CLINICAL STUDY PROTOCOL

(ICTU Adopted)

Full Study Title: PROstate Cancer Screening Trial using A Group of Radiological Approaches including MRI and ultrasound

Short Study title / Acronym: IP1 - PROSTAGRAM

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ABBREVIATIONS

AE	Adverse Event
AI	Artificial Intelligence
bp-MRI	Bi-parametric MRI
CAD	Computer Aided Detection
CWS	Cancer Worry Scale
CRF	Case Report Forms
CCI	Charlson Co-Morbidity Index
CI	Chief Investigator
CRN	Clinical Research Network
DCE	Dynamic Contrast-enhancement
DRE	Digital Rectal Examination
DWI	Diffusion weighted imaging
GP	General Practitioner
HRQoL	Health-related quality of life
ISRCTN	International Standard Randomised Controlled Trial Number
MCCL	Maximum cancer core length
mp-MRI	Multi-parametric MRI
PCRMP	Prostate Cancer Risk Management Programme
PIS	Participant Information Sheet
SAE	Serious Adverse Event
SF-12	12-item Short-Form Health Survey
SOP	Standard Operating Procedure
STAI	State-Trait Anxiety Inventory
TRUS-biopsy	Transrectal ultrasound-guided biopsy
TSC	Trial Steering Committee

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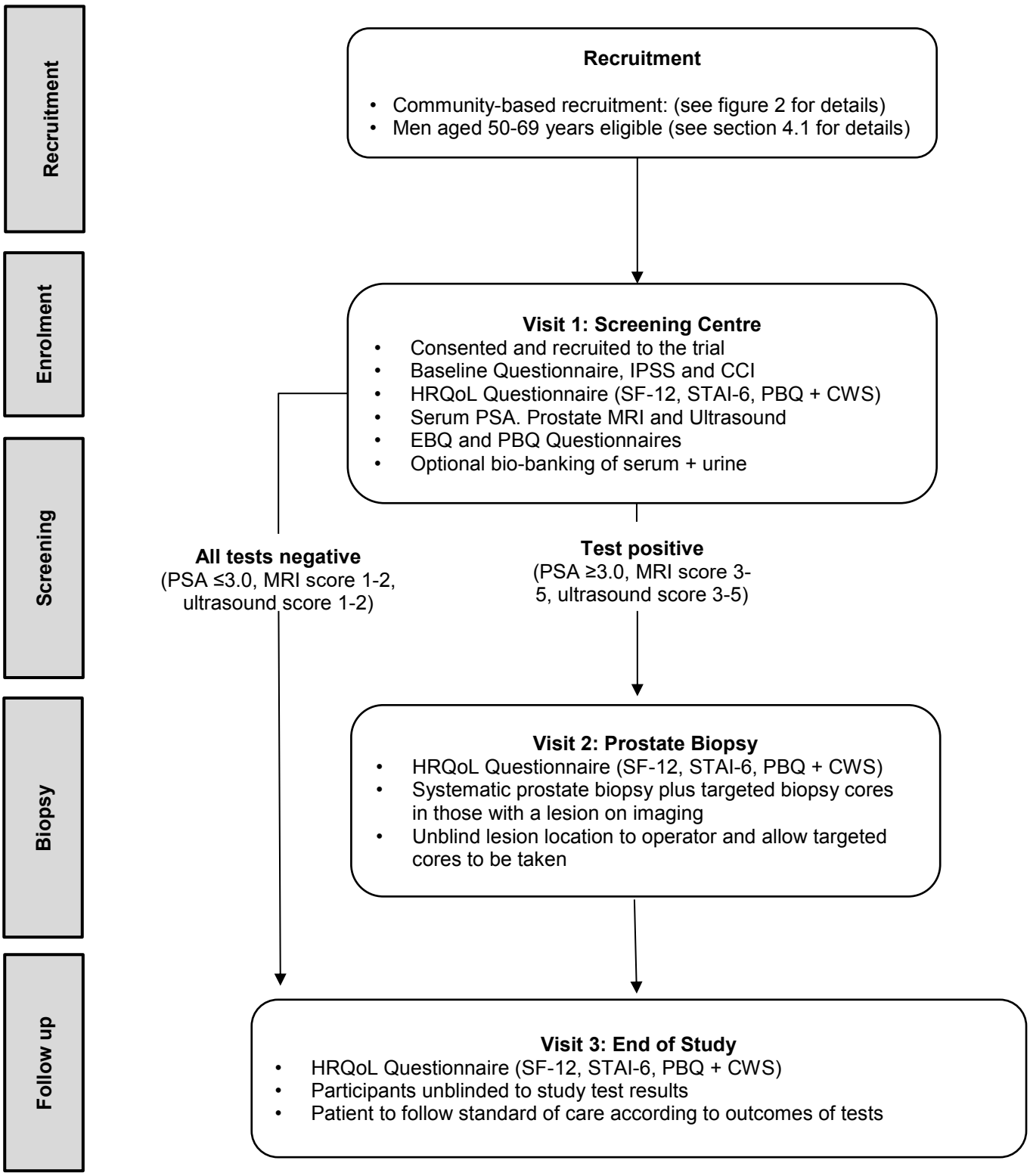
Figure 1: Trial Schema



