health system<sup>2,3</sup>. mpMRI offers reliable visualisation and

characterisation of csPCa compared to the traditional transrectal ultrasound (TRUS), and is seen to

lesions compared to satellite lesions, thus enabling better selection of patients for prostate biopsy<sup>4</sup>.

In a meta-analysis of 42 studies, the pooled negative predictive value of mpMRI was reported to be

systematic TRUS-guided biopsy (38% versus 26%)<sup>6</sup>. Nevertheless, mpMRI is not without limitations.

90.8 – 97%<sup>5</sup>. mpMRI-targeted prostate biopsy has been reported to detect more csPCa than

Variable imaging quality, interreader variability, low specificity and missed or underestimated

tumours remain an issue<sup>7,8</sup>. The PAIREDCAP trial reported 15% of patients with negative mpMRI

Along with mpMRI, prostate-specific membrane antigen positron emission tomography (PSMA-PET)

decades<sup>10,11</sup>. Prostate specific membrane antigen (PSMA) is a type II transmembrane protein that is

is one of the key advancements to emerge in prostate cancer assessment over the last two

have greater sensitivity of detection for lesions greater than 1cm, Gleason score of ≥7 and index

become available under Australian government funded rebate for diagnostic evaluation of suspected

cancer (csPCa, Grade group  $\geq 2$ ) and assess tumour burden.

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44 45	100
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50 51 52	103
53 54	104
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#### overexpressed on PCa cell membranes in all but 5 – 10% of cases, showing high specificity and

findings were found to have csPCa on systematic prostate biopsy<sup>9</sup>.

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sensitivity relating to tumour aggressiveness and metastatic potential<sup>12,13</sup>. 18F-Choline PET scans have been shown to improve risk stratification when used in conjunction with mpMRI<sup>14</sup>. 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 <sup>15-18</sup>. 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<sup>15</sup>.

The use of PSMA PET/CT as a first line diagnostic tool for suspected prostate cancer is under investigation<sup>19,20</sup>. The PRIMARY study<sup>19</sup> 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<sup>10,21</sup>. 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%)<sup>22</sup>. Finally, PSMA-PET/CT in addition to mpMRI showed increased sensitivity when detecting extraprostatic extension and seminal vesical invasion<sup>23</sup>, although specificity reduced slightly<sup>23</sup>, 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<sup>24,25</sup>. 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

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2 3 4	132	comparison trial that aims to provide high quality evidence regarding the diagnostic accuracy of 18F-
5 6 7	133	DCFPyI-PSMA PET/CT in conjunction with mpMRI prostate for primary diagnosis of prostate cancer.
8 9	134	
10 11 12	135	
13 14 15	136	Methods and Design:
16 17 18	137	Ethics
19 20 21	138	This clinical trial has been approved by the St Vincent's Hospital, Melbourne Human Research Ethics
22 23	139	Committee (HREC 230/19) and is registered on the Australian New Zealand Clinical trials registry
24 25	140	(ACTRN12620000261910). It will be conducted in accordance with the International Conference on
26 27 28	141	Harmonisation protocols and Good Clinical Practice. In addition, the trial will be conducted in
28 29 30	142	compliance with all applicable laws and regulatory requirements relevant to the use of new
31 32	143	therapeutic agents in Australia and any other participating country. Funding will be acquired through
33 34	144	Cyclotek (manufacturer of DCFPYL), General Electrical Healthcare, and philanthropic grants.
35 36 37	145	The trial schema is outlined in Figure 1.
38 39 40	146	
41 42 43	147	Patient and public involvement
44 45 46	148	No formal patient advisory committee was set up and there was no patient or public involvement in
47 48	149	the design and planning of the study. The study was so designed as the mpMRI, PSMA-PET and
49 50	150	prostate biopsy procedures used are not novel concepts or techniques, and are widely available in
51 52 53	151	Australia as part of the Medicare system for which consumer and stakeholder comment is sought
55 55	152	prior to inclusion of these interventions. Nevertheless, the patients are invited to provide feedback
56 57	153	at each point of contact with the healthcare system. In addition, the results are intended for
58 59 60	154	publication in peer reviewed medical journals.

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2 3	155	
4	133	
5 6 7	156	Study design
8 9 10	157	This is a prospective single arm paired comparison diagnostic phase III trial in patients who are being
11 12	158	considered for diagnostic prostate biopsy to detect prostate cancer. We aim to evaluate the role of
13 14	159	PSMA-PET/CT in those with high clinical suspicion of prostate cancer. The PSMA-PET/CT, by
15 16 17	160	identifying a suspicious lesion, is likely to impact the decision for prostate biopsy and the target
18 19	161	location. The diagnostic accuracy of the imaging studies will be assessed by comparison of imaging
20 21	162	results to prostate biopsy results.
22 23 24	163	
25 26 27	164	Patient screening, eligibility, and enrolment
28 29 30	165	Patients with features suspicious for PCa based on an abnormal PSA or DRE will be screened by a
31 32	166	urologist for trial eligibility in the study according to the inclusion and exclusion criteria listed below
33 34	167	in Table 1 <sup>26</sup> . A target of 240 subjects will be recruited from multiple sites.
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1 2 3	169	
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5 6		Table 1. Study inducion and ovelusion exiteria
7		Table 1. Study inclusion and exclusion criteria         [Adapted from New Medicare Benefits Scheme (MBS) for mpMRI of the prostate][20]
8		Inclusion criteria
9 10		<ul> <li>Men (≥18 years) with an elevated PSA who are suitable for an eligible MBS mpMRI</li> </ul>
11		<ul> <li>Men (218 years) with an elevated PSA who are suitable for an eligible MBS inplicit.</li> <li>prostate:</li> </ul>
12		(MBS items 63541 and 63542) AND who have NOT had recent (≤3 years) prostate biopsy
13 14		or mpMRI prostate.
15		For MBS items 63541 and 63542 (NK) the patient must be suspected of having prostate
16 17		cancer based on (*):
17 18		a) DRE which is suspicious for prostate cancer; or
19		b) in a person aged less than 70 years, at least prostate specific antigen (PSA) tests
20		performed within an interval of 1-3 months are greater than 3.0 ng/ml, and the
21 22		free/total PSA ratio is less than 25% or the repeat PSA exceeds 5.5 ng/ml; or
23		c) in a person aged less than 70 years, whose risk of developing prostate cancer based
24 25		on family history is at least double the average risk, at least two PSA tests performed
25 26		within an interval of 1- 3 months are greater than 2.0ng/ml, and the free/total PSA ratio
27		is less than 25%; or
28 29		d) in a person aged 70 years or older, at least two PSA tests performed within an
29 30		interval of 1- 3 months are greater than 5.5ng/ml and the free/total PSA ratio is less
31		than 25%.
32 33		NB: Relevant family history is a first degree relative with prostate cancer or suspected of
33 34		carrying a BRCA 1, BRCA 2 mutation.
35		Patient has provided written informed consent for participation in trial
36 27		<ul> <li>In the opinion of the investigator, willing and able to comply with required study</li> </ul>
37 38		procedures
39		Exclusion criteria
40 41		Known diagnosis of prostate cancer.
41 42		• Previous prostate biopsy within 3 years of randomization. A transurethral resection of the
43		prostate performed for primary purpose of alleviating lower urinary tract symptoms is
44 45		considered acceptable.
46		<ul> <li>Previous mpMRI prostate within 3 years of randomization.</li> <li>History of other active maligner activity the last 2 years with the supertion of non-</li> </ul>
47		<ul> <li>History of other active malignancy within the last 3 years, with the exception of non- melanoma skin cancer or melanoma in-situ.</li> </ul>
48 49		<ul> <li>Any absolute contra-indication to 3T mpMRI prostate, or previous history of total hip joint</li> </ul>
49 50		• Any absolute contra-indication to st inplote prostate, or previous history of total hip joint replacement.
51		<ul> <li>Significant intercurrent morbidity that, in the judgement of the investigator, would limit</li> </ul>
52 53		compliance with study protocols.
55 54		DRE= digital rectal examination; mpMRI = multiparametric magnetic resonance imaging; PSA=
55		prostate specific antigen
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172 Follow-up	
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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. 

