CLINICAL STUDY PROTOCOL

(ICTU ADOPTED)

Full Study Title:
Imperial Prostate 7 - **P**rostate **A**ssessment using **C**omparative **I**nterventions – **F**ast mri and **I**mage-fusion for **C**ancer

Short Study title / Acronym:
IP7-PACIFIC

Sponsor:
Imperial College London

Version no:
3.0

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This protocol has regard for the HRA guidance

RESEARCH REFERENCE NUMBERS

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Bi-parametric MRI
Visual-registration targeted biopsy
Image-fusion targeted biopsy
Randomised controlled trial

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This protocol describes the IP7-PACIFIC trial and provides information about procedures for enrolling participants to the trial. The protocol should not be used as a guide for the treatment of other participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study, but centres enrolling participants for the first time are advised to contact the Trial Coordination centre to confirm they have the most recent version. Problems relating to this trial should be referred, in the first instance, to the Trial Coordination centre.

This trial will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research and the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. It will be conducted in compliance with the protocol, the Data Protection Act 2018 and other regulatory requirements as appropriate.

ABBREVIATIONS

AE	Adverse Event
bp	Biparametric
CI	Chief Investigator
CRF	Case Report Form
DMC	Data Monitoring and Ethical Committee
DRE	Digital Rectal Examination
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EPIC	Expanded Prostate Index Composite
HADS	Hospital Anxiety and Depression Scale
HRA	Health Research Authority
ICHNT	Imperial College Healthcare NHS Trust
ICMJE	International Committee of Medical Journal Editors
ICTU	Imperial Clinical Trials Unit
ISUP	International Society of Urologic Pathology
ITT	Intention to Treat
LSLV	Last Subject Last Visit
MDT	Multidisciplinary team
mp	Multi-parametric
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NHSCR	National Health Service Care Register
PSA	Prostate Specific Antigen
PSS	Personal Social Services
QA	Quality Assurance
QALAY	Quality-Adjusted Life-Year
QC	Quality Control
REC	Research Ethics Committee
RGIT	Research Governance and Integrity Team
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure

TMG	Trial Management Group
TSC	Trial Steering Committee

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TRIAL SUMMARY

TITLE	Imperial Prostate 7 - **P**rostate **A**ssessment using **C**omparative **I**nterventions – **F**ast mri and **I**mage-fusion for **C**ancer
OBJECTIVES	To evaluate the role of biparametric MRI and image-fusion targeted biopsies for the detection of prostate cancer
Primary Objective (Randomisation 1)	To determine whether biparametric MRI (bpMRI) could be recommended as an alternative to multiparametric MRI (mpMRI) for the detection of clinically significant prostate cancers in patients at risk
Primary Objective (Randomisation 2)	To determine whether image-fusion targeted biopsy is better than visual-registration (cognitive) targeted biopsy at detecting clinically significant prostate cancers in patients requiring prostate biopsy due to a suspicious MRI
Secondary Objectives	To evaluate the NHS healthcare burdens of bpMRI compared to mpMRI, and image-fusion technology compared to visual-registration targeting, in terms of adverse events, proportion of patients biopsied and proportion of patients diagnosed with clinically significant and insignificant cancers that do not require treatment To determine the impact of bpMRI and image-fusion targeting on detecting clinically significant cancer using other commonly used histological definitions of clinical significance To evaluate NHS costs and cost-effectiveness of bpMRI compared to mpMRI, and image-fusion technology compared to visual-registration targeting as well as model the various combinations of MRI and targeting strategies
DESIGN	Randomised controlled trial
SAMPLE SIZE	3600
INCLUSION AND EXCLUSION CRITERIA	
Randomisation 1	*Inclusion* - Age 18 years or above (no upper limit) - Patients with a prostate (either cis-male gender or trans-female gender with no prior androgen deprivation hormone use at all). - Referred to hospital and advised to undergo a prostate MRI because of an abnormal digital rectal examination (regardless of PSA level) and/or an elevated PSA (within 6 months of screening visit) PSA >/=3.0ng/ml for age 50-69 years

	PSA >/=5.0ng/ml for age >/=70 years If family or ethnic risk for prostate cancer, PSA >/=2.5ng/ml for age 45-49 years *Exclusion* - PSA >50ng/ml - Prior prostate MRI or prostate biopsy in the two years prior to screening visit - Prior diagnosis of prostate cancer - Contraindication to MRI or gadolinium contrast - Previous hip replacement to both hips - Contraindication to performing a biopsy guided by a transrectal ultrasound probe
Randomisation 2	*Inclusion* Visible suspicious finding on mpMRI or bpMRI from randomisation 1 requiring a targeted biopsy (MRI score 3, 4, 5 on either Likert or PIRADS [latest version as defined in MRI Reporting SOP] schema) *Exclusion* As above for randomisation 1 Patient refusal for biopsy
MAIN STUDY PROCEDURES	*Randomisation 1* Multi-parametric MRI compared to biparametric MRI *Randomisation 2* Targeted biopsy performed using image-fusion targeted and systematic biopsies compared to visual-registration targeted and systematic biopsies in patients with visible suspicious finding on either bpMRI or mpMRI. Duration of follow-up: For up to 12 weeks after enrolment.
OUTCOME MEASURES (PRIMARY ENDPOINTS)	
Randomisation 1	Proportion of clinically significant cancers, defined as any amount of Gleason >/=3+4 (ISUP Grade Group >/=2) on biopsy, detected in the randomised population of patients at risk.
Randomisation 2	Proportion of clinically significant cancers, defined as any amount of Gleason >/=3+4 (ISUP Grade Group >/=2) on biopsy, detected in the randomised population of patients biopsied for a suspicious MRI.
OUTCOME MEASURES (SECONDARY ENDPOINTS)	
	Proportion recommended for biopsy in randomised arm Proportion actually biopsied in each randomised arm

	Proportion diagnosed with clinically insignificant prostate cancer (defined as any Gleason 3+3=6 [ISUP Grade Group 1]) Proportion of clinically significant and insignificant cancers using other histological definitions of clinical significance - PROMIS 1 and 2 - any Gleason >/=4+3 [ISUP Grade Group >/=3] - Gleason >/=3+4 [ISUP grade Group >/=2] or any Gleason 3+3 [ISUP Grade Group 1] of >/=6mm - Gleason >/=3+4 [ISUP grade Group >/=2] with >/=10% pattern 4 OR presence of cribriform pattern OR presence of intraductal components Detection rates for each randomised group of known prognostic risk categories. These are D'Amico, National Comprehensive Cancer Network (NCCN) and Cambridge Prognostic Groups (CPG). Adverse events and patient reported outcomes Outcomes by centre stratified by size and type of MRI scanner, route of biopsy and amount of systematic sampling. Healthcare resource utilisation, costs and cost-effectiveness of using fastMRI compared to mpMRI and image-fusion compared to cognitive targeted biopsies Consent for linkage to national databases to collect medium and long-term outcomes including new diagnostic tests, prostate cancer diagnoses and treatments, deaths and prostate cancer deaths

1. BACKGROUND

Every year, 150,000 men suspected of prostate cancer are referred to UK hospitals, rising to 250,000/year by 2030 [Cancer Research UK, 2020]. The prostate cancer diagnostic pathway has undergone a transformation over the last two years [NHS England Timed Pathway, 2018]. Studies from the UK, such as NIHR-HTA PROMIS (CI: Emberton/Ahmed) [Ahmed et al, 2017; Brown et al, 2018], NIH PICTURE (CI: Ahmed) [Simmons et al, 2017], and NIHR PRECISION (CI: Emberton/Moore) [Kasivisvanathan et al, 2018], along with many other high-quality international studies, have shown that mpMRI before biopsy can allow one-third of men to avoid an immediate biopsy, reduce overdiagnosis with 40% fewer clinically-unimportant cancers and detect about 15% more clinically-important cancers [Drost et al, 2019]. Such a pathway change was shown to be cost-effective for the NHS [Faria et al, 2018], with NHS England, NICE, European and American guidelines changing their recommendations [NHS England Timed Pathway, 2018; NICE Guideline, 2019; Bjurlin et al, 2019, EAU Prostate Cancer Guidelines, 2019].

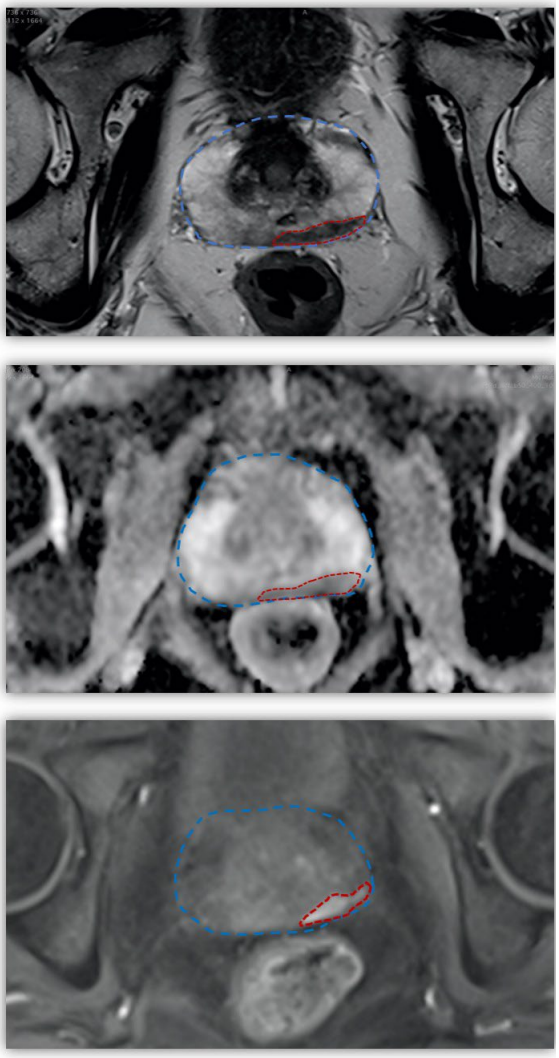


Figure 1: A 66 year old patient with PSA 6.3ng/ml. (a) Axial T2-weighted images shows an area with low signal intensity in the left peripheral zone which on (b) diffusion weighted imaging (DWI) (ADC) shows a suspicious area that also (c) shows avid enhancement on dynamic contract enhanced (DCE) imaging. The targeted and systematic biopsies confirm clinically significant prostate cancer Gleason 4+3=7, 9mm in the 6 targeted cores only. Systematic biopsies showed no cancer in non-suspicious areas. In this case, the bpMRI (data from (a) and (b) alone) would have been sufficient for diagnosis without the need for contrast in (c) as used in mpMRI.

Since biopsies can cause side-effects such as pain, bleeding and infection, a non-suspicious mpMRI can allow some men to avoid an invasive biopsy as the probability of clinically significant prostate cancer is low. In the UK, a decision on whether to carry out a biopsy is then based on the mpMRI findings in combination with other clinical factors; about a quarter can avoid an immediate biopsy due to a low risk of harbouring clinically significant prostate cancer. In most centres, if a biopsy is indicated, it is guided by ultrasound with the operator estimating where to deploy the biopsy needle in order to take tissue samples; what is commonly referred to as visual-registration targeting. We want to test two major changes that might further improve this new pathway.

First, mpMRI takes 40 minutes, requires intravenous gadolinium contrast and costs £239 (NHS HRG 2020 Tariff) in the UK NHS. Administration of gadolinium requires medical supervision due to a risk of anaphylaxis. Further, there is concern about its deposition in the brain although there is uncertainty about whether this causes harm. In addition, many hospitals struggle with scanner time and this can lead to patients with suspected prostate

cancer and other medical conditions waiting longer [Royal of College of Radiology 2017]. A 15 minute, bpMRI that does not involve injection of gadolinium contrast and costs £141 (NHS HRG 2020 Tariff) might be as accurate as mpMRI in ruling-out and detecting clinically significant prostate cancer.