TRIAL SUMMARY

TITLE	PROSTAGRAM: PROstate Cancer Screening Trial using A Group of Radiological Approaches including MRI and ultrasound
AIM	To assess the role of using image-based biomarkers in the community to screen for clinically significant prostate cancer in men
PRIMARY OBJECTIVES	To determine the positive test rate of prostate MRI in the general male population aged 50 to 69 years
SECONDARY OBJECTIVES	***Other performance objectives*** To determine the prevalence of positive test rate of prostate ultrasound in the general male population aged 50 to 69 years To determine the distribution of MRI and US scores in a screened population To evaluate a suitable threshold score that defines positivity of MRI or US in a screening population To estimate the overall agreement between Prostate specific antigen (PSA), US and MRI in the proportion of men with a positive result. Then to compare the overall agreement in proportion of men diagnosed with clinically significant prostate cancer on biopsy. To explore combinations and sequences of prostate MRI, US and PSA that might be an optimal screening strategy to evaluate in a future definitive study To estimate the overall agreement of Imaging findings, PSA and Digital rectal examination (DRE) To report the clinical outcomes of men with a positive PSA, US and/or MRI result ***Fluidic Biomarker objectives*** To determine the positive test rate and the distribution of biomarker panel scores in the general male population aged 50 to 69 years To collect and store serum and urine samples in a biobank to evaluate new serum biomarkers ***Feasibility Objectives*** To evaluate the feasibility of undertaking a screening cohort study comparing the diagnostic performance of prostate MRI and/or US and/or serum prostate specific antigen (PSA) testing To determine the recruitment rates to the study across different ethnic groups To determine the eligibility rates across each screening test To determine the compliance/retention of participants with study processes

	To assess the acceptability of study processes and informational content. To estimate the costs of undertaking a subsequent diagnostic paired cohort validating study **MRI Reporting and CAD/AI Objectives** To evaluate the diagnostic performance of a CAD/AI algorithm as a standalone reader To evaluate the effect of CAD/AI as a second reader on diagnostic performance of radiologists To evaluate the effect of CAD/AI on interobserver variability of radiological interpretation of prostate MRI To define a suitable threshold MAI score to detect clinically significant cancer ***Other Objectives*** To determine the health-related quality of life outcomes To assess risk perception and prostate cancer worry and anxiety of prostate cancer during the study To establish the prevalence of post-biopsy adverse events To collect the long-term health outcomes of those men who consent to longitudinal follow-up To build a databank of ultrasound and MRI meta-files matched with histopathology for future research and education
DESIGN	A prospective cross-sectional study assessing the feasibility of using imaging as a screening test for clinically significant prostate cancer in men from the community Please note: Study tests are blinded to the reporters.
SAMPLE SIZE	366 (406 with dropouts) men aged between 50 and 69 years inclusive
INCLUSION/ EXCLUSION CRITERIA	Participants must be fit to undergo all procedures listed in the protocol Estimated life expectancy of 10 years or more No PSA test or prostate MRI within the prior two years of screening/consent visit No previous history of prostate cancer, prostate biopsy or treatment for prostate cancer. No evidence of a urinary tract infection or history of acute prostatitis within the last 6 months
MAIN STUDY PROCEDURES	Main procedures include 1. Serum PSA 2. Prostate MRI 3. Prostate shearwave ultrasound 4. Serum biomarker panel