191 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

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3 4	195	lesion described as PI-RADS 3 or greater will be considered a positive lesion with a targeted prostate
5 6	196	biopsy recommended. The presence of extracapsular extension, seminal vesicle invasion,
7 8	197	locoregional disease and subjective likelihood of csPCa will be recorded. The initial report of the
9 10 11	198	mpMRI prostate will be blinded to the PSMA-PET/CT result.
12 13 14	199	
15 16 17	200	PSMA-PET/CT
18 19	201	All participants will undergo PSMA-PET/CT imaging with18F-DCFPyL according to standard protocol
20 21 22	202	(Appendix 3) at the participating site, on the same day as the mpMRI. The 18F-DCFPyL radiotracer
23 24	203	will be produced in Australia and New Zealand by Cyclotek Pty Ltd, who will provide the local site
25 26	204	with a Quality Control Release notification form. A single, intravenous bolus dose of 18F-DCFPyL
27 28	205	PSMA (250MBq +/-50 MBq) will be administered with an uptake time of 120 minutes post 18F-
29 30 31	206	DCFPyL injection. 18F-PSMA PET with CT chest, abdomen and pelvis will be performed for anatomic
32 33 34	207	localisation and attenuation correction
34 35 36	208	PSMA-PET/CT images will be reported at a per-patient and per-lesion level by an experienced reader
37 38	209	at each site. The initial report of PSMA-PET/CT will be blinded to the mpMRI prostate result. To
39 40	210	standardise lesion imaging reporting, the intraprostatic lesions will be described according to the
41 42	211	sector map specified in PI-RADS version 2.1 for mpMRI prostate. The PSMA intensity score
43 44 45	212	(SUVmax), focality and ratio to background will be assessed. The reader will report disease location
46 47	213	and extent, as well as assign a subjective likelihood for the presence of csPCa. All lesions with
48 49	214	SUVmax scores of 4.0 or higher are deemed appropriate for targeted biopsy. While results of the
50 51 52	215	PRIMARY trial were disseminated after our protocol was designed, it also uses a SUVmax of 4.0 as at
52 53 54	216	this stage the sensitivity for csPCa was 92% <sup>19</sup> . This may be adjusted following quantitative analysis of
55		
56	217	thresholds, (liver and background prostate in particular), for the presence of malignancy, although

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219 220 Co-registration of the PSMA-PET/CT with mpMRI prostate 221 After both diagnostic imaging arms have been independently reported, co-registration of the two 222 modalities will be performed using the GE Advantage Workstation® (General Electric, Boston, 223 Massachusetts, United States) software Reporting of co-registered PSMA-PET/CT with mpMRI 224 images will be performed by an experienced dual-trained radiologist with PET accreditation and 225 experience of reporting prostate mpMRI. A synoptic report will describe lesions seen on the mpMRI 226 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 227 228 the presence of csPCa will be reported. Lesions will be numbered to enable accurate cataloguing at 229 time of prostate biopsy, and visually represented on the PI-RADS version 2.1 prostate map. è.e 230 231 **Prostate Biopsy** 232 Prostate biopsy procedure 233 The referring urologist will have access to reports and images for both diagnostic imaging modalities 234 and PSMA-PET/MRI co-registration results in order to make a clinical decision regarding prostate 235 biopsy. Subjects with any positive and/or equivocal findings in either diagnostic imaging arm are 236 recommended to undergo a targeted biopsy of all lesions and a systematic biopsy for 237 histopathological analysis. Targeting is accomplished via cognitive fusion at time of biopsy. The study 238 recommends a standardised transperineal ultrasound guided template biopsy format perfumed 239 under general anaesthesia. A minimum of four cores of any targeted lesion and minimum 24 240 systematic cores to be taken. Subjects with no abnormalities on mpMRI and PSMA PET/CT are 241 recommended to have a systematic biopsy (24 cores). All biopsies are performed by surgeons

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3 4	242	already trained in and practicing the transperineal biopsy route, thus minimising variability and
5 6 7	243	possible confounders.
8 9	244	
10 11 12 13	245	Histopathology
14 15	246	Biopsy specimens will be labelled based on location and whether obtained through targeted or
16 17	247	systematic prostate biopsy. Reporting of the prostate biopsy will be performed by genito-urinary
18 19 20	248	histopathologists at each site using standardized proformas, detailing the number of cores taken,
20 21 22	249	location (including the index lesion), histological subtype, and International Society of Urological
23 24	250	Pathology (ISUP) grade group, number of positive cores per site, percentage and longest length of
25 26 27	251	cancer in one core and perineural invasion <sup>27</sup> .
28 29 30	252	
31 32 33	253	Study assessment
34 35	254	Study objective and endpoints
36 37 38	255	The endpoints of this study are summarised in Table 2. The primary objective is to assess for
39 40	256	diagnostic superiority of PSMA-PET/CT in combination with mpMRI in detection of lesions with any
41 42	257	ISUP grade prostate cancer. Specifically, cancer detection rates, sensitivity, specificity, negative
43 44 45	258	predictive values, positive predictive values and AUC are explored. The secondary outcomes involve
46 47	259	detection of csPCa.
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## Table 2. PEDAL Study endpoints