Further, capacity constraints mean that many hospitals are unable to scan all the men referred with suspected prostate cancer quickly enough to meet NHS cancer waiting time targets. Indeed, the extra prostate mpMRI scans might lead to patients with other medical conditions having to wait longer. An April 2017 Royal College of Radiology report stated that of 53 organisations surveyed, the mean anticipated increase in workload for scanning was 13%. This survey was conducted prior to the PROMIS study was published and might be an underestimate as it did not take into account the number of expected prostate mpMRI scans. A bpMRI would free up over 4,500 days of scanner time every year within the NHS, equivalent to approximately 100,000 extra bpMRI scans per year. This is because examination time for scanning is different to MRI time slots which have to include the time taken to safety-check, set-up intravenous access and set up the contrast pump, get patients into the magnet/positioned, perform planning sequences, localisers, and after scanning getting the patient off the table. The immediate cost saving to NHS commissioners in tariff payments of not having to use contrast-enhanced mpMRI would be £6.7 Million every year, with further potential savings from not requiring on-site medical cover and reductions in the length of time to review scans as there are fewer images to look at, so helping to free up expert radiology time. The NHS will also be able to scan more patients in a timely fashion.

Second, for those men needing a targeted biopsy, visual-registration requires highly skilled operators that are not available everywhere. This means that clinically significant cancers might be missed. Image-fusion technology that overlays MRI and ultrasound images might improve the detection of clinically significant prostate cancer as they can guide the biopsy needle to within 2-3mm accuracy.

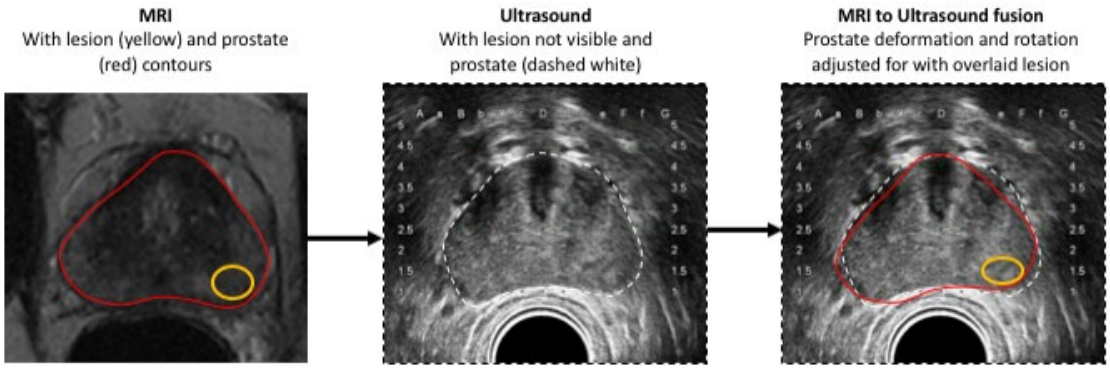


Figure 2. MRI to ultrasound image fusion for targeted biopsy. The lesion is not visible on ultrasound so visual-registration targeting would be based on the operator looking at the MR-images on a separate screen (which is often in a different room) and then estimating where to deploy the needles. With image-fusion, tissue deformation and rotation can be taken into account with the lesion demonstrated as an overlaid contour on the ultrasound.

bpMRI and mpMRI

Systematic reviews of non-randomised comparisons have shown bpMRI might be as accurate as mpMRI [Woo et al, 2018; Niu et al, 2018; Kang et al, 2018; Chen et al, 2017; Alabousi et al, 2019]. The most recent included studies up to October/2017 [Alabousi et al, 2019] (25 mpMRI studies with 7000 patient vs. 12 bpMRI studies with 2716 patients) showed no significant difference in pooled sensitivity (mpMRI: 86%, 95%CI 81–90; bpMRI: 90%,

95%CI 83–94) or specificity (mpMRI: 73%, 95%CI 64–81; bpMRI: 70%, 95%CI 42–83). Our updated (Oct/2017-July/2019) systematic review reinforced this finding from 11 further studies with 3488 patients [Bass et al, 2021]. This is reinforced by further analyses of our paired-cohort studies, PROMIS and PICTURE. PROMIS used template mapping biopsies as a reference test and blinding between those assessing imaging and biopsy in 576 men. It has shown similar sensitivity between mpMRI and bpMRI (95% vs. 94%) and specificity (38% vs. 37%) [Kirkham et al, 2019]; these data are supported by the PICTURE [Eldred-Evans et al, 2019]. Recently, another case series of 264 UK patients showed that bpMRI detected 93.5% of clinically significant prostate cancers compared to 94.6% with mpMRI [Zawaideh et al, 2020]. The BIDOC study has also shown high accuracy of bpMRI [Boesen et al, 2018].

Whilst useful and encouraging the studies are limited in informing NHS practice. For example, in many studies the radiologist gave a bpMRI score first. They then gave a score based on the mpMRI of the same men. In a number of studies, there may have been reporter bias, as the radiologists knew that the actual decision for doing a biopsy would be based on the mpMRI result. As a result, we do not know whether radiologists would score the bpMRI, and whether urologists would make similar recommendations about biopsy, if the mpMRI was not available. Clinicians and guideline committees are aware of this and in order to provide convincing high quality, reliable evidence concerning a recommendation about use of bpMRI that would change routine practice, a randomised controlled trial is required in which prostate cancer detection is compared in men receiving only bpMRI to men receiving mpMRI. Indeed, the systematic reviews all caution against applying these results to clinical practice due to heterogeneity among the included studies and lack of level 1 clinical utility comparative studies to assess biopsy avoidance, clinically significant prostate cancer detection and over-diagnosis of clinically insignificant prostate cancer [Brizmohun et al, 2018; Padhani et al, 2018; Coakley et al, 2017; Schoots et al, 2020].

Visual-registration and image-fusion targeted biopsies

We [Valerio et al, 2015; Bass et al, 2020] and others [Verma et al, 2017; Gayet et al, 2016; Sarkar et al, 2018; Tang et al, 2018; Wegelin et al, 2017] have conducted systematic reviews showing that further research is required on image-fusion. We recently updated the systematic review by Wegelin et al with inclusion dates updated to Dec/2015 to July/2019); we found 32 further studies with image-fusion and 6 studies with visual-registration showing residual uncertainty remains and higher quality comparative studies are required [Bass et al, 2021]. The Chief Investigator has also led the Wellcome-funded SmartTarget [Hamid et al, 2019] and NIH PICTURE [Simmons et al, 2018] paired-cohort validation studies showing image-fusion targeting increased clinically significant prostate cancer detection by approximately 10-15% compared to visual-registration alone. Again, high quality randomised comparative data assessing clinical utility are now required to definitively determine clinical and cost-effectiveness of image-fusion targeting over visual-registration if guidelines and clinical practice are to change.

2. OBJECTIVES AND ENDPOINTS

2.1 Primary Objectives

Randomisation-1: bpMRI versus mpMRI

In those patients suspected to have prostate cancer, to determine whether bi-parametric MRI (bpMRI), compared to multi-parametric MRI (mpMRI), is able to accurately rule-out and detect clinically significant prostate cancer (any Gleason score >/=7 [ISUP Grade Group >/=2]), without increasing the number of patients biopsied or diagnosed with clinically insignificant prostate cancer.

Randomisation-2: Visual-registration targeting versus image-fusion targeting

In those patients recommended to have a prostate biopsy due to a suspicious MRI (bpMRI or mpMRI), to determine if new technology using MRI to ultrasound image-fusion to carry out targeted prostate biopsies is better at detecting clinically significant prostate cancer (any Gleason score >/=7 (any Gleason score >/=7 [ISUP Grade Group >/=2]), compared to biopsies carried out using visual-registration targeting.

2.2 Secondary Objectives

Clinical

- To determine whether bpMRI is non-inferior to mpMRI in terms of the proportion of patients recommended for biopsy.
- To evaluate adverse events from MRI scans and biopsies.
- To determine the differences between proportions of patients diagnosed with clinically insignificant prostate cancers following bpMRI or mpMRI.
- To measure the proportion of patients declining a biopsy when advised to have it and the proportion of patients who choose to have a biopsy when it is not advised by their clinical team.
- To determine the impact of bpMRI, when compared to mpMRI, on detecting clinically significant prostate cancer using other accepted histological definitions of cancer significance in combination with staging criteria for clinical significance [Ahmed et al, 2011; Matoso and Epstein, 2019; Ahmed et al, 2012; Eggener et al, 2015; Ploussard et al, 2011].
- To evaluate the impact of the different MRI scores (on a scale from 1 to 5) on biopsy recommendations, and potential subsequent diagnosis of clinically significant and clinically insignificant prostate cancers, using all histological thresholds of significance, and within each randomised group.
- To investigate clinical risk factors (age, total PSA, PSA-density, family history, ethnicity, prior prostate biopsy before the 2 years exclusion criteria) in relation to diagnosis of clinically significant prostate cancer using all the definitions of significance.
- Detection rates for each randomised group following each randomisation of known risk groupings. These are D'Amico [D'Amico et al, 1998], National Comprehensive Cancer Network (NCCN) [Mohler et al, 2019] and Cambridge Prognostic Groups (CPG) [Gnapragasam et al, 2018].
- To compare the Likert and PIRADS [latest version as defined in MRI Reporting SOP] reporting schemes in terms of proportions biopsied, and subsequently diagnosed with clinically significant and clinically insignificant prostate cancers, within each randomised group, using all histological thresholds of significance.
- Patient reported outcome and experience measures using validated questionnaires.

- To evaluate the impact of difference centres by size, stratified by MRI scanner type, biopsy route and amount of systematic biopsies taken, on cancer detection rates and patient reported outcomes.

Health economics

- To estimate incremental cost to the NHS and Personal Social Services (PSS) and incremental cost per clinically significant cancer detected and incremental cost per correct diagnosis.
- Modelled healthcare resource utilisation, NHS and PSS costs and incremental cost per QALY of using bpMRI compared to mpMRI; and using image-fusion compared to visual-registration. The model will incorporate the costs and impacts of potential changes in rates of biopsy and cancer treatment with different types of MRI and different type of biopsy strategy

2.3 Primary Endpoint

Randomisation-1: bpMRI versus mpMRI

Proportion of clinically significant cancers, defined as any amount of Gleason >/=3+4 (ISUP Grade Group >/=2) on biopsy, detected in the randomised population of patients at risk.

Randomisation-2: Visual-registration targeting versus image-fusion targeting

Proportion of clinically significant cancers, defined as any amount of Gleason >/=3+4 (ISUP Grade Group >/=2) on biopsy, detected in the randomised population of patients biopsied for a suspicious MRI.

2.4 Secondary Endpoints

Clinical

In each of the randomised groups, secondary outcomes are:

- MRI and biopsy-related adverse events and serious adverse events
- The proportion of patients advised to undergo a needle biopsy and the proportion of patients undergoing a prostate biopsy after MRI. We will document common reasons for patients who are advised to undergo a biopsy who decline and reasons for patients who are advised against a needle biopsy who still choose to have a biopsy. We shall record the number of patients with a non-suspicious bpMRI/mpMRI that are recommended for biopsy and the types cancers subsequently detected.
- The proportion of patients diagnosed with clinically insignificant prostates cancers, defined as any Gleason 3+3=6 on needle biopsy carried out after MRI. These will also be stratified by MRI score, presence of clinical risk factors and whether the biopsy was carried out on clinician recommendation or patient choice.
- The proportion of patients diagnosed with clinically significant and clinically insignificant prostate cancers using other histological thresholds, on prostate biopsy carried out after MRI. Similarly, as above, we will also evaluate these proportions by MRI score at patient and lesion level (on a scale of 1 to 5) and by presence or absence of clinical risk parameters.