	5. Blood / urine for biobanking (Optional) 6. If MRI or US positive: Systematic prostate biopsy (10-12 core transrectal or transperineal) plus targeted biopsy cores in those with a MRI lesion (score 3-5) Duration: The total duration of this study will be up to 24 months
PRIMARY ENDPOINTS	The proportion of men with a positive MRI defined by a score of 3 or greater
SECONDARY ENDPOINTS	***Other performance objectives*** (MRI and US) The proportion of men with screen-positive prostate ultrasound defined by a score of 3 or greater The proportion of participants within each MRI score or US score of 1, 2, 3, 4 or 5 An evaluation of proportion of participants across each MRI and US score with no cancer, insignificant cancer and significant cancer with each test. A comparison of the proportion of participants with a positive result for each screening test. A comparison of the proportion of men subsequently diagnosed with a clinically significant prostate cancer as defined by pre-specified histological definitions Comparison of different testing combinations in terms of biopsy rates, detection of insignificant cancer and significant cancers The correlation between imaging findings and DRE The proportion of men who go onto definitive local or systemic treatment. In men who undergo radical prostatectomy the proportion who are upgraded at final histology ***Fluidic Biomarker objectives*** The proportion of participants within a positive Episwitch biomarker panel and distribution of score To establish a biobank of fluidic samples matched with histopathology for future research ***Feasibility Objectives*** Feasibility will be measured based on a point-estimate of recruitment rates across different recruitment strategies. Recruitment rates will be defined as the number of individuals who: i. Contact the study team with an expression of interest in participation ii. Attend the screening clinic iii. Offer informed consent and are enrolled into the study The proportion of men from different ethnic groups accepting the initial invitation to participate and subsequently participating within the study

	Eligibility will be assessed against pre-defined eligibility criteria. The reasons for ineligibility will be recorded and compared across each screening test The retention/compliance rate will be defined as the number of participants completing screening tests and any follow-up biopsy recommendation. The reasons for withdrawal will be documented with an optional survey offered to individuals. The individual costs for recruitment and screening will be recorded in a resource utilisation log. These will be scaled up to provide an estimate of the cost for the subsequent study **MRI Reporting and CAD/AI Objectives** Sensitivity analysis of the CAD/AI system with histology and/or radiologist consensus as the reference standard Comparison of radiologist diagnostic performance for detection of clinically significant cancer with and without the CAD/AI The Interobserver agreement with and without the use of CAD/AI as second reader Receiver operating characteristic (ROC) to compare the diagnostic performance of CAD/AI at different MAI scores ***Other Objectives*** Changes in Health-related quality of life (HRQOL) measured by SF-12 (12-item Short-Form Health Survey) at baseline and follow-up Changes in worry and anxiety scores measures by Cancer worry scale (CWS) and State-Trait Anxiety Inventory (STAI). Rates of biopsy related adverse events (infectious complications, urinary retention, haematuria requiring admission) Linkage to national database An open access secure and quality controlled databank of ultrasound and MRI meta-files matched with histopathology for future research and education

1. BACKGROUND

1.1 Prostate Cancer Screening

Prostate cancer is one of the most common causes of cancer death in men, resulting in 11,300 deaths per year(1). The lifetime risk of dying from prostate cancer among UK men is 4.3%(2). Prostate cancer mortality rates are consistently higher than breast cancer mortality on an age standardised basis(3). These mortality figures mean that there has been a long-standing discussion regarding the introduction of a population-based screening program equivalent to the breast cancer-screening program.

The aim of a screening programme would be to detect clinically significant prostate cancer at a curable stage and thereby reduce cancer-specific mortality. The mortality risk for prostate cancer is primarily determined by how advanced the cancer is at diagnosis. The 5-year survival for men with distant metastases is 30% but if diagnosed when localised to the prostate the 5-year survival rate is equivalent to the general population(2). Localised disease is generally asymptomatic and there is a long latent period between the early malignant phase and progression to metastatic cancer. These characteristics mean that a successful screening programme has potential to significantly improve prostate-cancer specific mortality by detecting the disease at an earlier stage prior to progression to metastatic disease.

There is high-quality evidence from the large European Randomised Study of Screening for Prostate Cancer (ERSPC) that prostate cancer screening can reduce prostate cancer mortality by at least a relative risk reduction of 21% compared to little to no PSA testing(4). However, these mortality benefits need to be considered in view of the potential for harms from a population-based screening programme. The UK National Screening Committee (UK NSC) has reviewed the updated evidence for prostate cancer screening and recommended against a universal screening programme due to the limitations of Prostate-Specific Antigen (PSA) as a screening test. The summary report describes PSA as “a poor test for prostate cancer and a more specific and sensitive test is needed”(5).