	Primary endpoint
	<ul> <li>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.</li> </ul>
	Secondary endpoints
	<ul> <li>Detection of clinically significant (ISUP Grade Group ≥2) primary prostate cancer at prostate</li> </ul>
	biopsy
	<ul> <li>Detection of radiologically significant lesions in the prostate at PSMA-PET/CT and MRI co- registration.</li> </ul>
	Detection of radiological evidence of metastatic lesions on PSMA-PET/CT and/or mpMRI
	Prostate.
	<ul> <li>Number of adverse events reported during and post-administration of radiotracer for PSMA PET/CT.</li> </ul>
	ISUP= International Society of urological Pathology; mpMRI= multiparametric magnetic resonance
	imaging; PSMA=prostate specific membrane antigen; PET/CT=positron emission tomography /
262	computed tomography,
-	
263	
264	Sample size and Power Calculation
265	The trial will proceed to recruit to an ideally powered sample size of 240 subjects to achieve a power
266	of 0.80. Sample size calculations were based on the primary endpoint of detection of all ISUP grade
267	prostate cancer detection. Area under the receiver operator characteristic (ROC) curve (the AUC),
268	sensitivity and specificity for mpMRI and PSMA-PET/CT are 0.84, 0.603 and 0.89 <sup>28</sup> , and 0.91, 0.88 and
269	0.93 <sup>29</sup> respectively. The following assumptions were made for sample size calculations: 50% of men
270	who undergo prostate biopsy will be diagnosed with prostate cancer, , the proportion of cases
271	(PSMA PET/CT as opposed to mpMRI) is 20% higher, the absolute margin of improvement is 7% (0.35
272	to 0.42) to declare PSMA-PET/CT is superior, the estimated correlation between the two tests is 80%
273	and a two-sided type I error of 5%. In addition, this sample size makes allowance for a dropout rate
274	of 10%.

1								
2 3	275							
4	275							
5 6 7	276	Blinding						
8 9 10	277	Blinding occurs at the level of the clinician reviewing the imaging and biopsy specimens. Separate						
11 12	278	clinicians review the mpMRI, PSMA-PET/CT and co-registered PMSA-PET/CT and mpMRI images,						
13 14 15 16 17 18 19	279	with each clinician blinded to the results of the other two imaging assessment modalities. The						
	280	uropathologist will receive tissue samples labelled as a systematic or targeted biopsy and its						
	281	position, however is blinded to the results of PI-RADS score or PSMA-PET/CT positivity.						
20 21 22	282							
23 24 25 26 27 28 29 30 31 32 33 34 35 36 37	283	Results and Outcomes						
	284	Summary tables will be prepared giving numbers of participants by arm, disease assessment						
	285	compliance, eligibility infringements and losses to follow-up. Baseline characteristics by treatment						
	286	arm will be summarized in frequency tables by the use of descriptive statistics for variables. Ninety-						
	287	five percent confidence intervals (95% CI) for differences between arms of all important endpoints						
	288	will be calculated, and p-values will be two-sided. Exact tests will be performed with binary outcome						
38 39	289	data.						
40 41	290							
42 43 44	291	Diagnostic Accuracy						
45 46	292	To determine diagnostic accuracy of PSMA PET/CT compared to mpMRI prostate in the detection of						
47 48	293	csPCa, findings of imaging will be compared to prostate biopsy histopathology to determine						
49 50 51	294	presence or absence of cancer. Clinically significant prostate cancer at prostate biopsy is defined as						
52 53	295	ISUP Grade Group $\geq$ 2. For the primary objective, positivity will be defined by histological						
54 55	296	confirmation of cancer at prostate biopsy.						
56 57 58 59 60	297							

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298	Accuracy of each diagnostic imaging arm will be assessed by the AUC. mpMRI accuracy will be
299	compared to PSMA PET/CT alone, and in combination with mpMRI. Point estimates of the sensitivity
300	and specificity of each modality alone will be determined, and approximations to their distributions
301	will be estimated using the normal approximation to the binomial distribution. Using independence
302	of the sensitivity and specificity, the AUC will be calculated as the mean of the estimated sensitivity
303	and specificity, and its variance as the sum of the variances of the sensitivity and specificity.
304	Equivocal lesions will be considered negative for clinical purposes, however these lesions will be
305	targeted during biopsy and a sensitivity analysis will be performed in which lesions rated as
306	equivocal will be considered positive for malignancy. The difference between the AUCs will be used
307	to characterise the true underlying difference between AUC's of the two modalities and to apply a
308	hypothesis test for the existence of a clinically important difference between them (the null
309	hypothesis will be a 7% difference).
310	Risks of PSMA-PET/CT
311	Risks of PSMA-PET/CT
312	Several preclinical and clinical studies have shown the safety of 18F-PSMA. The critical dose-organs
313	are the kidneys (0.0945 mSv/MBq) and urinary bladder (0.085 mSv/MBq) and were calculated from
314	human biodistribution data using OLINDA/EXM (Organ Level Internal Dose Assessment/Exponential
315	Modelling) software. Based on the FDA, a single-organ dose of 0.05 Sv is allowable. This corresponds
316	to an activity of 400 MBq (10.8 mCi) of 18F-PSMA for a 70-100 kg male subject with a prostate
317	cancer, well above the doses used in this study. Accordingly, the effective dose expected to the
318	whole body is 0.0066 Sv, which is below the 0.03 Sv upper limit recommended by the Food and Drug
319	Administration (FDA).
320	
321	Adverse events and contraindications