- The proportion of patients diagnosed with clinically significant and clinically insignificant prostate cancers using all histological thresholds on targeted biopsy using 4 targeted cores only compared to 6 targeted cores for the first targeted lesion.
- Detection rates for each randomised group of known prognostic risk categories. These are D'Amico, National Comprehensive Cancer Network (NCCN) and Cambridge Prognostic Groups (CPG).
- A comparison of the two MRI scoring systems, Likert and PIRADS [latest version as defined in MRI Reporting SOP], in terms of the proportion of patients biopsied and subsequently diagnosed with clinically significant and clinically insignificant prostate cancer, using each of the histological thresholds, on a prostate biopsy. Our study would be an opportunity to conduct a robust comparison of the two reporting systems in a large sample and allow inclusion in meta-analyses with studies that used either one alone.
- Characteristics of cancer in targeted versus systematic biopsies and by MRI score, PSA, PSA density, age, ethnicity, family history and history of prior prostate biopsy with a multivariable evaluation to determine patients might avoid systematic sampling in future.
- External validation of the Imperial RAPID Risk Score (MRI+) and Imperial RAPID Risk Score (Systematic+) within each randomised group of the IP7-PACIFIC study
- Impact of prostate biopsy in each randomised group on patient reported outcomes and patient reported experience measures using an updated version of the Prospective cohort study (Prostate Biopsy Effects: ProBE) questionnaire [Rosario et al, 2012] and the EQ-5D-5L health-related quality of life questionnaire, and stratified by type of biopsy (transrectal vs. transperineal; for transperineal biopsy, limited systematic vs. sectoral systematic.
- Analysis of biopsy rates and detection of cancer (by all histological thresholds) as well as patient reported outcomes and experience measures in randomised group will be conducted by centre using centre size. MRI scanner type (1.5Tesla vs. 3.0Tesla), type of biopsy route used (transrectal vs. transperineal), number of systematic biopsy taken (limited systematic vs. extended systematic biopsy), type of analgesia/anaesthetic (local anaesthetic, sedation or general anaesthetic) as additional stratification factors.

Definitions of clinical significance on biopsy

As well as the primary outcome definition of any amount of Gleason 3+4 or greater on any one or more biopsy cores, we will also use the following histological thresholds:
i) any amount of Gleason 4+3=7 or more
ii) any amount of Gleason >/=4+3 OR Gleason 3+3=6 of >/=6mm (PROMIS definition 1)
iii) any amount of Gleason >/=3+4 OR Gleason 3+3=6 of >/=4mm (PROMIS definition 2)
iv) any amount of Gleason >/=3+4 OR Gleason 3+3=6 of >/=6mm
v) Gleason 3+4=7 with >10% pattern 4 OR cribriform pattern OR a ductal component

Health economic

- Incremental cost per clinically significant cancer detected and incremental cost per correct diagnosis.
- Modelled healthcare resource utilisation, NHS and PSS costs and incremental cost per QALY of using bpMRI compared with mpMRI. The model will incorporate the costs and impacts of potential changes in rates of biopsy and cancer treatment with different types of MRI.
- Modelled healthcare resource utilisation, NHS and PSS costs and incremental cost per QALY of using image-fusion compared to visual-registration

2.5 Summary Table of Objectives and Endpoints

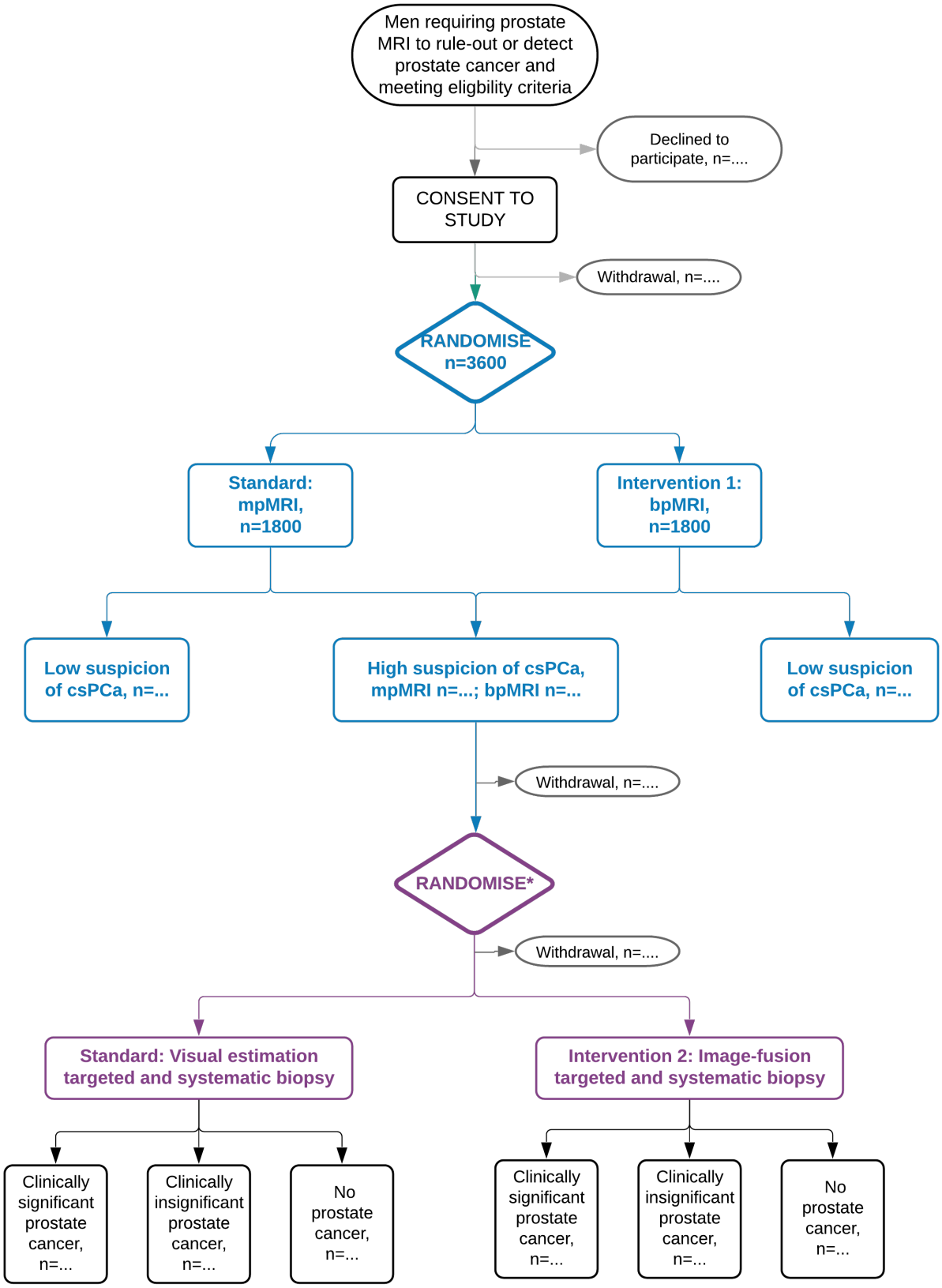
Objectives	Endpoints	Timepoint(s) of evaluation of this endpoint (if applicable)
Primary Objective	As above	Maximum 12 weeks following enrolment
Secondary Objectives	As above	Maximum 12 weeks following enrolment

3. STUDY DESIGN

IP7-PACIFIC incorporates two linked RCTs which will test whether bpMRI and image-fusion make a difference if used in clinical practice, across multiple centres, without the incorporation bias inherent in paired-cohort studies [Stabile et al, 2018]. Our design provides economies of scale and scope compared to addressing these research gaps with two separate RCTs.

Since bpMRI is an abbreviated examination, clinicians and patients require reassurance that it is no worse than mpMRI. Therefore, we plan a non-inferiority evaluation. The second randomisation will involve co-enrolment of a subgroup of the first randomised group i.e., patients referred for biopsy following a positive MRI result. To justify the extra cost for the technology, we would expect image-fusion to detect more clinically significant cancers than visual-registration targeting.

3.1 Design


Men requiring prostate MRI to rule-out or detect prostate cancer and meeting eligbility criteria
Declined to participate, n=....
CONSENT TO STUDY
Withdrawal, n=....
RANDOMISE n=3600
Standard: mpMRI, n=1800
Intervention 1: bpMRI, n=1800
Low suspicion of csPCa, n=...
High suspicion of csPCa, mpMRI n=...; bpMRI n=...
Low suspicion of csPCa, n=...
Withdrawal, n=....
RANDOMISE*
Withdrawal, n=....
Standard: Visual estimation targeted and systematic biopsy
Intervention 2: Image-fusion targeted and systematic biopsy
Clinically significant prostate cancer, n=...
Clinically insignificant prostate cancer, n=...
No prostate cancer, n=...
Clinically significant prostate cancer, n=...
Clinically insignificant prostate cancer, n=...
No prostate cancer, n=...

4. PARTICIPANT ENTRY

4.1 Study setting and population

Patients referred to hospital urology departments by their GP due to a clinical suspicion of prostate cancer (elevated serum prostate specific antigen [PSA], abnormal feeling prostate on rectal examination, or both). These patients are normally recommended to undergo a prostate MRI as part of standard care.

Randomisation-1: bpMRI versus mpMRI

Patient population

Inclusion criteria

- Age 18 years or above (no upper limit)
- Patients with a prostate (either cis-male gender or trans-female gender with no prior androgen deprivation hormone use at all).
- Referred to hospital and advised to undergo a prostate MRI because of an abnormal digital rectal examination (regardless of PSA level) and/or an elevated PSA (within 6 months of screening visit)

PSA >/=3.0ng/ml for age 50-69 years
PSA >/=5.0ng/ml for age >/=70 years
If family or ethnic risk for prostate cancer, PSA >/=2.5ng/ml for age 45-49 years

Explanatory note: Patients with elevated age-specific PSA or abnormal digital rectal examination of the prostate (or both) with PSA levels as determined by NICE guidance and local NHS Cancer Alliance or regional guidance. Recent UK consensus guidance [Prostate Cancer UK, 2016] from over 300 UK healthcare professionals and patients affected by prostate cancer and endorsed by the British Association of Urological Nurses (BAUN), the British Association of Urological Surgeons (BAUS) and the Primary Care Urology Society (PCUS) also stipulates that patients with a family history (1 or more first degree male relatives) or ethnic risk group (those identifying as of Black-African/Black-Caribbean) should be further investigated with PSA >/=2.5 when aged 45-49 years. We will also approach these patients if they are referred by their GP to secondary care. No upper age limit will be set.

Exclusion criteria

- PSA >50ng/ml. The rationale being that above this PSA level, rates of clinically significant prostate cancer are quite high.
- Prostate MRI or prostate biopsy within the previous 24 months from the date of screening. A prior prostate MRI which is negative will add selection bias and change prior probabilities of disease whilst a prior biopsy can cause artefact changes which affect the quality of the images. These artefact changes can take a number of months to dissipate and in some patients up to 12-18 months after the biopsy.
- Prior prostate cancer diagnosis at any time-point. Patients on active surveillance will have differing prior probabilities of clinically significant prostate cancer to those referred with a clinical suspicion and are therefore excluded.
- Any absolute contraindication to MRI, gadolinium or biopsy. Patients with bilateral hip prostheses are excluded. These prostheses often cast a large imaging artefact over the prostate area on MRI and radiologists prefer a mpMRI scan because the diffusion images

can be particularly affected. In other words, there is lack of equipoise in these patients for randomisation between mpMRI and bpMRI.
- Contraindication to performing a biopsy guided by a transrectal ultrasound probe
- Unable to give informed consent to the study

Randomisation-2: Visual-registration targeting versus image-fusion targeting

Inclusion

Suspicious finding on mpMRI or bpMRI from randomisation-1 requiring targeted biopsy (MRI categories 3, 4 or 5)

Exclusion
As above for randomisation 1
Patient refusal for biopsy

5. PROCEDURES AND MEASUREMENTS

Randomisation 1: bpMRI versus mpMRI

Biparametric MRI (bpMRI) of the prostate followed by prostate biopsy in those with an ongoing clinical suspicion compared to multi-parametric MRI (mpMRI) of the prostate followed by prostate biopsy in those with an ongoing clinical suspicion. Sites and clinicians will be assessed for quality of conduct and reporting of MRI and biopsy. Standardisation and training meetings will be held of radiologists (to ensure consistency of reporting) and biopsy operators (to ensure a uniform high quality approach to biopsy). Radiologists will issue both a PIRADS [latest version as defined in MRI Reporting SOP] and Likert score.