Due to the limitations of PSA, there is no country or international body, which recommends routine PSA screening for all men. Instead, the majority recommend informing men about the benefits and risks of PSA screening so that each man can make an informed decision with knowledge of the controversy around PSA. The potential risks to be considered include false-positives leading to high rates of biopsy, biopsy-related complications and over-diagnosis of low risk cancer that is then often unnecessarily treated using radical therapy. There is a large reservoir of low-risk prostate cancers within the population estimated at approximately 1 in 3 of men above the age of 50 years. The detection of such indolent low risk disease leads to men being subjected to the harm of a cancer diagnosis and often radical treatment that does not confer a survival benefit over a median of 10 years follow-up compared to no treatment. Yet, radical therapy confers genito-urinary harms such as incontinence, impotence and rectal toxicity. Those men who choose active surveillance rather than radical active treatment are then placed on intensive monitoring regimens that often include repeated PSA testing, repeat 1-2 yearly biopsies and the potential for psychological distress.

PSA is unable to reliably discriminate between clinically insignificant and clinically significant cancers that pose a threat to quality of life or life expectancy. In the ERSPC study it was estimated that 50% of cancers were over-diagnosed and would not have caused any morbidity or mortality during the man's lifetime (6). PSA is also non-specific and can be elevated due to benign enlargement of the prostate gland, inflammation or infection, which triggers unnecessary biopsies. Due to these problems, it is accepted that the harms of PSA screening outweigh the proven mortality benefit from a prostate cancer-screening programme.

This study aims to evaluate the feasibility of a different approach to prostate cancer screening that might retain the reductions in mortality whilst minimising the harms hitherto seen.

1.2 Intervention Details

1.2.1 MRI

The rapid advances in imaging technology has created potential for new image-based screening tests. Prostate MRI has emerged as the dominant technique for diagnosis and staging of clinically localised prostate cancer. There has been extensive research into the role of prostate MRI in men referred with a suspicion of prostate cancer. The NIHR-HTA/MRC PROMIS trial was led by the same Chief Investigator of this study(7) and showed that it has a high sensitivity and negative predictive value for clinically significant prostate cancer while limiting the detection of low-risk cancer in the UK in men who present with an elevated PSA in secondary hospital care. These performance characteristics may differ when used as a screening test in the community where we would expect a lower prevalence of disease and different population characteristics.

As an image-based screening test, prostate MRI has potential to significantly reduce the problem of too many prostate biopsies and over-diagnosis of clinically insignificant cancers. A further advantage of image-based screening is that it allows suspicious areas to be visualised and targeted with biopsies thus improving the detection of clinically significant cancers. Prostate diagnostics are currently widely based on transrectal ultrasound-guided (TRUS) biopsy, which involves taking 10–12 biopsy cores through the rectum. This technique is blind to the location of the cancer in the prostate, which is in contrast to other solid organs cancers where the lesion is identified by imaging in order to direct biopsies to the area of suspicion. The random deployment of needles increases the overdiagnosis rate and has poor diagnostic performance for ruling in or out clinically significant cancer. This technique also carries a risk of infectious complications as the needles transverse the rectal mucosa.

In an imaged-based screening programme, such as in breast cancer mammography for instance, the lesion can be visualised thus allowing a targeted biopsy to be performed. A targeted biopsy approach has been shown to have improved accuracy, better sampling efficiency and reduced histopathological burden in men who present with an elevated PSA in secondary care(8). There is some evidence that the reduction in number of cores from targeting leads to less pain, fewer LUTS and potentially lower rates of infectious complications and sepsis(9).

Image-based screening tests have been successfully adopted in other cancer screening programmes. Breast mammography for instance is an established screening programme across the majority of developed countries and there is mounting evidence for the efficacy of CT colonoscopy for bowel cancer screening(10) and lung CT for lung cancer [ref]. Although MRI is starting to become a standard investigation in the prostate cancer diagnostic pathway in secondary care, there have been a number of small but limited studies evaluating its role as a potential screening test in the community.