1 ว		
2 3 4	322	No adverse effects due to intravenous administration of 18 F-PSMA for imaging have been reported
5 6	323	in the published literature. There are no known contraindications for 18F-PSMA. Overall,18F-PSMA
7 8 9	324	PET scan may be used in clinical research with no risk to subjects with PCa.
10 11	325	Acute adverse events, defined as those experienced by the subject at the time of radiotracer
12 13 14	326	administration and during the two hours following injection will be recorded. Any toxicity will be
15 16	327	graded by NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 <sup>30</sup> .
17 18 19	328	
20 21 22	329	Discussion
23 24 25	330	The drive to accurately detect intraprostatic and extraprostatic disease at the time of prostate
26 27	331	cancer diagnosis has led to the intense interest in PSMA-PET/CT as an adjunct to mpMRI prostate.
28 29 30 31 32	332	PSMA PET/CT has shown to be highly useful in the setting of high-risk disease and biochemical
	333	failure post-radical treatment <sup>31,32</sup> , however its utility as a diagnostic tool for prostate cancer
33 34	334	evaluation until recently <sup>19</sup> , there has had minimal high-quality prospective data. Our hypothesis is
35 36	335	that PSMA-PET/CT will be superior in diagnostic accuracy to mpMRI prostate at identifying cancer
37 38	336	within the prostate. As mpMRI prostate is established in its ability to successfully identify prostate
39 40 41	337	cancer, this is a high standard to achieve. Even if PSMA-PET/CT does not supersede mpMRI prostate
42 43	338	in diagnostic accuracy, establishing comparable diagnostic accuracy may result in a viable alternative
44 45	339	for men who have contraindications to mpMRI.
46 47 48	340	The trial may also demonstrate (i) a synergistic effect in cancer diagnosis by the combination of the
49 50	341	two imaging techniques, (ii) a benefit for PSMA-PET/CT in men with equivocal mpMRI prostate
51 52 53 54 55	342	findings; (iii) benefit for men with concerning clinical features but negative/equivocal mpMRI
	343	prostate; and (iv) provide an all-encompassing diagnostic and staging scan for men who have high
56 57 58 59 60	344	risk features for metastatic disease at diagnosis. Unlike the PRIMARY trial, our PSMA-PET/CT

1

2 3	345	protocol encompasses chest, abdomen and pelvis, so will be able to add valuable information to this
4 5		
6 7	346	outcome.
8 9 10	347	Proprietary software from the GE Advantage® Workstation will perform co-registration between
10 11 12	348	mpMRI prostate and PSMA-PET/CT images will be utilised in this trial. Co-registration has potential
13 14	349	to improve targeting of prostate biopsy techniques, and help provide an alternative to expensive,
15 16 17	350	difficult to access hybrid PET/MRI machines.
18 19	351	After diagnostic accuracy of PSMA-PET/CT is established, its potential for significant economic
20 21	352	impact as a diagnostic test can be thoroughly investigated. Reductions in prostate biopsy,
22 23 24	353	efficiencies in consolidation of diagnostic and staging imaging tests, and using software co-
24 25 26	354	registration as an alternative to hybrid PET/MRI all represent potential economic benefits to our
27 28 29	355	health system.
30 31	356	The PEDAL trial commenced in March 2020, and although recruitment has been delayed due to
32 33	357	Covid 19 related adjustments in health care delivery the current aim is to complete recruitment in 36
34 35	358	months. This innovative study will add valuable evidence to demonstrate the diagnostic accuracy of
36 37 38	359	PSMA-PET/CT. It has potential to significantly impact how prostate cancer is diagnosed.
39 40 41	360	Funding statement
42 43	361	This clinical trial is supported by Cyclotek (Aust) Pty Ltd and their key partners, the Australian
44 45 46	362	Government as part of its CRC Projects Program, General Electrical Healthcare, Macquarie University
47 48	363	and the EJ Whitten Prostate Cancer Research Centre at Epworth Healthcare. We are also grateful for
49 50	364	philanthropic donations from Reese Limited, the Pitcher and Cicutto families via the St Vincent's
51 52 53	365	Foundation.
54 55 56	366	
57 58 59	367	Participating Centres
60	368	• St Vincent's Hospital, Melbourne VIC

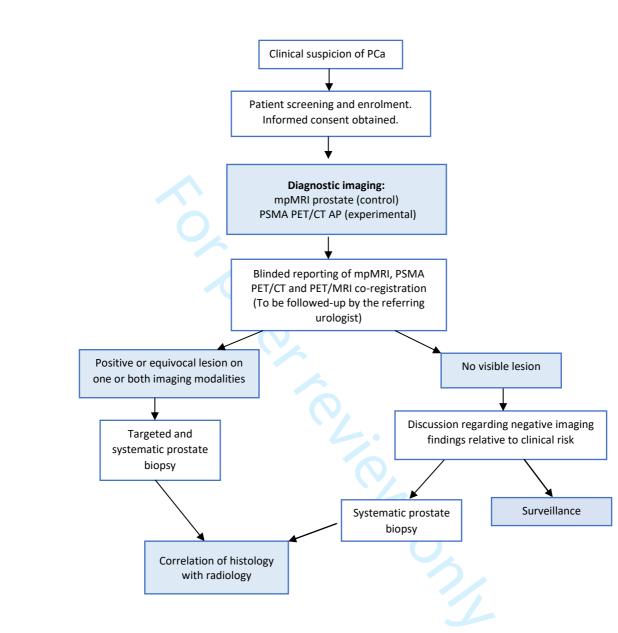
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2 3 4	369	• St Vincent's Private Hospital, Melbourne VIC
5 6	370	• The Royal Melbourne Hospital, VIC
7 8	371	• Epworth Healthcare, VIC
9 10	372	Sydney Adventist Hospital, NSW
11 12 13	373	Pacific Radiology Canterbury, Christchurch NZ
14 15	374	Declaration of Interests
16 17	574	
18 19	375	The authors confirm that there are no relevant financial or non-financial competing interests to
20 21	376	report.
22 23 24	377	
24 25 26		
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36 37		report.
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3 4	378	CONTRIBUTORSHIP STATEMENT
5 6	379	• Dr. Vy Tran: protocol design, ethical submission, procurement of funding, data collection,
7 8	380	statistical analysis, manuscript preparation, patient care, supervision
9 10 11	381	Dr Anne Hong: manuscript preparation, statistical analysis
12 13	382	• A/Prof. Tom Sutherland: protocol design, ethical submission, procurement of funding, data
14 15	383	collection, statistical analysis, manuscript preparation, patient care, supervision
16 17	384	• Dr. Kim Taubman: protocol design, ethical submission, procurement of funding, data
18 19 20	385	collection, statistical analysis, manuscript preparation, patient care, supervision
21 22	386	• Dr. Su-Faye Lee: protocol design, ethical submission, procurement of funding, data
23 24	387	collection, statistical analysis, manuscript preparation, patient care, supervision
25 26	388	Dr. Daniel Lenaghan: patient care, supervision
27 28 29	389	Dr. Kapil Sethi: patient care, supervision
30 31	390	A/Prof. Niall Corcoran: patient care, supervision
32 33	391	A/Prof. Nathan Lawrentschuk: patient care, supervision
34 35	392	Prof. Henry Woo: patient care, supervision
36 37 38	393	Dr. Lisa Tarlinton: patient care, supervision
39 40	394	Prof. Damien Bolton: manuscript preparation, supervision
41 42	395	• Dr. Tim Spelman: patient care, data collection, statistical analysis, supervision
43 44	396	Ms. Lauren Thomas: patient care, data collection
45 46 47	397	• Mr. Russell Booth: patient care, data collection
48 49	398	• Dr. Justin Hegarty: patient care, data collection
50 51	399	Dr. Elisa Perry: patient care, data collection
52 53	400	• A/Prof. Lih-Ming Wong: protocol design, ethical submission, procurement of funding, data
54 55 56	401	collection, statistical analysis, manuscript preparation, patient care, supervision
57 58	402	
59 60		