Both bpMRI and mpMRI can be carried out on the same NHS scanners. A study-specific imaging protocol will set out the criteria that all centres will have to comply with, which will be in line with UK and international guidelines with images and radiologists undergoing quality control. bpMRI will comprise multiplanar T2-weighted and axial diffusion-weighted components whereas mpMRI will have these combined with gadolinium contrast-medium enhancement. Minor imaging protocol differences between scanners are often necessary to optimise individual MRI devices and this optimisation will be undertaken as described below, if necessary. Most centres have already started such quality control programmes as a result of work that some of our group (Ahmed, Walls, Padhani) have contributed to through Prostate Cancer UK and NHS England.

Quality control (MRI/reporting)

MRI conduct: A study-specific MRI QA/QC Standard Operating procedure (SOP) building on our experience in the PROMIS, PICTURE and PROSTAGRAM studies will determine MRI conduct. Scanners will be either 1.5T or 3.0T in order to reflect current UK practice at each recruiting centre and would need to meet the required standards set out for the UK as stipulated in the recent NICE (2019) and other guidance [Padhani et al, 2018]. Our lead radiology co-investigators (Padhani and Sokhi) along with Darren Walls (Research Radiographer, UCL, of the Society of Radiographers' MRI Subgroup) will conduct a quality review of MRI scans of all centres at the beginning to ensure bpMRI and mpMRI are of optimal standard. Walls led a prostate MRI protocol document for UK hospitals to deliver prostate MRI in an optimal manner [MRI protocol document, SOR/PCUK, 2018]. MRI sites not meeting the standards will be helped achieve them; in our experience with PROMIS this

process took 6 weeks on average. However, since NICE recommended the use of mpMRI pre-biopsy, most centres have already gone through such a process within their local Cancer Alliance networks or are soon due to undergo such a process. This was made possible through a programme of work instigated by NHS England and the devolved nations that the CI, Ahmed, has been engaged with through his role as Chair of the NHS England Prostate Clinical Expert Group, membership of PCUK's Prostate MRI national expert group for standardisation of mpMRI conduct and as clinical lead of RM Partners Cancer Alliance's Rapid Assessment for Prostate Imaging and Diagnosis (RAPID) programme [RM Partner RAPID Pathway, 2018]. Patient preparation will follow up-to-date guidance at time of set-up; the current guidance is set out in two guideline documents [PI-RADS v2.1 manual, 2019; Brizmohun et al, 2018].

Radiology expertise: We will include a number of centres with a range of patient volumes. NHS Cancer Alliances have been engaged in a standardisation programme since 2017 for prostate MRI conduct and reporting and our proposal will involve additional training and standardisation meetings before and straight after the pilot to incorporate any learning from the pilot itself. Reporters will also need to have completed or be a Faculty member of the free PCUK/RCR-approved online course (https://www.raiqc.com/sign-in/) or equivalent British Society of Uro-radiology or European Society of Uro-radiology course. Further, we will adopt a recent UK certification consensus (of which Ahmed and Padhani were members) so that only level 2 and 3 radiologists are asked to participate [Barrett et al, 2020]; level 1 are non-radiology specialists and junior radiologists neither of whom would be appropriate as reporters in current NHS practice and thus in this study [Westphalen et al, 2016].The certification process will broadly follow these principles:

- Questionnaire (similar to Table E1 of Westphalen et al, 2016) and also ask about biopsy operators/pathology experience and pathology compliance with WHO/ISUP (RCPath) standards.
- Submission of overall findings from 100 cases (both positive and negative) from biopsy-naïve patients to include data on experience, image quality (internally rated), scoring (Likert/PIRADS [latest version as defined in MRI Reporting SOP]) breakdown and distribution with biopsy outcome where done. This can be from an existing or completed audit, and can be overall summary metrics rather than a full anonymised submission of 100 cases.

In addition, bpMRI and mpMRI scans will be double reported to evaluate inter-observer variability as per the Statistical Analysis Plan.

Reporting scheme: NICE currently recommends the use of the Likert scoring system with data showing its equivalence to PIRADS scoring. Our systematic review showed that of 44 studies, 21 used Likert scoring and 14 used PIRADS scoring with the other studies not stating the scoring system they used. In the PIRADS and Likert scoring systems, contrast-enhancement is used in interpreting equivocal lesions. Since neither PIRADS or Likert can be fully applied for bpMRI, and as there is current heterogeneity of MRI scoring practice and uncertainty around which scoring system to use, we propose that both PIRADS (as per latest version determined in the MRI SOP) and Likert should be used in bpMRI and mpMRI evaluations. Our UK clinician survey indicated that 40% use Likert scoring and 53% use PIRADS; all who agreed to take part in the study also agreed to report both scores in the study.

Decision for biopsy

Decision to recommend biopsy: The decision-making around which groups of patients to recommend a biopsy will be in concordance with NICE guidance 2019 and reflect the

majority of our clinicians' view in our recent survey. We have wide clinical consensus that those patients with a suspicious MRI (score 4 and 5 on either Likert or PIRADS [latest version as defined in MRI Reporting SOP]) should be advised to undergo a biopsy. Patients with a non-suspicious (score 1, 2) or equivocal MRI (score 3) (on either Likert or PIRADS [latest version as defined in MRI Reporting SOP]) with one or more risk factors (PSA density >/=0.12ng/ml/ml or >/=0.15ng/ml/ml, family history or ethnic risk) may also be recommended to have a biopsy. Normal practice at each centre will be declared prior to study recruitment. We shall report the number of patients recommended for biopsy included in the analysis who had a non-suspicious bpMRI/mpMRI and of these, the numbers of clinically significant and clinically insignificant cancers subsequently detected. We shall also report the number of patients who were recommended to have a biopsy but chose not to have it.

Follow-up of patients not undergoing a biopsy: Patients will be discharged back to the GP by their clinical team after their MRI with individual advice about the level of PSA that should lead to a referral back to hospital. Sometimes the clinical team reviews a patient 6-12 months later with another PSA level. The NICE guidance have set out key parameters for follow-up within primary or secondary care for patients who do not have a biopsy or end up with a negative biopsy and this will be the approach we advise centres to take (see sections 1.2.10-1.2.13, 9th May 2019, NICE Guidance NG131 [4]). Some patients with significant lower urinary tract symptoms will need ongoing follow-up and care as well as any relevant procedures for benign prostatic hyperplasia. The trial protocol will not stipulate the type of follow-up that occurs after biopsy as this is beyond the remit of the current proposal. We will collect information on whether additional tests or procedures were carried out within the 3 months of trial follow-up using our patient questionnaire. Future long-term outcomes through national database linkage will be collected, however, only if funding for such research activity is successful.

Randomisation-2: Visual-registration targeting versus image-fusion targeting

Targeted biopsy with either commercially available CE-marked image-fusion devices or visual-registration. The study will pragmatically permit any CE-marked image fusion device depending on local availability. For centres that do not have image-fusion devices, we have incorporated costs for hiring these for centres. All patients will undergo non-targeted systematic </=12 core biopsies or transperineal sectoral biopsies as well. The type of systematic biopsy approach will need to be declared by each centre at the beginning of the study and reasons for deviations from the standard systematic biopsy approach will be collected.

Biopsy

Expertise: There are no guidelines on what level of biopsy experience is required by clinicians in the NHS nor whether there should be minimum annual numbers for being designated as competent in targeted biopsy. Therefore, a robust study-specific standardisation programme will be used for all clinicians carrying out biopsy. For those centres using certain biopsy image-fusion devices, company-specific training modules and competency sign-off will need to occur. Whilst a minimum number of targeted biopsies has not been recommended in any guideline, our clinical opinion from experienced biopsy operators is that a minimum of 100 cases should have been carried out using the technique being proposed. We will also record the experience of each biopsy operator in terms of number of biopsies (to the nearest 50), years of experience and the specialty of operator (radiology, urology, nursing).

Targeting and systematic biopsy protocol: We will follow standard care for centres in terms of type of analgesia/anaesthesia. Our clinician survey shows centres are using local anaesthetic, sedation or general anaesthetic; transperineal or transrectal route and visual-registration or image-fusion targeting. The exact anaesthesia type (local only, sedation, general anaesthetic) will be recorded. Number of systematic cores will be as described above with 6 cores per target (divided into 4+2 for the first lesion only) and unlimited targets in total per patient [Hansen et al, 2020; Leyh-Bannurah et al, 2020; Kenigsberg et al, 2018]. Targeted biopsies will be carried out first, in order to minimise the impact of swelling on obtaining accurate sampling of targets.

Histology

The histological report will evaluate the following aspects for each target and each location of systematic biopsies carried out according to Royal College of Pathology (UK) guidance [Royal College of Pathology Guidelines, 2016]: number of biopsies, number positive for cancer, core length in mm, cancer presence, maximum cancer core length in mm (where continuous and discontinuous numbers are given, for the purpose of analysis, the continuous number will be used), primary, secondary and highest Gleason grade, percent pattern 4 and presence of cribriform pattern when Gleason 3+4, perineural invasion/lymphovascular invasion/intraductal components/neuroendocrine differentiation; and vii) other features (high grade prostatic intraepithelial neoplasia/atypical acini/inflammation/atrophy). See Biopsy Reporting SOP.

Definition of clinically significant prostate cancer on histology

We know that some prostate cancers are clinically significant, and that other prostate cancers are clinically insignificant. Whilst there is still some uncertainty about exactly what entails clinical significance, particularly with respect to whether patients diagnosed with low volume Gleason 3+3 or Gleason 3+4 cancer should be on active surveillance, most physicians, researchers and guideline panels agree detection of Gleason >/=3+4 (ISUP grade Group >/=2) is the key target condition for any screening or diagnostic pathway. As a result, this is the primary histological threshold we will measure.

There is also acknowledgement that a low amount of cancer or low percent pattern 4 is perhaps not as aggressive. So, whilst the primary outcome measure will be the detection of any Gleason >/=3+4, there are important secondary definitions of clinical significance that we will measure as well. These definitions will incorporate the wide and divergent views on clinical significance but incorporate evidence on the amount of pattern 4 and maximum cancer core length as being significant elements [26-30]. These definitions will be:

- any amount of Gleason 4+3=7 or more

- any amount of Gleason >/=4+3 OR Gleason 3+3=6 of >/=6mm (PROMIS definition 1)

- any amount of Gleason >/=3+4 OR Gleason 3+3=6 of >/=4mm (PROMIS definition 2)

- any amount of Gleason >/=3+4 OR Gleason 3+3=6 of >/=6mm (PROMIS definition 3)

- any amount of Gleason 3+4=7 with cribriform pattern or a ductal component or >/=10% pattern 4 or any Gleason >/=4+3 [van Leenders et al, 2020].

Further, we will use risk groups as defined by D'Amico, NCCN and CPG (using the latest versions that are published at the time of the Statistical Analysis Plan being finalised).

Validated patient reported outcome measures

The ProBE PETB questionnaire included: Hospital Anxiety and Depression Scale (HADS) score, and urinary, bowel, and sexual symptoms assessed by using the validated University of California, Los Angeles petb

state Cancer Index questionnaires. The UCLA-PCI questionnaires have now been converted into the Expanded Prostate Index Composite (EPIC).

- We will compose a modified questionnaire to incorporate the latest versions of EPIC into the ProBE questionnaire. So, the questionnaire in IP7-PACIFIC will incorporate the following: HADS, EPIC (Urinary, Erectile and Bowel domains) and the EuroQol (EQ-5D-5L) will be used in the study as a generic measure of health-related quality-of-life which can be linked to public preferences [Janssen et al, 2013].