A pilot study embedded within the existing Göteborg arm of the ERSPC screening trial reported the diagnostic performance of MRI at different PSA thresholds(11). In this study, MRI was used as an adjunct to PSA and the participants did not reflect an average-risk screened population as they were recruited from the final screening round and had been screened up to 9 times using serum PSA with a third having undergone a previous biopsy(11, 12). Under these conditions, when MRI was combined with a low PSA threshold of ≥ 1.8ng/ml, the sensitivity was 73% with a negative predictive value of 92% in detecting and ruling out Gleason >/=7 cancers. Nam et al(13) carried out a feasibility/pilot study of MRI as a potential screening test in the community. Of the 47 recruited men, 18 (38.3%) had cancer while 29 (61.7%) had no evidence of cancer. The adjusted OR of prostate cancer was significantly higher for MRI score than for prostate specific antigen level (2.7, 95%CI 1.4-5.4, p=0.004 vs 1.1, 95%CI 0.9-1.4, p=0.21). Among the 30 men with a normal PSA (defined as less than 4.0ng/ml) the positive predictive value in those with an MRI score of 4 or more was 66.7% (6/9) and the negative predictive value in those with an MRI score of 3 or less was 85.7% (18/21, p=0.004).

The NIHR-HTA/MRC PROMIS trial used a multi-parametric MRI (mp-MRI) technique, which combined anatomical T2-weighted imaging with functional techniques such as diffusion-weighted imaging (DWI) and dynamic contrast-enhanced (DCE) sequences. This protocol requires the administration of intra-venous contrast and 30-40 minutes scanning time. A screening MRI will need to be short duration and free of any intravenous contrast agent. The initial results from shorter non-contrast biparametric-MRI (bp-MRI) protocols are encouraging and suggest that fast protocols with image acquisition times of under 15 minutes without contrast can have a similar diagnostic performance to standard mp-MRI in a pre-biopsy setting(14). This is supported by several meta-analyses which have suggested that there is little to no incremental benefit from adding dynamic contrast sequences(15, 16) and the most recent PI-RADS v2 guidelines commented that the added value of DCE has not been firmly established(17). The guidelines acknowledge that elimination of DCE may be the next logical step once there is high-quality evidence to support this decision(18).

At present, the role of DCE in PIRADSv2 has been restricted to assessment of indeterminate lesions in the peripheral zone. Within a screening protocol, the follow-up for indeterminate lesions may be surveillance or based on a patient-recall system, which further limits the role of DCE with a potential screening test based on MRI. The benefits of a non-contrast approach has been investigated by the chief investigator (CI) of this study in the PICTURE study. This subanalysis found that the incremental benefit of contrast was marginal in men who had previously undergone TRUS biopsy(19). There was no significant improvement in sensitivity from the addition of DCE but it did reduce specificity which would be expected as

there are a number of benign conditions which trigger false positives on DCE including focal prostatitis and mixed BPH nodules in the central gland(20). The PICTURE study validated each mp-MRI sequence against transperineal template mapping biopsy.
Certainly, the higher acquisition times and the risk of contrast enhancement from the gadolinium at a population level make it unfeasible to incorporate. An image-based screening protocol needs to be simple and practical without significantly affecting the accuracy of the test. It is not practical within a screening programme to verify all participants' renal function, gain intravenous access and administer contrast.
The omission of DCE shortens examination time and once the need for contrast is eliminated, many of the practical challenges associated with mp-MRI are removed and scans can be performed across a wider range of locations and times.

1.2.2 Ultrasound

There are newer ultrasound techniques emerging, which have a number of potential advantages compared to MRI. Ultrasound imaging is lower cost, more accessible and operators are widely available Conventional grey-scale ultrasound is a mainstay within prostate cancer diagnostics as it is used to visualise the prostate in order to guide biopsies in zones of the prostate. The standard grey-scale or b-mode imaging has limited sensitivity and specificity for detection of significant prostate cancer (21, 22).
There have been growing interest in combining b-mode ultrasound with additional modalities such as elastography, which is a technique, used for the cancer detection based on tissue stiffness. It is known that malignant tissue is less elastic due to increased cell density and differing collagen distribution.
Shearwave elastography (SWE) is a novel type of elastography presses tissue using acoustic radiation force, measuring the speed of progress of the resultant shear wave. In contrast to other ultrasound techniques, which are non-quantitative, SWE provides an absolute numerical result, which can generate a threshold for screening. It is also avoids the technical challenge and learning associated with manual tissue compression with standard elastography are avoided. A meta-analysis of SWE has shown a combined sensitivity of 84% and specificity 86% for detection of prostate cancer(23)