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4	403	Refer	rences
5			
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53	497		Med Mol Imaging 2021; <b>48</b> : 2038-2046.
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2 3	1	Appendix 1: Multiparametric Magnetic Resonance Imaging Protocol					
4 5							
6 7 8	2	IMAGING ACQUSITION:					
8 9 10	3	MRI prostate imaging is acquired as per international guidelines specified by Prostate Imaging-					
11 12 13	4	Reporting and Data System, version 2.1 (PIRADS V2.1).					
14 15	5	A multi-parametric MRI scan will be performed according to the following technical protocol,					
16 17	6	consistent with the highest standards of prostate MRI after appropriate bowel preparation (suggest					
18 19 20	7	Microlax suppository morning of diagnostic imaging) and buscopan or glucagon injection (where not					
21 22	8	contraindicated):					
23 24 25	9	3-Tesla magnet field strength					
26 27	10	32-channel cardiac coil, anteriorly and spinal coil posteriorly					
28 29	11	• T2 sequences to show pathology, aid localisation of the lesion, and to fuse with ultrasound					
30 31 32	12	for those Urologists using co-registration biopsy method.					
32 33 34	13	• High resolution T2 FSE in 3 planes: axial, coronal and sagittal					
35 36 27	14	<ul> <li>3D T2 sequence</li> </ul>					
37 38 39	15	Diffusion-Weighted Imaging (DWI) with software derived Apparent Diffusion Co-efficient (ADC)					
40 41 42	16	quantitative analysis maps, and multiple b-values (acquired b50, acquired b1400, calculated b2000);					
43 44	17	Dynamic Contrast Enhanced imaging (DCE) 3D imaging, with IV gadolinium DTPA bolus determined					
45 46	18	by body weight, at 2.5ml/second followed by T1 DCE TRICKS (Time-Resolved Imaging of Contrast					
47 48 49	19	KineticS).					
50 51 52	20	Analysis of DCEI according to PI-RADS DCEI analytic guidelines using PROCAD software					
53 54 55	21	<ul> <li>No use of Endo-rectal coils or MR Spectroscopy as per current guidelines</li> </ul>					
56 57 58	22	Approximate scan time 30 to 40 minutes					
59 60	23	CONTRAINDICATIONS TO MRI					

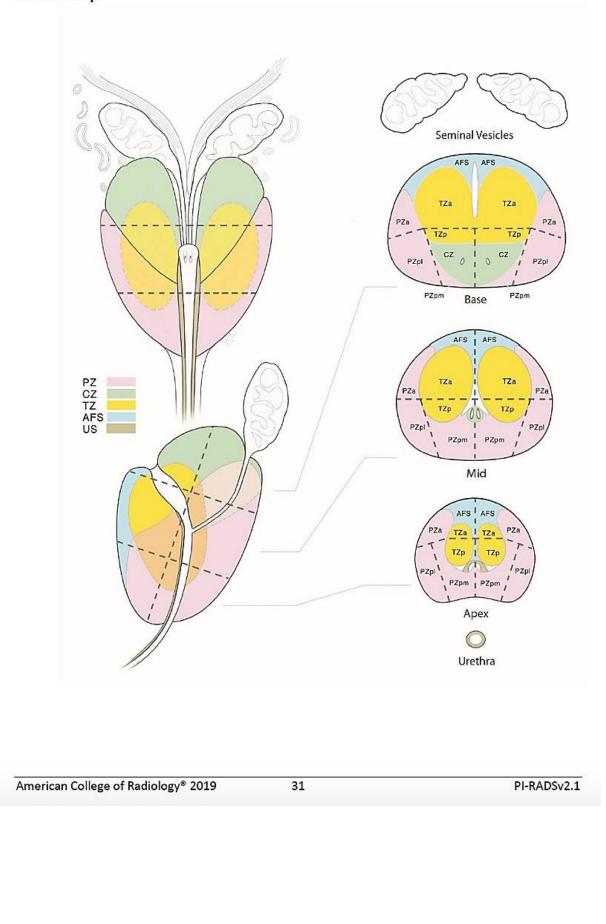
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3 4	24	Patient with any contraindication to MRI will not undergo MRI. This includes, but not restricted, to
5 6	25	pacemaker or other electronic implants, total hip joint replacement, known metal in the orbit, MR
7 8	26	incompatible surgical or cerebral aneurysm clips, shrapnel, non-removable body piercings.
9 10 11	27	REPORTING OF MPMRI PROSTATE
12 13 14	28	The mpMRI will be reported by experienced subspecialist Radiologists according to the Prostate
15 16	29	Imaging-Reporting and Data System, version 2.1, with each lesion categorised on a scale from 1 to 5.
17 18 19	30	OPTIMIZATION OF CO-REGISTRATION BETWEEN MPMRI PROSTATE AND PSMA-PET/CT
20		
21	31	To enable better co-registration of mpMRI to PSMA-PET/CT:
22	21	
23 24		
25	32	<ul> <li>option to use of suppositories to help eliminate gas/faeces from rectum</li> </ul>
26 27 28	33	ensure flat pelvis
29 30	34	<ul> <li>Use of structured knee bolster and strapping of feet to aid pelvic alignment</li> </ul>
31 32	35	
33 34 35	36	
36 37		
38	37	Appendix 2: Prostate Imaging-Reporting and Data System (version 2.1) Sector Map
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2 3		
4	41	Appendix 3: 18F-DCFPyL PSMA administration and PET/CT Imaging Protocol
5		
6	42	RADIOPHARMACEUTICAL
7		
8 9	40	195 DCEDul will be preduced at Cueletels (Aust) Dry Ltd under CMD License Number MI 12002005 LL
10	43	18F DCFPyL will be produced at Cyclotek (Aust) Pty Ltd under GMP Licence Number MI-12092005-LI-
11	44	000904-2 and (parametric) release after certain quality control tests are performed and transported
12		bobber 2 and (parametric) release arter certain quanty control tests are performed and transported
13	45	to the imaging site under regulatory criteria for dangerous goods. Cyclotek will provide the imaging
14 15		
16	46	site with a Quality Control Release notification form. Patients will complete the radiopharmaceutical
17		
18	47	consent form at their local site prior to injection.
19 20		
20 21	48	18F-DCFPYL PSMA INJECTION DOSING AND ADMINISTRATION
22	10	
23		
24	49	Patients will be administered a single, intravenous 250MBq bolus dose of 18F-DCFPyL PSMA
25 26	F.0	(accortable, 200, 200, 4Da depending on patient unight and activity provided on day of seen). The
20	50	(acceptable: 200-300MBq depending on patient weight and activity provided on day of scan). The
28	51	administered activity of 18F-DCFPyL PSMA is approximately 3MBq per kilogram body weight up to
29	71	
30	52	350 maximum dose.
31 32		
33		
34	53	18F-PSR PET/CT imaging protocol for initial diagnosis/staging of Prostate Ca Imaging Protocol
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36 27	54	Patient Preparation:
37 38		
39	55	• No fasting required. (*Must be well hydrated, approximately 1-2 litres of plain water in the 2 hours
40	55	• No fasting required. ( Must be wen hydrated, approximately 1-2 intes of plain water in the 2 hours
41	56	before appointment.)
42 42		
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45	57	• The activity is administered intravenously through a cannula either utilising the automatic injector
46	го	and a 100ml Calina has as via hand injection through the cannula utilizing the Embourings chiefd and
47	58	and a 100ml Saline bag or via hand injection through the cannula utilising the 5ml syringe shield and
48 49	59	2x10mls saline flushes.
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52	60	<ul> <li>The dose pre and post syringe activities and times must be recorded to work out the exact</li> </ul>
53	<b>C1</b>	a destruitate un dis satisfant for a de suite satisfant dis s
54 55	61	administered activity for the injection time.
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57	62	• Uptake Time: 120 minutes post 18F-DCFPyL injection. The patient is free to leave the department
58		
59 60	63	if they wish during this waiting time.
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• Patient to void before the scan