- Patients will be asked to self-report pain and discomfort (referred to as pain hereafter) immediately after and seven days after biopsy on a 4-point Likert-type scale as none, mild, moderate, or severe. Specific related complications such as fever, flu-like shivers, pain, haematuria, haematochezia, and haemoejaculate will be self-reported at 7-14 days after biopsy (or after MRI if no biopsy carried out) and at 35 to 90 days after prostate biopsy as absent or present following biopsy on a purpose designed questionnaire. For each symptom, patients will be asked to score the degree of "problem" as none, minor, moderate, or major. This will be used to derive a binary outcome for each symptom (present/moderate/severe problem vs. absent /minor problem).

The timepoints for the questionnaires are also referenced in the Patient Reported Outcomes and Experience Questionnaire as follows:

- Hospital Anxiety and Depression Scale (HADS) score questionnaire
  - Time-points: After Consent, 7-14 days after biopsy (or after MRI if no biopsy) and 35-90 days after biopsy

- EPIC (urinary, erectile, bowel)
  - Time-points: After Consent, 7-14 days after biopsy (or after MRI if no biopsy) and 35-90 days after biopsy

- EuroQol (EQ-5D-5L)
  - Time-points: After Consent, 7-14 days after biopsy (or after MRI if no biopsy) and 35-90 days after biopsy

- Questionnaire on MRI related side-effects
  - To be given to all patients to be completed after the MRI but before the biopsy (if they have a biopsy)
  - Questionnaire on biopsy related side-effectsTo be given to all patients who have had a biopsy
  - Time-points: 7-14 days after biopsy and 35-90 days after biopsy

These can be completed on paper and uploaded to the eCRF or completed electronically. We will ask consent from patients to be contacted by the central study team in order to issue and collate these directly from the central trials team. Completeness of data and patient questionnaire response rates is an important outcome in IP7-PACIFIC as it informs our analysis of side-effects and adverse events. We will prompt patients to complete the questionnaires sent to them by text or email with up to two reminders; this will be coordinated

by the central trials team. The researchers at the participating centres may also co-ordinate with the departmental clinic appointments in order to hand the questionnaires to the patient personally.

5.1 Identification and recruitment of patients

Patients referred by their GP to hospital due to a clinical suspicion of prostate cancer (elevated serum prostate specific antigen (PSA), abnormal prostate on rectal examination, or both) and agreeing to undergo a prostate MRI as part of standard care will be approached to participate. Potential participants will be patients who are referred to the respective centre for investigation of their prostate for possible malignancy. The dedicated Recruitment Officer will contact the eligible patients by telephone before the patient is seen in clinic once the local clinical care team has obtained the participants permission for this to occur. The patient will be asked for permission to receive the literature pertaining to the IP7-PACIFIC study including REC approved PIS, ICF and contact information for the research team. All patients will have the opportunity to discuss all aspects of the study with their GP, family members, and their Recruitment Officer prior to the clinic appointment at their participating centre but given before consenting to the study. Consent can be obtained remotely using a consent form on the RedCap database with a unique identifier given to the patient. Remote consent with the patient printing out a paper version of the ICF and scanning or posting it back to the trials team is also acceptable. Written or electronic consent can also be taken at a face-to-face visit.

5.2 Screening and pre-randomisation evaluations

Written informed consent will be obtained before the subject undergoes any study related procedures such as screening for eligibility. There are no pre-screening or screening tests required.

Pre-screening log: Collects the number of eligible patients who were given the PIS, provides information regarding the number of drop-outs/withdrawals, the reasons behind why the patients decided not to enrol onto the study and the acceptance rate of the study within the patient population. This activity is included as part of ‘approach potential participant to discuss study’ within the SoECAT.

Screening log: Collects and tracks details of all the patients with completed informed consent and any reasons for screen failures and patient withdrawals. This activity is included as part of ‘informed consent’ or as part of any subsequent visits within the SoECAT.

Consent for both randomisations will be sought at the outset to make the study conduct efficient, minimise drop-out and help centres meet NHS 28-day faster diagnosis targets. We intend to follow patients up to a maximum 12 weeks post-enrolment, so we will also collect information about what treatment options are available for patients who have diagnosed prostate cancer and what treatment they chose through multidisciplinary team (MDT) outcomes in the clinical records and clinic letters or entries by clinicians in the health records. Most patients with localised prostate cancer will be able to choose from a number of options that straddle active surveillance, focal therapy, radical surgery or radiotherapy (with some men started on androgen deprivation therapy), depending on cancer risk. Recent NHS guidance in 2019 was changed to allow for patients with intermediate and low risk cancer to take longer than the previous 31/62-day targets permitted so patients’ decision about final treatment choice can sometimes take up to 3 months. This means we will be able to collect final treatment decisions for most of our participants with this information collated directly from health records; this information is unlikely to be available prior to database lock for

many patients recruited and biopsied in the last 3 months of recruitment, so the eCRF will reflect this but given the size of the study is unlikely to have an impact on these findings.

Participants will be asked consent to collect long-term healthcare information from national records (i.e., Office for National Statistics, NHS Digital, Office for Health Improvement and Disparities, and/or other applicable NHS information systems, or national databases) and through a direct approach from the research team at any timepoint within 10 years of consent. We will ask patients to give permission to be contacted by a member of the central / local study research team within 10 years of signing their consent form, after the study has ended to complete a questionnaire about their health status (including details of any other tests and treatment they have had since the study) and quality of life. If the patient decides to take part a member of the study research team may send this request to the patient's home address.

If funding can be successfully obtained for this longitudinal data collection, it will allow us to determine whether patients had further diagnostic tests, prostate cancer diagnosis and its risk (stage, grade, PSA level), as well as any subsequent treatments and cancer-related outcomes (progression, metastases, cancer-related mortality).

If Funding is successful for longitudinal data collection, an amendment submitted via the HRA will be necessary.

Health Status

At the screening visit, patients will also be asked to give consent for identifiable data to be linked with the national databases (ONS and HES database). The identifiable fields (NHS number) required for linkage will be encrypted using a one-way encryption algorithm. We will ask patients if they are happy to give consent for their health status to be followed up over time. This will be done by linking the patient's identifiable data with records held by the NHS and maintained by the NHS Information Centre and the NHS Central Register, or any applicable NHS information system. This will allow us to track what happens after the study finishes and observe if anyone gets further tests/investigations, a diagnosis of cancer in future and its risk (stage, grade, PSA level) and the treatment they have had.

As prostate cancer is often a slow-growing disease which may not develop or progress for many years we will also ask patients to give consent for us to keep personal data stored or accessed for an additional 10 years on the NHSCR (National Health Service Care Register) so that data from national registries can be evaluated. For instance, long-term survival information to be flagged through national registries, for example NHS Digital (previously the Health and Social Care Information Centre); Office of National Statistics (ONS) in England/Wales; General Register Office in Scotland; Hospital Episode Statistics (HES) or Office for Health Improvement & Disparities.

5.3 Randomisation and Blinding

Biases and blinding

- Randomisation controls for performance and incorporation biases with respect to the clinical utility of bpMRI in comparison to mpMRI.
- Pathologists will be blinded to MRI type by ensuring the pathology request forms do not provide this information.

Imaging scan data

Imaging scans are performed as part of this study. We will also ask for consent from patients to store and use their scan data in future research (academic or commercial) to see if new ways of looking at these scans can detect cancer better in the future. All scans need to be electronically transferred for collation at Imperial in order to facilitate double reporting and therefore will be available for data banking within the Research Data Store (https://www.imperial.ac.uk/admin-services/ict/self-service/research-support/rcs/rds/).

Randomisation process

In randomisation-1, patients with suspected prostate cancer will be allocated in a 1:1 ratio to bpMRI or mpMRI, and those with a suspicious MRI (either bpMRI or mpMRI) who are recommended to undergo targeted biopsy will be allocated 1:1 to image-fusion or visual-registration biopsy (along with non-targeted systematic biopsy as per guidance). Randomisation-2 will be stratified for type of MRI to which participants in the first randomisation are allocated.

5.4 Visit Schedule

	Screening			
Visit	**1**	**2**	**3**	**4**
Week	0	1-8	1-8	2-12
Informed consent	X			
Inclusion & exclusion criteria	X			
Demographics	X			
Targeted medical history	X[1]			
MRI		**X**		
Biopsy (in some patients)			**X[2]**	
Patient questionnaires	X[3]	**X[3]**		**X[3]**
Biopsy results				**X[4]**
Adverse events			**X[5]**	**X[5]**

[1] Prostate MRI or prostate biopsy in the past and outcome (occurring more than 2 years prior to screening visit), current use of 5-alpha reductase inhibitors (e.g., finasteride or dutasteride), use of testosterone supplementation or androgen suppression medication, family history of prostate cancer (defined as any immediate family relative diagnosed with prostate cancer at any time), ethnicity (using the UK Office for National Statistics groupings).
[2] Biopsy may occur on same day as MRI in some centres
3 Questionnaires which require baseline data will be given for completion before the MRI or biopsy. The schedule of questionnaires is referenced in section 5 Validated patient reported outcome measures and also within the Patient Reported Outcomes and Experience Questionnaire .
4 Adverse events will be assessed up to Visit 4 after first randomisation by electronic questionnaire sent by the central trial team directly to the patient via the RedCap system or given to the patient by local site on printed paper. Additionally, any adverse events noted by the local clinical team on patient records will be recorded in the eCRF where applicable.
5 Biopsy outcomes will be assessed from clinical report directly from medical records

5.5 Follow-up

Any incidental findings should be identified at the study visits and reviewed by the site teams and if necessary will be reported to the clinical care team and subjects GP.

These reflect standard care and there will be no additional follow-up visits required for the study.

6. INTERVENTION

6.1 Permanent Discontinuation of Study Intervention and Withdrawal from Study

(i) Permanent discontinuation of study intervention

Subjects may discontinue study intervention for the following reasons:

- At the request of the subject.
- Adverse event/ Serious Adverse Event
- If the investigator considers that a subject's health will be compromised due to adverse events or concomitant illness that develop after entering the study.

(ii) Withdrawal from Study

Withdrawal from the study refers to discontinuation of study intervention and study procedures and can occur for the following reasons:

- Subject decision
- Loss to follow-up

(iii) Procedures for Withdrawal from Study

Patients may decide to opt out of IP7-PACIFIC at any time. This is entirely within their right to do so. Such cases will be reported to the Research Team Office so that no further data are entered onto the database, as specified in the patient information leaflet and appropriate Standard Operating procedure. Data captured before consent was withdrawn will be used in the study, but no further data, beyond this date will be collected or used in any analysis. Reason for withdrawal should be recorded in the eCRF and medical records, if given by the patient. Our sample size calculation assumes a 10% withdrawal rate but if this exceeds that number, we will continue to recruit patients until the target number for each randomisation is met.

7. SAFETY REPORTING

7.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical trial subject undergoing a trial intervention and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the trial interventions, whether or not considered related to the interventions being evaluated.

7.2 Adverse Event recording

For the purposes of the study, AEs will be followed up according to local practice until the event has stabilised or resolved, or the Follow-up Visit, whichever is the sooner. All AEs and

SAEs will be recorded throughout the study and all SAES, where in the opinion of the Chief Investigator, the event is 'related' and 'unexpected' should be reported to the sponsor and also be reported to the REC.

(i) Severity of Adverse Events

Mild: Awareness of event but easily tolerated
Moderate: Discomfort enough to cause some interference with usual activity
Severe: Inability to carry out usual activity

(ii) Causality of Adverse Events

Unrelated: No evidence of any causal relationship
Unlikely: There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible: There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable: There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definite: There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

7.3 Serious Adverse Events (SAE)

(i) Definition of SAE

An SAE is defined as any event that
- Results in death;
- Is life-threatening*;
- Requires hospitalisation or prolongation of existing inpatient's hospitalisation**;
- Results in persistent or significant disability or incapacity;
- Is a congenital abnormality or birth defect;

* "Life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
** "Hospitalisation" means any unexpected admission to a hospital department. It does not usually apply to scheduled admissions that were planned before study inclusion or visits to casualty (without admission).