1.2.3 Fluidic Biomarkers

There are fluidic biomarkers that might also allow men at risk to consider avoiding an immediate biopsy. The advantage of a blood-based biomarker lies in the simplicity, reproducibility and non-invasiveness of the test. These biomarkers and biomarker panels have also shown the ability to reduce the risk of diagnosing clinically insignificant lesions whilst identifying some clinically significant cancers. Studies in this area have some limitations with heterogeneous populations, use of different thresholds for defining a suspicious test and using TRUS-biopsy as the reference standard (24, 25). Nonetheless, the 4-kallikrein and phi fluidic biomarker panels might allow up to 24%-42% and 29%-36% men to avoid biopsy whilst missing 6%-12% and 9%-10% significant (Gleason >/=7) cancers, respectively (26-30). Some, such as phi and PCA3, have not been convincing when compared to an imaging-based pathway (31). Others have recently been found to work in a complementary manner to MRI raising the prospect of further refinements to decisions about whether to biopsy(32).

There has been widespread interest in novel biomarkers as an alternative or adjunct to PSA screening. A range of urine tests and plasma protein biomarkers have been proposed to address the limitations of PSA(33). We will incorporate an optional biobanking of blood following standard operating protocols so that novel biomarker panels can either be developed and/or tested within the cohort of men in this study.

We will prospectively test the Episwitch biomarker panel. There are multiple genetic changes associated with prostate cancer, including mutations in p53 (up to 64% of tumours), p21 (up to 55%), p73 and MMAC1/PTEN tumour suppressor genes, but these mutations do not explain all the observed effects on gene regulation [8]. In human cells, epigenetic mechanisms involving dynamic and multi-layered chromosomal loop interactions are powerful regulators of gene expression [9]. Chromosome conformation capture (3C) technologies allow these signatures to be recorded and have gained considerable attention for disease diagnosis [10-13].
A significant proportion of chromosomal conformations are controlled by non-coding RNAs, which regulate the tumour-specific conformations [14]. Tumour cells have been shown to secrete non-coding RNAs that are endocytosed by neighbouring or circulating cells and change their chromosomal conformations in a process called “horizontal transfer” [15, 16]. RNA in blood has low stability and poor detection rates. Circulating DNA present in plasma does not retain 3D conformational topological structures present in the intact cellular nuclei. Prostate tumours undergo long-range epigenetic alterations in 3-dimension chromosome conformations and distinct epigenetic signatures were found in circulating DNA from PCa patients [17]. Previous work has shown the presence of melanoma-specific chromatin conformations in peripheral blood mononuclear cells (PBMCs) and primary tumours of melanoma patients [18, 19]. Fractionation studies showed that the detected signature comes from lymphocytes and not circulating tumour cells [18].
The Episwitch assay is a next generation assays detects epigenetic regulatory signature changes in the structures of chromosomes at the loci implicated in the onset and progression of the disease.

1.2.4 Computer Aided Detection for screening (CAD)

An image-based national screening programme requires a large scanning capacity and produces many scans requiring interpretation by radiologists with the relevant experience and subspecialty training. It is important that a screening prostate MRI provides consistent results when performed across diverse centres and interpreted by different clinicians. There is interobserver variability in all radiological reporting but the rates for prostate MRI have not reached the level achieved with mammograms for breast cancer screening(34).
Computer-aided detection (CAD) or Artificial Intelligence (AI) systems can potentially be an utilised to reduce interobserver variability and improve radiological reporting capacity. The CAD/AI system acts as a supplement to human readers and marks potential areas of concern so the radiologist can decide if the area warrants further investigation. It can assist radiologists to identify cancers, which might otherwise be missed. There has been widespread use of CAD/AI systems in breast cancer screening programs particularly in the United States’ Medicare population where it is estimated it is used in 74% of screening

mammograms(35). There is extensive evidence that the system can improve the sensitivity of mammography and improve radiology reporting workflow (36). CAD/AI systems are being investigated in other image-based screening modalities particularly CT-colonography with encouraging results(37).