 66 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<sup>™</sup> iterative technique with β value of 400. Q-Clear<sup>™</sup> 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 

1		
2 3 4	88	kV 140, Smart mA 200, noise index 32
5 6	89	4.0min over pelvis (2)
7 8	90	3.5min for rest of body (4)
9 10	91	Total: 6 beds ~ 22min
11 12 13	92	Image Reconstruction: Images are reconstructed using the Q.Clear GE reconstruction method with a
14 15	93	β value of 400.
16 17	94	Workstation used for scan interpretation: GE AW Server 3.2 Ext 1.0 or Inteleviewer.
18 19	54	Workstation used for scan interpretation: GE AW Server 3.2 Ext 1.0 or Inteleviewer.
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# **BMJ Open**

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

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### 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

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#### 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 biopsynaïve men, resulting in a significant impact on patient management.

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

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## 

### 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  $\geq$ 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

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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

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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-DCFPyI-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

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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.

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	<b>ible 1. Study inclusion and exclusion criteria</b> dapted from New Medicare Benefits Scheme (MBS) for mpMRI of the prostate][20]
In	clusion criteria
In	<ul> <li>Men (≥18 years) with an elevated PSA who are suitable for an eligible MBS mpMRI prostate:         <ul> <li>(MBS items 63541 and 63542) AND who have NOT had recent (≤3 years) prostate bid or mpMRI prostate.</li> <li>For MBS items 63541 and 63542 (NK) the patient must be suspected of having prostancer based on (*):</li></ul></li></ul>
Fv	procedures clusion criteria
	<ul> <li>Known diagnosis of prostate cancer.</li> <li>Previous prostate biopsy within 3 years of recruitment. A transurethral resection of prostate performed for primary purpose of alleviating lower urinary tract symptoms considered acceptable.</li> <li>Previous mpMRI prostate within 3 years of recruitment.</li> <li>History of other active malignancy within the last 3 years, with the exception of non melanoma skin cancer or melanoma in-situ.</li> <li>Any absolute contra-indication to 3T mpMRI prostate, or previous history of total hi</li> </ul>
	<ul> <li>replacement.</li> <li>Significant intercurrent morbidity that, in the judgement of the investigator, would compliance with study protocols.</li> </ul>
DI	RE= digital rectal examination; mpMRI = multiparametric magnetic resonance imaging; PS/

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## 

### 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

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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

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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.

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# 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 coregistration.
- 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%.

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#### 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**

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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. Ninetyfive 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  $\geq$ 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

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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

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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<sup>®</sup> 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-

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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**

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### **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**

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1	
2 3 4	The authors confirm that there are no relevant financial or non-financial competing interests to
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## 

## 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

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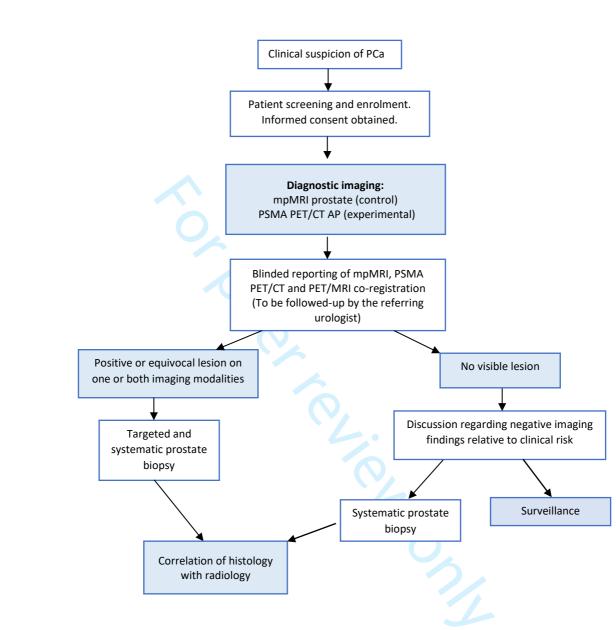
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## **FIGURE LEGEND**

Figure 1: trial schema.