Medical judgement should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/reactions that are not immediately life-threatening, or do not result in death or hospitalisation but may jeopardise a subject, or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

7.4 Reporting of SAEs

Reporting of all SAEs *(for exceptions see below)*, occurring during the study must be performed as detailed in SAE reporting instructions. If the investigator becomes aware of safety information that appears to be related to the trial, involving a subject who participated in the study, even after an individual subject has completed the study, this should be reported to the Sponsor.

All SAEs will be reviewed by the Chief Investigator or a designated medically qualified representative to confirm expectedness and causality.

Reporting of SAEs and review by the CI will be via the trial data collection system (CRF/eCRF).

List of Expected Adverse Events

There are number of expected potential adverse events after interventions that may occur and require hospitalisation but will not require reporting as SAEs but will be collected in the eCRF. These include:

- Gadolinium or buscopan related allergic reactions of any severity
- Claustrophobia leading to abandoning of MRI scan
- Vasovagal fainting episode before, during or after MRI or biopsy
- Urinary retention and any admission required for this
- Urinary tract infection and any admission required for this
- Epididymo-orchitis and any admission required for this
- Dysuria
- Debris in urine and any admission required for this
- Haematuria and any admission required for this
- Erectile dysfunction and any other sexual sequelae side-effects such as dry orgasm, lack of orgasm, poor libido

(i) Related SAEs

Related: resulted from administration of any of the research procedures

(ii) Unexpected SAEs

Unexpected: type of event is not listed in the protocol as an expected occurrence

(iii) Reporting of SAEs that are related and unexpected

SAEs that are *related and unexpected* should be notified to the relevant REC and the Sponsor in accordance with local requirements. Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the *NRES SAE form for non-IMP studies*. The Chief Investigator must also notify the Sponsor of all SAEs where in the opinion of the Chief Investigator, the event is ‘related’ and ‘unexpected’ . Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details of sponsor for reporting SAEs are as follows:

The Research Governance and Integrity Team:

Imperial College London and Imperial College Healthcare NHS Trust.
Email: rgit@imperial.ac.uk

Chief Investigator:
Professor Hashim U. Ahmed
Imperial College London, Charing Cross Campus
E-mail: pacific@imperial.ac.uk
Tel: 020 7589 5111 (Mon to Fri 09.00 –17.00)

Follow-up of patients who have experienced a related and unexpected SAE should continue until recovery is complete or the condition has stabilised. Reports for related and unexpected SAEs should be unblinded prior to submission if required by national requirements.

(iv) Annual reporting of Serious Adverse Events

Annual Progress reports will be submitted to the Sponsor and the Research Ethics Committee in accordance with local requirements. The Annual Progress Report will detail all SAEs recorded.

7.5 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant REC of the measures taken and the circumstances giving rise to those measures.

8. STATISTICAL ANALYSES

8.1 Sample Size and power considerations

Randomisation 1: bpMRI vs mpMRI

Consistent with NIHR-HTA PROMIS [Ahmed et al, 2017], NIHR PRECISION observed a 38% detection of clinically significant prostate cancer (defined as any Gleason >/=3+4 [ISUP Grade Group >/=2]) in patients with suspected prostate cancer having pre-biopsy mpMRI compared to 26% having a traditional biopsy alone without pre-biopsy MRI [Kasivisvanathan et al, 2018]. To preserve at least 50% of the improvement in detection rates implies exclusion of a 6% absolute reduction from a 38% detection rate in order to recommend a switch from mpMRI to bpMRI. We have chosen a non-inferiority margin of 5% which strikes a balance between our clinician survey, the patient perspective, ensuring improvement on the previous standard of care and an achievable sample size. To provide 90% power to confirm non-inferiority and exclude an absolute 5% reduction in detection rate of clinically significant prostate cancer from an estimated 38% in both arms, using an overall 0.05 significance level for a one-sided test, requires 3230 men (1615/arm). A target sample size of 3600, would therefore account for an assumed attrition rate of about 10%.

Randomisation 2: Image-fusion vs visual-registration biopsy

The expected detection rates of clinically significant prostate cancer (defined as any Gleason >/=3+4 [ISUP Grade Group >/=2])are 55% (visual-registration) and 65% (image-fusion). Our clinician and patient groups indicated that >/=10% improved detection rate using image-fusion is acceptable for adoption. In PRECISION and PROMIS, approximately 70-75% were recommended for biopsy following mpMRI. Assuming 70% will be recommended for biopsy and conservatively assuming a further 10% attrition, we anticipate at least 2000 patients from randomisation-1 would be eligible for randomisation-2. This provides ample power (>95%) to detect the absolute 10% difference described above using a two-sided test at the 5% significance level. Include the number of subjects to be enrolled, reason for choice of the sample size, including details of the sample size estimation and the power of the study and clinical justification.

8.2 Planned recruitment rate

With up to 30 recruiting centres (up to 10 pilot centres initially for 12 months and all remaining sites then recruiting for a further 18 months), we would expect to comfortably meet our target of 3600, even if the patient acceptance rate was as low as half the 60% reported in the PRECISION RCT [5].

8.3 Statistical Analysis

Interim monitoring & internal pilot

We will monitor recruitment, statistical assumptions and safety at 6 months and formally review 12 months recruitment into the internal pilot. During the first 12 months, our targets are for gradual opening of at up to 10 centres (although more can be opened if possible), 700 recruited for randomisation-1 and 400 for randomisation-2. At this stage, stopping guidance will be based on ability to recruit, and on discussion with the independent trials steering committee.

Our independent data monitoring committee will provide stopping guidance based on interim futility or demonstrated superiority analyses when at least 50% of our overall sample size for randomisation-1 has provided primary outcome data. They will also consider the underlying assumptions for randomisation-2 and make recommendations regarding continuation of randomisation-2 at this point.

We will monitor recruitment, statistical assumptions and safety regularly throughout the trial. There will be an independent Trial Steering Committee (TSC) and Data and Ethics Monitoring Committee (DMEC). The first 12 months of recruitment will be an internal pilot with an emphasis on ability to recruit, with targets at this stage being 700 patients recruited from at least 10 centres and obtaining primary outcome data on 80% of all participants randomised up to 4 months prior to data-extraction (accounting for expected timeframe: 3 months for conduct of MRI and biopsy and histology results to be made available followed by up to 30 days to transfer data to the database).

Proposed length of internal pilot phase: 12 months

Pilot Trial Targets	Red	Amber	Green

% Recruitment threshold	<50%	50 – 99.9%	≥100%
Recruitment rate / site / month	2.8	2.9-5.8	≥5.8
Number of sites opened	5	6-9	≥10
Total number of participants recruited	<350	350-699	≥700
% Primary outcome data threshold (all randomised 60 days prior to data extraction)	<40%	40-80%	≥80%

In summary, if at least 700 (100%) patients are recruited in the pilot, we would expect the TSC to recommend continuation of the trial (in line with NIHR guidance regarding green threshold). If the pilot recruits less than 350 patients (<50%), then this indicates a recommendation for stopping unless there is a very good reason for delay and a convincing solution can be employed. If the pilot recruits 350-699 (50-99%) then, in discussion with the TSC and funder, measures to improve recruitment may be needed in the main trial. We shall use the % targets (100%, 50-99%, <50%) to inform study management setting site-specific targets, depending on the expected recruitment as declared by each of our pilot sites. We shall monitor site recruitment regularly as part of study management and if sites are under-performing or delayed in set-up, we shall consider opening sites from a reserve list.

Randomisation-2 will be stratified by arm allocated in randomisation-1. Potential effects of co-enrolment are likely small but will be monitored. Comparisons will be adjusted for trial arm of the other trial and if we were to anticipate an increase in SEs by 5% from using adjusted effect estimates, we would maintain an adequate level of power (>80%) in our respective randomised comparisons.

Main study clinical outcomes analysis

For each randomisation, the number and proportion of clinically significant cancers detected in the randomised population will be reported by trial arm. Group differences will be quantified by the risk difference with two-sided confidence intervals at a level appropriate to the significance level pre-specified in the sample size. Detection rates will be compared by trial arm using mixed models with adjustment for trial arm allocation of co-enrolled trial and random effect by centre. The treatment effect coefficients will be presented with confidence intervals and associated p-value. The primary analysis will be conducted on an intention-to-treat (ITT) basis, where patients with missing outcomes are assumed not to have clinically significant prostate cancer. A modified ITT analysis will be performed excluding patients who did not complete the diagnostic tests, and for the non-inferiority comparison a per protocol analysis including only those undergoing randomly assigned interventions. A pre-specified statistical analysis plan will be drafted detailing intended analyses for primary and secondary outcomes. It will be approved by the IDMC and agreed prior to analysis.

Cost-effectiveness analysis

A within trial cost-effectiveness analyses will estimate the incremental cost per true positive detected and incremental cost per correct diagnosis. Estimates of diagnostic performance will be based on the trial analysis and costs will be estimated from the NHS and PSS perspective using a micro-costing approach for tests. Deterministic (to explore plausible alternatives e.g., quantity of resources used or unit costs) will be combined with stochastic

sensitivity analysis (used to explore statistical imprecision in estimates of costs, effects and cost-effectiveness).

We will also conduct a model-based cost-utility analysis, taking the form of a discrete event simulation as the model will explore the impact of allowing more patients to be imaged and the impact on services later in the care pathway. Stakeholders and literature reviews will inform the structure of the model. Data from the trial and secondary sources such as systematic reviews and other evaluations will be synthesised to build and parametrise the model. As outcomes for individuals modelled will occur beyond a 12-month period both health benefits and costs will be discounted using the current recommended rate of 3.5% for both costs and benefits [34]. The time horizon will be the patients' remaining life-years. The results will be reported as total costs, total QALYs and incremental costs per QALY. Both probabilistic and deterministic sensitivity analysis will be conducted.

Justification for an economic evaluation

It is possible that there will be time and other resource saving with bpMRI compared with mpMRI and hence the delivery and interpretation of bpMRI may be less costly than mpMRI. An earlier NIHR-HTA report from 2013 by Mowatt and colleagues [2013] estimated a range of timings per patient with ~12minutes difference between bpMRI and mpMRI. These estimates are applicable to the process of MRI prior to 2013 and before the NIHR-HTA PROMIS and NIHR PRECISION studies reported in 2017. Furthermore, these estimates are not based upon direct observation across a range of centres working with different scanner makes and models (an issue highlighted in recent work in work by Prostate Cancer UK, https://prostatecanceruk.org/media/2496787/mpmri-imaging-guidance-document-final.pdf). In this work, in comparison to the earlier work by Mowatt and colleagues, our estimates of the costs of the diagnostic tests will be based on a micro-costing approach using patient level data. The costs used by Mowatt and colleagues were based on expert opinion from the very small number of clinicians involved in the study and are now over ten years old. The prospective nature of our proposed multicentre study should provide more up to date, precise and transferable data applicable to NHS practice.

Our proposed study design is a non-inferiority study. However, it is only non-inferior with respect to the primary outcome and one form of imaging may be superior in other aspects (for example one form of imaging may be less costly). It is possible that even though the study is designed to be a non-inferiority study that clinically important differences may not be ruled out by the final analysis. To mitigate against this possibility and still provide information to guide NHS-decision making we propose to conduct (as described below) a cost-utility analysis.

The proposed economic evaluation work described below will also allow us to consider whether the resource implications of adopting a potentially less time-consuming imaging methods as well as any knock-on effects elsewhere in the system caused by changes in the imaging process.

Within trial analysis

A within trial cost-effectiveness analyses will estimate the incremental cost per true positive detected and incremental cost per correct diagnosis. Estimates of diagnostic performance will be based on the trial analysis and costs will be estimated from the NHS and PSS perspective. The costs of the tests will be based upon a micro -costing approach for tests. Costs components will include cost of staff time to deliver and interpret the tests. In sensitivity analysis we will also consider the additional costs of training additional health

personnel, and the time spent in familiarising with the technology. Data on the resources needed to deliver and interpret the tests will be collected via a case report form and from study centres. Other care provided up to the end of the trial follow-up will also be collected via a case report form.

Unit costs of these resources will come from study centres and routine data sources (e.g. salary scales, etc). These unit costs will be combined with resource use to estimate the cost for each trial participant. Regression techniques will be applied to data on total costs to determine any difference between the two testing strategies. We will assume effects (clinically significant cancers detected) are the same when the estimates of effects (including the extremes of a confidence interval) rule out a minimally important question. In this case, we will present the results as a cost-minimisation analysis. However, if the confidence intervals do not rule out a minimally important difference, we will conduct a formal cost-effectiveness analysis. This will incorporate a stochastic analysis to explore statistical imprecision in the estimates of costs, effects and cost effectiveness. The results of this will be presented as cost and effect plots and cost-effectiveness acceptability curves. Further deterministic sensitivity analysis will be conducted to explore plausible alternatives e.g. around the quantity of resources used or unit costs.

Model based analysis

The model based analysis will be required to explore the impact of two different features: (i) changes in the number of patients who can be imaged as a result of possible reductions in imaging time; (ii) estimation of long-term impacts should clinically important differences not be ruled out. For (i) the focus will be on prostate cancer patients as these could also be considered as a proxy for other patients that could benefit for imaging.

For (ii) the results of the within trial economic evaluation if presented as an incremental cost effectiveness ratio will be difficult to interpret as there is no readily accepted threshold values for society's willingness to pay per additional clinically significant cancer detected. Therefore, we will conduct a model-based cost-utility analysis.

For a model addressing both (i) and (ii) the results will be reported as incremental cost per QALY gained (but see section on resource impact below). Both costs and QALYs will estimated over the estimated patient lifetime. As outcomes for individuals modelled will occur beyond a 12-month period both health benefits and costs will be discounted using the current recommended rate of 3.5% for both costs and benefits at the base case [NICE Guideline, 2013].

We anticipate a Discrete Event Simulation (DES) [Karnon et al, 2012] will be used as the model will explore the impact of allowing more patients to be imaged to determine the long-term impact on services later in the care pathway. However, the precise form of the model will be developed during the course of the study to best address the decision problem and we shall draw upon the advice of the clinical study teams and PPI Group. The model structure is likely to include a short-term decision tree element where that mirrors the within trial analysis and reports costs and outcomes up to the management decision following imaging e.g. biopsy or not. The model will then extrapolate the impact on patients' health (measured in QALYs) and NHS and PSS costs as a consequence of that decision. This will include the impact of 'incorrect or sub-optimal' decisions and the impact of correct decisions. The model will include subsequent treatment/management of prostate cancer, and the impact of recurrence or progression and subsequent management.

Stakeholders and literature reviews will inform the structure of the model. Data from the trial and secondary sources such as existing systematic reviews, primary evidence and other

economic evaluations conducted in the area of prostate cancer research will be synthesised to build and parametrise the model. Costs will include costs of tests and costs after follow-up, which will include adverse effects of the tests and costs of treatment and management of prostate cancer. These data will come from the trial and from existing sources e.g. NHS reference costs. Data will also include specificity and sensitivity of the tests (from the trial), incidence and risk of progression of the disease (assembled from the literature). The clinical and epidemiological data will be used to calculate path probabilities, combined with EQ-5D utility scores assembled from the literature to allow the estimation of QALYs.

Both probabilistic and deterministic sensitivity (to explore other forms of uncertainty e.g.to explore variations in management, in costs or utility values) analysis will be conducted with the results presented as cost/QALY plots and cost-effectiveness acceptability curves.

Resource impact assessment

As the adoption of the bpMRI may provide some resource savings, we will estimate the resource impacts of adopting bpMRI at scale. This will include the shorter-term impacts on imaging services as well as subsequent impacts on urological cancer services caused by any changes in throughput of patients. These resource impacts (both short-term and long-term) will be based upon findings and estimates from the economic evaluations described above. The NICE guidance and tool for resource impact assessment will be used [https://www.nice.org.uk/About/What-we-do/Into-practice/resource-impact-assessment].

9. REGULATORY, ETHICAL AND LEGAL ISSUES

9.1 Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformity with *[* the seventh revision of the 1964 Declaration of Helsinki.

9.2 Good Clinical Practice

The study will be conducted in accordance with the guidelines laid down by the International Conference on Harmonisation for Good Clinical Practice (ICH GCP E6 guidelines).

9.3 Research Ethics Committee (REC) Approval

(i) Initial Approval

Prior to the enrolment of subjects, the REC must provide written approval of the conduct of the study at named sites, the protocol and any amendments, the Subject Information Sheet and Consent Form, any other written information that will be provided to the subjects, any advertisements that will be used and details of any subject compensation.

(ii) Approval of Amendments

Proposed amendments to the protocol and aforementioned documents must be submitted to the REC for approval as instructed by the Sponsor. Amendments requiring REC approval may be implemented only after a copy of the REC's approval letter has been obtained. Amendments that are intended to eliminate an apparent immediate hazard to subjects may

be implemented prior to receiving Sponsor or REC approval. However, in this case, approval must be obtained as soon as possible after implementation.

(iii) Annual Progress Reports

Annual Progress Reports will be submitted to the Research Ethics Committee (REC) and the Sponsor in accordance with local / national requirements. The Annual Progress Report will also detail all SAEs recorded.

(iv) End of Trial Notification

The REC will be informed about the end of the trial, within the required timelines.

9.4 HRA approval

Health Research Authority (HRA) approval will be obtained prior to starting the study. Each participating site will confirm capacity and capability prior to commencing. The HRA and all participating sites also need to be notified of all protocol amendments to assess whether the amendment affects the institutional approval for each site.

9.5 Non-Compliance and Serious Breaches

All protocol deviations and protocol violations will be reported via the eCRF and reviewed by the Chief Investigator and reported to the ICTU QA manager on a monthly basis. Protocol violations will be reported to the Sponsor.

An assessment of whether the protocol deviation/violation constitutes a serious breach will be made.

A serious breach is defined as:

A breach of the conditions and principles of GCP in connection with a trial or the trial protocol, which is likely to affect to a significant degree:

- The safety or physical or mental integrity of the UK trial subjects; or
- The overall scientific value of the trial

The Sponsor will be notified within 24 hours of identifying a likely Serious Breach. If a decision is made that the incident constitutes a Serious Breach, this will be reported to the REC within 7 days of becoming aware of the serious breach.

9.6 Insurance and Indemnity and Sponsor

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

Imperial College London will act as the main Sponsor for this trial. Delegated responsibilities will be assigned to the NHS trusts taking part in the trial.

9.7 Trial Registration

The study will be registered on a trial database ISRCTN and clinicaltrials.gov in accordance with requirements of the International Committee of Medical Journal Editors (ICMJE) regulations.

9.8 Informed Consent

All subjects must sign and personally date the REC approved Informed Consent Form after having received detailed written and verbal information about the reason, nature and possible risks associated with the research study. The ICF can be issued and signed electronically, remotely by postage of consent form or in person.

Subjects should be provided with a copy of the signed Subject Information Sheet/Informed Consent Form document. The original Informed Consent Form should be retained with the source documents.

9.9 Contact with General Practitioner

It is the investigator's responsibility to inform the subject's General Practitioner (where applicable) by letter that the subject is taking part in the study provided the subject agrees to this, and information to this effect is included in the Subject Information Sheet and Informed Consent. A copy of the letter should be filed in the subjects medical records.

9.10 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained. On the CRF subjects will be identified by a subject ID number only. Documents that are not submitted to the Sponsor (e.g., signed informed consent form) should be kept in a strictly confidential file by the investigator.

The investigator shall permit direct access to subjects' records and source document for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor, NHS, Regulatory Authorities and REC.

For trial follow-up purposes, the trial management team are required to contact each participant directly for collation of patient questionnaires. To allow for this, the team will require the names, addresses and email address where applicable of each participant. These details, i.e., the names, address and email address will be housed separately to the electronic CRF and pseudonymised, i.e., linked by the participant's unique trial identifier and will be stored, securely walled off on Imperial College London University computers with access only granted to the study research team.

Queen Mary University of London (QMUL) to be sent patients NHS number and name to perform linkage to the NHS Information Centre and the NHS Central Register or any applicable NHS information system, if subject have given permission for this in their consent.

9.11 Data Protection and Patient Confidentiality

The investigators and study site staff will comply with the requirements of the Data Protection Act 2018 concerning the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

9.12 End of Trial

Last Subject Last Visit (LSLV) - defines the date that the last subject completed the study

9.13 Study Documentation and Data Storage

The investigator must retain essential documents until notified by the Sponsor, and for at least ten years after study completion. Subject files and other source data (including copies of protocols, CRFs, original reports of test results, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) must be retained. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

10. DATA MANAGEMENT

10.1 Source Data

All written or electronic patient health records held by the hospital or GP or other medical facility.

10.2 Language

CRFs will be in English. Generic names for concomitant medications should be recorded in the CRF wherever possible. All written material to be used by subjects must use vocabulary that is clearly understood and be in the language appropriate for the study site.

10.3 Database

We will use the REDCap online database application for electronic data capture (EDC) to record case report form data for patients participating in the study (www.imperial.ac.uk/joint-research-compliance-office/project-planning/nhs-project-planning/electronic-data-capture-non-ctimps/). REDCap is a regulatory compliant database that has been used in clinical trials for over 15 years and is sponsor approved for non-CTIMP studies such as this proposal. Study staff at each participating site will enter baseline and follow up data into the online database. The database is password protected and users will have passwords to access, enter and use the data for the full study duration. All members of the research team will receive training appropriate to their role and duties and will respect and comply with patient confidentiality.

10.4 Data Collection

eCRFs will be based on relevant data collection tools tested in previous studies that we have undertaken and will undergo review by the study team, relevant clinical staff and the statistician prior to use. Patient level data collection will include baseline factors, MRI results, biopsy recommendations, biopsy details and results, adverse events and post biopsy complications. Self-reported, validated patient questionnaires will be used to assess health-related quality of life. These will be collected at baseline and once at last follow-up. Details of procedures for CRF/eCRF completion will be provided in a study manual.

10.5 Archiving

All trial documentation, including that held at participating sites and the trial coordinating centre, will be archived for a minimum of 10 years following the end of the study.

11. STUDY MANAGEMENT STRUCTURE

11.1 Trial Steering Committee

A Trial Steering Committee (TSC) will be convened including as a minimum an independent Chair, independent clinician, the Chief Investigator and Trial Manager. The role of the TSC is to provide overall supervision of trial conduct and progress. Details of membership, responsibilities and frequency of meetings will be defined in a separate Charter (See CR014). A lay person will be included.

11.2 Trial Management Group

A Trial Management Group (TMG) will be convened including the Chief Investigator, co-investigators and key collaborators, trial statistician and trial manager. The TMG will be responsible for day-to-day conduct of the trial and operational issues. Details of membership, responsibilities and frequency of meetings will be defined in separate terms of Reference. (See CR014). One to two lay people will be included.

11.3 Data Monitoring Committee

The DMEC will comprise two independent clinicians with experience in clinical trials and an independent statistician. The DMEC charter will be based on the DAMOCLES study group template. Its roles will include: monitoring the data (including interim analyses) and making recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue; reviewing the interim analyses; advising the TSC regarding the release of data and/or information; and considering data emerging from other related studies. Refer to the separate DMC charter for further details (See CR014).

11.4 Early Discontinuation of the Study

In case of early discontinuation of the study, the Follow-up Visit assessment should be performed for each subject, as far as possible. The statistical criteria for termination of the study will be detailed in the statistical analysis plan (SAP).

11.5 Risk Assessment

A study-specific risk assessment will be performed prior to the start of the study to assign a risk category of ‘low’, ‘medium’ or ‘high’ to the trial. Risk assessment will be carried out by the ICTU QA Manager in collaboration with the Study Manager and the result will be used to guide the monitoring plan. The risk assessment will consider all aspects of the study and will be updated as required during the course of the study.