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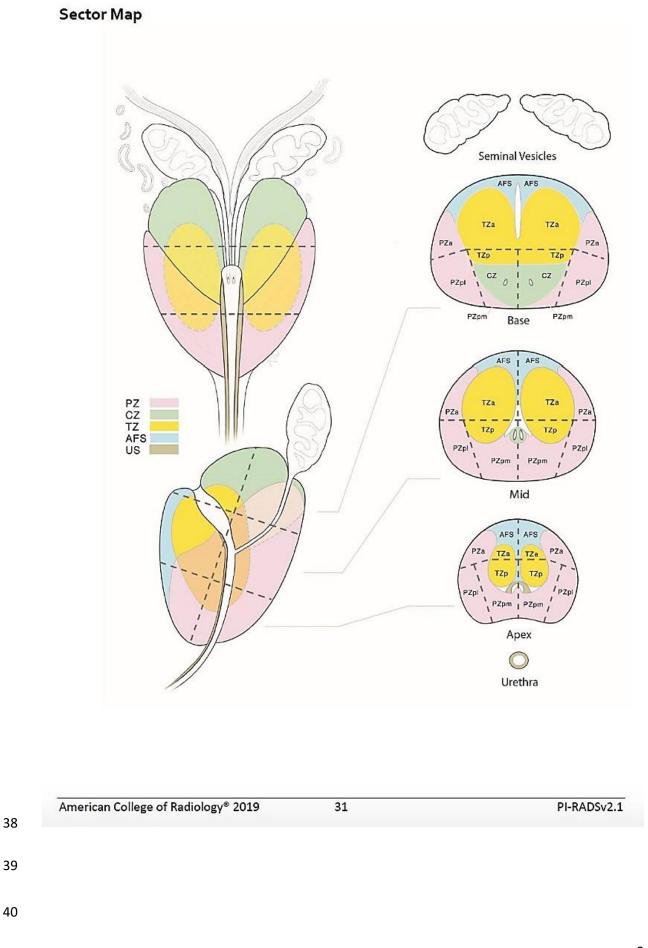
2 3	1	Appendix 1: Multiparametric Magnetic Resonance Imaging Protocol
4 5		
6 7 8	2	IMAGING ACQUSITION:
9 10	3	MRI prostate imaging is acquired as per international guidelines specified by Prostate Imaging-
11 12 13	4	Reporting and Data System, version 2.1 (PIRADS V2.1).
14 15	5	A multi-parametric MRI scan will be performed according to the following technical protocol,
16 17 18	6	consistent with the highest standards of prostate MRI after appropriate bowel preparation (suggest
19 20	7	Microlax suppository morning of diagnostic imaging) and buscopan or glucagon injection (where not
21 22 23	8	contraindicated):
23 24 25	9	3-Tesla magnet field strength
26 27 28 29 30 31 32	10	<ul> <li>32-channel cardiac coil, anteriorly and spinal coil posteriorly</li> </ul>
	11	• T2 sequences to show pathology, aid localisation of the lesion, and to fuse with ultrasound
	12	for those Urologists using co-registration biopsy method.
33 34 35	13	<ul> <li>High resolution T2 FSE in 3 planes: axial, coronal and sagittal</li> <li>3D T3 converses</li> </ul>
36 37	14	o 3D T2 sequence
38 39	15	Diffusion-Weighted Imaging (DWI) with software derived Apparent Diffusion Co-efficient (ADC)
40 41 42	16	quantitative analysis maps, and multiple b-values (acquired b50, acquired b1400, calculated b2000);
43 44	17	Dynamic Contrast Enhanced imaging (DCE) 3D imaging, with IV gadolinium DTPA bolus determined
45 46 47	18	by body weight, at 2.5ml/second followed by T1 DCE TRICKS (Time-Resolved Imaging of Contrast
48 49	19	KineticS).
50 51 52	20	Analysis of DCEI according to PI-RADS DCEI analytic guidelines using PROCAD software
53 54 55	21	<ul> <li>No use of Endo-rectal coils or MR Spectroscopy as per current guidelines</li> </ul>
56 57 58	22	Approximate scan time 30 to 40 minutes
59 60	23	CONTRAINDICATIONS TO MRI

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3	24	Patient with any contraindication to MRI will not undergo MRI. This includes, but not restricted, to
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5	25	pacemaker or other electronic implants, total hip joint replacement, known metal in the orbit, MR
6		
7 8	26	incompatible surgical or cerebral aneurysm clips, shrapnel, non-removable body piercings.
9		
10		
11	27	REPORTING OF MPMRI PROSTATE
12		
13	28	The mpMRI will be reported by experienced subspecialist Radiologists according to the Prostate
14 15		
15 16	29	Imaging-Reporting and Data System, version 2.1, with each lesion categorised on a scale from 1 to 5.
17		
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19	30	OPTIMIZATION OF CO-REGISTRATION BETWEEN MPMRI PROSTATE AND PSMA-PET/CT
20		
21	31	To enable better co-registration of mpMRI to PSMA-PET/CT:
22 23		
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25	32	<ul> <li>option to use of suppositories to help eliminate gas/faeces from rectum</li> </ul>
26		
27	33	ensure flat pelvis
28	24	
29 30	34	<ul> <li>Use of structured knee bolster and strapping of feet to aid pelvic alignment</li> </ul>
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38	37	Appendix 2: Prostate Imaging-Reporting and Data System (version 2.1) Sector Map
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3 4 5	41	Appendix 3: 18F-DCFPyL PSMA administration and PET/CT Imaging Protocol
6 7	42	RADIOPHARMACEUTICAL
8 9 10	43	18F DCFPyL will be produced at Cyclotek (Aust) Pty Ltd under GMP Licence Number MI-12092005-LI-
11 12	44	000904-2 and (parametric) release after certain quality control tests are performed and transported
13 14 15	45	to the imaging site under regulatory criteria for dangerous goods. Cyclotek will provide the imaging
16 17	46	site with a Quality Control Release notification form. Patients will complete the radiopharmaceutical
18 19	47	consent form at their local site prior to injection.
20 21 22	48	18F-DCFPYL PSMA INJECTION DOSING AND ADMINISTRATION
23 24 25	49	Patients will be administered a single, intravenous 250MBq bolus dose of 18F-DCFPyL PSMA
26 27	50	(acceptable: 200-300MBq depending on patient weight and activity provided on day of scan). The
28 29	51	administered activity of 18F-DCFPyL PSMA is approximately 3MBq per kilogram body weight up to
30 31 32	52	350 maximum dose.
33 34 35	53	18F-PSR PET/CT imaging protocol for initial diagnosis/staging of Prostate Ca Imaging Protocol
36 37 38	54	Patient Preparation:
39 40	55	• No fasting required. (*Must be well hydrated, approximately 1-2 litres of plain water in the 2 hours
41 42 43	56	before appointment.)
44 45	57	• The activity is administered intravenously through a cannula either utilising the automatic injector
46 47 48	58	and a 100ml Saline bag or via hand injection through the cannula utilising the 5ml syringe shield and
49 50	59	2x10mls saline flushes.
51 52 53	60	• The dose pre and post syringe activities and times must be recorded to work out the exact
54 55	61	administered activity for the injection time.
56 57 58	62	• Uptake Time: 120 minutes post 18F-DCFPyL injection. The patient is free to leave the department
59 60	63	if they wish during this waiting time.