11.6 Monitoring

The study will be monitored periodically by trial monitors to assess the progress of the study, verify adherence to the protocol, ICH GCP E6 guidelines and other national/international requirements and to review the completeness, accuracy and consistency of the data. Monitoring procedures and requirements will be documented in a Monitoring Plan, in accordance with the risk assessment.

11.7 Quality Control and Quality Assurance

Quality Control will be performed according to ICTU internal procedures. The study may be audited by a Quality Assurance representative of the Sponsor and/or ICTU. All necessary data and documents will be made available for inspection.

The study may be subject to inspection and audit by regulatory bodies to ensure adherence to GCP and the UK Policy Framework for Health and Social Care Research .

11.8 Peer review

This study has been peer reviewed by funder Cancer Research UK, within the ICTU-Surgery Trials Forum at Imperial College London and detailed review by the NCRI (UK) Prostate Research Group.

Our proposal was discussed and reviewed positively at the NCRI Prostate Research Group who made recommendations that have been incorporated into our proposal. The review process was led by members not involved in this proposal and coordinated by Dr Fay Cafferty (Statistician, MCR CTU at UCL). First, strengthening radiology and biopsy operator training; we have now dedicated two standardisation meetings for both MRI and biopsy as well as incorporating the recent UK consensus on certification levels with only level 2 and 3 radiologists to be part of the study. Second, ensuring that sites represent a good mix of NHS centres, so the results are relevant; we have now obtained interest from over 30 NHS sites which have various referral bases and caseloads of patients undergoing MRI and biopsy. Third, incorporating a very careful on-site measurement of timings associated with scans rather than taking these from the imaging protocols; this will be carefully measured in scans carried out in the internal pilot to obtain accurate timings. Fourth, we were asked to consider how to reconcile that the international reporting standard (PIRADS scoring [latest version as defined in MRI Reporting SOP]) was different to that recommended in the NICE guidance (Likert scoring); our survey showed that radiologists used both in equal measure. Reassuringly, all radiology respondents indicated that they would be willing to use both reporting systems in our study with many commenting that they often do this anyway in routine practice. Our study would be an opportunity to conduct a robust comparison of the two reporting systems. Finally, the NCRI group recommended that we are clearer on guidance to centres about which men would be advised to undergo biopsy; we will adopt NICE guidance that stipulates clinicians consider other factors such as age, ethnic risk, and family history to determine which men with negative or equivocal scans to biopsy.

Our clinician and NHS centres survey, discussion with NCRI Prostate Research Group and patient groups indicate strong support for this study. the clinician survey in April 2020 had a 70% response rate with 75 clinicians from 55 centres replying; 54 were urologists and 22 radiologists. There was a high level of equipoise with 96% (72/75) saying they would be willing to randomise patients to the trial. We again explored what non-inferiority margin was acceptable. Of 74 responding to this question, 66% of clinicians indicated 5% non-inferiority margin, and a further 14% indicated that a higher non-inferiority margin (of between 6% and 10%) would be acceptable. In addition, we asked about non-inferiority with respect to a potential increase in the proportion of men being biopsied; again 5% was the most popular margin with 69% (51/74) choosing this, and a further 17% (13/74) choosing higher margins. This justifies the choice of 5% as the non- inferiority margin used in sample size calculations for both measures. We also obtained further details about current practice and areas in which clinicians would be willing to standardise practice for this study and these are detailed in the relevant sections.

11.9 Patient and Public Involvement

Patient and Public Involvement during the design phase

We recognise the value of patient involvement and embed this into all of our studies from time of inception through to delivery and then dissemination of findings. For this proposal, we took the following specific steps:

Robert Oldroyd and Derek Price, both diagnosed and treated for prostate cancer, will be members of the TMG. Robert is a co-applicant on the proposal and was involved in the outline stage. Both have read this proposal and made changes and recommendations. Robert and Derek are experienced patient representatives who have worked with us on other trials (Robert working on PROMIS; Derek on PROSTAGRAM). Both trials are related to prostate cancer diagnosis using imaging and completed successfully. Robert is a member of Prostate Cancer UK's PPI representatives' group, its Research Advisory Committee, and has served on a research ethics committee. Derek is PPI representative on the NCRI Prostate Research Group, is a member of PCUK's PPI group and as noted above, was PPI TMG member for PROSTAGRAM (n=410) investigating the use of a short MRI scan in the community to actually screen for prostate cancer.

An NIHR Enabling Involvement Fund grant, awarded to develop this study proposal by the NIHR Northwest London Research Design Service, allowed us to run two patient focus groups with six patients recruited through Prostate Cancer UK's patient network. These helped revise our plans for recruitment, consent and sample size. We especially sought their advice and help on acceptability of the trial, outcomes of importance and the non-inferiority margin. Our hypothesis is that the short bpMRI is non-inferior to the long mpMRI in terms of cancer detection and we wanted to find out whether men would agree to participate. The patients accepted that the evidence was strong enough for bpMRI and mpMRI to be compared within a randomised controlled trial. The focus group stated that the trial could provide some benefits if they could still get an accurate diagnosis without needing contrast. They stated however, that the main reason to participate would be to help the NHS be potentially more cost-efficient and some patients saw the value of freeing up scanner time for other types of diseases.

Further, we wanted their views on which outcome was important to them from a choice of cancer detection (all cancer vs. clinically significant cancer) and biopsy rates. They advised that the key outcome for patients was to demonstrate that the detection of clinically significant prostate cancer for bpMRI was non-inferior to mpMRI, but would also want biopsy rates to be looked at as well since it was important that MRI still allowed patients to avoid a biopsy if safe to do so. We have therefore made this a key secondary outcome.

With respect to what non-inferiority margin, needed for the sample size calculations, was acceptable. We provided visual displays to illustrate what we meant by this and clarified whether patients understood it; we then asked their views on the non-inferiority margin giving some options. Most indicated 5% would be acceptable whilst two indicated a value higher (but no higher than 10%). The value agreed by the majority reflected that provided by our clinician surveys (first of 20 and the second of 74 clinicians).

As well as Robert and Derek, the patients of the focus groups were keen and interested to support the study with ongoing PPI opportunities throughout the trial.

Patient and Public Involvement during the conduct phase

There are a number of approaches to this important aspect of study design, delivery, conduct and NHS/societal impact.

First, Robert and Derek will both be members of the TMG. Both will review all study-related documentation prior to submission to sponsor and research ethics committee. They will continue to review any study-related documentation and substantial amendments and advise the team on appropriate recruitment strategies for this group of patients where there might be unique challenges due to the urgent nature of the referrals and the speed with which the NHS conducts the diagnostic tests. Robert will attend the research ethics committee meeting with the lead applicant and the trial manager.

Second, patients who were part of the focus groups previously described have agreed to continue to be involved and review all patient-facing study documentation as part of a study-specific PPI group. They will also review our recruitment strategy since the first contact with patients will often be by telephone as patients referred by GPs on the 2-week wait cancer referral pathway are often booked directly for an MRI scan following a teleconsultation with their clinical team. The way we approach patients is critical for a successful study. In our previous studies, we have found that PPI input into the recruitment strategy through a semi-structured script was vital. The PPI group will also review any changes in patient-facing study documents and recruitment processes that might be required during the study period, particularly when we transition from the pilot to main phase.

Third, the research team will regularly engage with the PPI group with a meeting to be held before the pilot starts and near the end of the pilot to learn from any issues that have arisen. We will meet again every 6 months during the main phase to update the study PPI group and gain any further advice and guidance about trial issues that might arise. These meetings will be led by Derek or Robert and one of the joint-CIs.

Fourth, our PPI TMG members, Derek and Robert, and the study PPI group will help with aspects of the study design (such as validating the care pathways that form the basis of the economic modelling) and with our dissemination. Our dissemination strategy will include summary of results provided to participants, lay summaries of the main findings placed on our media outlets (Twitter, study-specific and institutional/group websites, Facebook), lay accessible summaries of peer-reviewed manuscripts and reports, and other media e.g., short summary videos for patients and clinicians housed on institutional websites and made freely available on YouTube. Derek and Robert have agreed to be part of any video to talk about their role on the study. This will also help in encouraging more individuals to get involved in research planning and delivery.

Fifth, all PPI representatives will have our formal training using structured courses, delivered by the Imperial Patient Experience Research Centre. Study staff will also be attending the appropriate courses on PPI engagement (see www.imperial.ac.uk/patient-experience-research-centre/ppi/ppi-training/. Further, all costs for re-imbursement of time and expenses are included in the budget, as per recommended guidance by INVOLVE, to allow for this regular input, review of study information, and attendance at meetings.

11.10 Publication and Dissemination policy

Our dissemination strategy will include summary of results provided to participants, lay summaries of the main findings placed on our media outlets (Twitter, study-specific and institutional/group websites, Facebook), through the websites and newsletter of a number of supporting organisations of which our team members have links including Prostate Cancer UK, Maggie's support group, Pelican Cancer Foundation and CRUK lay accessible summaries of peer-reviewed manuscripts and reports, and other media e.g., short summary videos for patients and clinicians housed on institutional websites and made freely available on YouTube. The social media presence of organisations involved will be used to highlight news about the trial.

Participants who have indicated they wish to receive a summary of the findings of the results will be sent this via post or email in the form of a newsletter.

Information concerning the study, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of the Sponsor. The investigator may use this information for the purposes of the study only.

It is understood by the investigator that the Sponsor will use information developed in this clinical study and, therefore, may disclose it as required to other clinical investigators. In order to allow the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to the Sponsor.

Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from the Sponsor.

Therefore, all information obtained as a result of the study will be regarded as CONFIDENTIAL, at least until appropriate analysis and review by the investigator(s) are completed.

Permission from the Executive/Writing Committee is necessary prior to disclosing any information relative to this study outside of the Trial Steering Committee. Any request by site investigators or other collaborators to access the study dataset must be formally reviewed by the TSC.

A Clinical Study Report summarising the study results will be prepared and submitted to the REC within a year of the end of study.

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13. REVISION HISTORY

Version	Date	Summary of changes
1.0	21APR22	First version
2.0	22MAY23	The protocol has been updated by removing of the requirement for a minimum of 24 hours before consenting to the study
3.0	11OCT23	Link referring to the PCUK/RCR-approved online course has been amended to https://www.raiqc.com/sign-in/ on page 22.

SIGNATURE PAGE 1 (CHIEF INVESTIGATOR)

The signature below constitutes approval of this protocol by the signatory, on behalf of the Protocol Development Group, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: IP 7 - Evaluating the role of biparametric MRI and image-fusion targeted biopsies for detection of prostate cancer

Protocol Number: Protocol number 22CX7488

Signed: _____

Professor Hashim U. Ahmed
Imperial College London

Date: _____

SIGNATURE PAGE 2 (SPONSOR)

The signatures below constitute approval of this protocol by the signatory.

Study Title: IP 7- Evaluating the role of biparametric MRI and image-fusion targeted biopsies for detection of prostate cancer

Protocol Number: Protocol number 22CX7488

Signed: _____

Name of Sponsor's Representative
Imperial College London

Date: _____

SIGNATURE PAGE 3 (LEAD STATISTICIAN AND CO-LEAD ON GRANT)

The signatures below constitute approval of this protocol by the signatory.

Study Title: IP 7- Evaluating the role of biparametric MRI and image-fusion targeted biopsies for detection of prostate cancer

Protocol Number: Protocol number 22CX7488

Signed: _____

Professor Rhian Gabe
Queen Mary University of London

Date: _____

SIGNATURE PAGE 4 (PRINCIPAL INVESTIGATOR)

The signature of the below constitutes agreement of this protocol by the signatory and provides the necessary assurance that this study will be conducted at his/her investigational site according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: IP 7- Evaluating the role of biparametric MRI and image-fusion targeted biopsies for detection of prostate cancer

Protocol Number: Protocol number 22CX7488

Address of Institution: _____

_____

_____

Signed: _____

Print Name and Title: _____

Date: _____