Patient to void before the scan

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<sup>™</sup> iterative technique with β value of 400. Q-Clear<sup>™</sup> 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

1		
2 3	88	kV 140, Smart mA 200, noise index 32
4 5		
6 7	89	4.0min over pelvis (2)
8 9	90	3.5min for rest of body (4)
9 10 11	91	Total: 6 beds ~ 22min
12 13	92	Image Reconstruction: Images are reconstructed using the Q.Clear GE reconstruction method with a
14 15	93	β value of 400.
16 17	94	Workstation used for scan interpretation: GE AW Server 3.2 Ext 1.0 or Inteleviewer.
18 19	-	Workstation used for scan interpretation: GE AW Server 3.2 Ext 1.0 or Inteleviewer.
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		Standard Protocol Items: Recommendations for Interventional Trials	
SPIRIT 2013 Check	klist: Rec	ommended items to address in a clinical trial protocol and related documents*	
Section/item	ltem No	Description	Addressed on page number
Administrative inf	ormatior	n Downlo	
Title	1	ਰ ਜ਼ਾਂ ਕੂੱ Descriptive title identifying the study design, population, interventions, and, if apple attentions, and if apple	<u>1</u>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	<u>143-145</u>
	2b	All items from the World Health Organization Trial Registration Data Set	<u>145</u>
Protocol version	3	Date and version identifier	<u>145</u>
Funding	4	Sources and types of financial, material, and other support	<u>192-198, 419-424</u>
Roles and	5a	Names, affiliations, and roles of protocol contributors	<u>5-24, 437-460</u>
responsibilities	5b	Name and contact information for the trial sponsor	<u>420-425</u>
	5c	Role of study sponsor and funders, if any, in study design; collection, managemers, a study a linterpretation 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	<u>151-153</u>
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups over seeing the trial, if applicable (see Item 21a for data monitoring committee) For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	<u>Not applicable</u>
		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	1

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1 2	Introduction		ight, i	
- 3 4 5	Background and rationale	6a	Description of research question and justification for undertaking the trial, including symmary of relevant studies (published and unpublished) examining benefits and harms for each intervention	<u>129-139</u>
6 7		6b	Explanation for choice of comparators	<u>165-171</u>
8 9	Objectives	7	Specific objectives or hypotheses	<u>269-275</u>
10 11 12 13	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, facting is single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploration is superiority)	<u>165-172</u>
14 15	Methods: Participa	nts, inte	erventions, and outcomes	
16 17 18	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of by the settings (eg, community clinic, academic hospital) and list of by the setting the setting be collected. Reference to where list of study sites can be obtained	<u>427-433</u>
19 20 21	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)	<u>183</u>
22 23 24 25 26 27 28	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including hor and when they will be administered	<u>165-172</u>
		11b	Criteria for discontinuing or modifying allocated interventions for a given trial parties to harms, participant request, or improving/worsening diseas	Not applicable
29 30 31		11c	Strategies to improve adherence to intervention protocols, and any procedures for the most itoring adherence (eg, drug tablet return, laboratory tests)	Not applicable
32 33		11d	Relevant concomitant care and interventions that are permitted or prohibited durined the trial	<u>179-181</u>
34 35 36 37 38 39	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	<u>277</u>
40 41 42	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)	<u>154</u>
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1 2	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was betermined, including clinical and statistical assumptions supporting any sample size calculations	<u>280-290</u>
3 4 5	Recruitment	15	으로 ਯ Strategies for achieving adequate participant enrolment to reach target sample size 음 고 급	<u>289-290</u>
6 7	Methods: Assignme	ent of ir	nterventions (for controlled trials)	
8 9	Allocation:		ember Ses reiginality in the second set of the second	
10 11 12 13 14 15	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random not be provided in a separate document that is unavailable to the sequence participants or assign interventions	Not applicable
16 17 18 19	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequer sealed envelopes), describing any steps to conceal the sequence until in the sequence are assigned	Not applicable
20 21 22	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who what a sign participants to interventions	Not applicable
23 24 25 26	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	<u>305-312</u>
27 28 29		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	<u>310-312</u>
30 31 32	Methods: Data colle	ection,	management, and analysis	
33 34 35 36 37	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 additive formation. Reference to where data collection forms can be found, if not in the protocol	<u>292-303</u>
38 39 40 41		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	<u>189-190</u>
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1 2 3 4	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	<u>287-291</u>
5 6 7	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where details of the statistical analysis plan can be found, if not in the protocol	<u>314-320</u>
8 9		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	<u>314-320</u>
10 11 12 13		20c	Definition of analysis population relating to protocol non-adherence (eg, as rando and any statistical methods to handle missing data (eg, multiple imputation)	<u>289-290</u>
14 15	Methods: Monitorin	ng	and of a second se	
16 17 18 19 20	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and report returns; statement of whether it is independent from the sponsor and competing interests; and reference whether further details about its charter can be found, if not in the protocol. Alternatively, an explanation of whether is needed	<u>291</u>
21 22 23 24		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
25 26 27	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneous ly peported adverse events and other unintended effects of trial interventions or trial conduct	<u>362-369</u>
28 29 30 31	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	<u>300-301</u>
32 33	Ethics and dissemi	nation	in on investigators and the sponsor ologies.	
34 35 36	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	<u>144-146</u>
37 38 39 40 41 42	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility crueria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial regiseries, journals, regulators)	<u>171-172</u>
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Conser	nt or assent	26a	Who will obtain informed consent or assent from potential trial participants or autherised surrogates, and <u>175-177</u> how (see Item 32)	
		26b	Additional consent provisions for collection and use of participant data and biolog as specimens in ancillary <u>175-177</u> studies, if applicable	
Confide	entiality	27	How personal information about potential and enrolled participants will be collected and ared, and maintained 292-303 in order to protect confidentiality before, during, and after the trial	
Declara interest		28	Financial and other competing interests for principal investigators for the overall transformed by $\frac{1}{2}$ and each study site $\frac{434-436}{434-436}$	
Access	s to data	29	Statement of who will have access to the final trial dataset, and disclosure of contrestinal agreements that <u>301-303</u> limit such access for investigators	
Ancillar trial car	ry and post- re	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those suffer harm from trial <u>362-366</u>	
Dissem	nination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, <u>64-68</u> the public, and other relevant groups (eg, via publication, reporting in results data as s, or other data sharing arrangements), including any publication restrictions	
		31b	Authorship eligibility guidelines and any intended use of professional writers	
Appen	dices	31c	Plans, if any, for granting public access to the full protocol, participant-level datas and statistical code for publicat for publicat	
	ed consent	32	سن الحكوب الحكوب المحتود المحت المحتود المحتود المح	<u>ed</u>
Biologio specim		33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular Not application analysis in the current trial and for future use in ancillary studies, if applicable	ible
Amend	lments to the p	rotocol	that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Groups under the Creative Commons	items.
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