There are similar CAD/AI systems available for prostate MRI and in the early stage of validation (38). The PROSTAGRAM study will embed a CAD/AI application to prospectively evaluate the feasibility of using a CAD/AI system within the workflow of radiological interpretation.

1.3 **Recruitment Strategies**

Screening tests are targeted at a large population of asymptomatic individuals, the majority of whom are healthy and do not have the target disease. The low prevalence of positive findings from screening necessitate a large sample size to evaluate performance characteristics of screening tests. Potential participants are recruited direct from the community, which requires different strategies to trials recruiting within existing clinical pathways.

The PROSTAGRAM trial will evaluate various recruitment pathways in order to establish the optimum recruitment strategy and identify potential barriers to recruitment. These include postal, sms, poster, websites and direct opportunistic approaches via the general practitioner.

Previous prostate cancer screening trials have used written invitations with subsequent 45% response rate to attend a prostate cancer-screening clinic (39). This is lower than the uptake for breast and cervical screening which have uptake rates consistently above 70%, although these are in the context of a national screening programme with extensive resources, advertising and public acceptance. A low uptake can have significant impact on the external validity of a screening test(40).

In addition, previous large screening trials have had a low screening uptake among certain ethnic groups. African/African-Caribbean men have been particularly under-represented in previous trials despite being at double the risk of mortality from prostate cancer (41). The current screening strategies are based on recommendations from studies of predominately Caucasian men despite the clear evidence that African/African-Caribbean men have a high lifetime risk of prostate cancer mortality. There is a need for further screening research in this population and the PROSTAGRAM study aims to achieve a participant recruitment which is representative across ethnic risk groups particularly African/African-Caribbean men.

1.4 **Rationale for study**

The UK National Screening Committee has recommended that further research is required into alternative screening tests before a population-based prostate cancer screening programme can be considered for approval(42). We propose that prostate MRI has certain performance characteristics, which make it attractive as a potential screening test. We have previously shown that prostate is a reliable pre-biopsy triage test in secondary care once

men have been referred to hospitals for an elevated serum PSA. However, its role as a screening test is unknown and warrants further investigation.

Our long-term objective is to evaluate whether a screening prostate MRI could be an alternative or complementary image-based screening test to PSA.

The current study has not been designed to establish the sensitivity and specificity of MRI as this has would require all participants to undergo a prostate biopsy as the reference standard for determining the presence of prostate cancer. It would not be appropriate in a screening study to require all participants to have a biopsy particularly when the diagnostic performance of prostate MRI has been well established in secondary care with prostate biopsy as the reference standard.

Instead, the primary objective will be to establish the prevalence of screen-positive prostate MRI in the general male population aged 50-69 years and collect information on the feasibility of a larger scale study. The results of this study will inform the design of a large diagnostic paired cohort validating study comparing PSA and MRI and other potential imaging or fluidic biomarkers. The subsequent study requires a large sample size and resource commitment due to the low prevalence of prostate cancer in a screened population. In this study, we will obtain point estimates on the prevalence of a suspicious test that triggers a biopsy; such information is currently not available and is required to inform the design and sample size calculations of the larger clinical study. This study will also evaluate the feasibility of a large screening MRI trial. We will optimise recruitment strategies and identify potential barriers to recruitment.

2. OBJECTIVES AND ENDPOINTS

2.1 **Primary Objective**

To determine the positive test rate of prostate MRI in the general male population aged 50 to 69 years

2.2 **Other test performance objectives (MRI and US)**

1. To determine the prevalence of positive test rate of prostate ultrasound in the general male population aged 50 to 69 years

2. To determine the distribution of MRI and US scores in a screened population

3. To evaluate a suitable threshold score that defines positivity of MRI or US in a screening population

4. To estimate the overall agreement between PSA, US and MRI in the proportion of men with a positive result. Then to compare the overall agreement in proportion of men diagnosed with clinically significant prostate cancer on biopsy.

5. To explore combinations and sequences of prostate MRI, US and PSA that might be an optimal screening strategy to evaluate in a future definitive study

6. To estimate the overall agreement of Imaging findings, PSA and DRE

7. To report the clinical outcomes of men with a positive PSA, US and/or MRI result

2.3 Fluidic Biomarker objectives

1. To determine the positive test rate and the distribution of biomarker panel scores in the general male population aged 50 to 69 years
2. To collect and store serum and urine samples in a biobank to evaluate new serum biomarkers

2.4 Feasibility Objectives

1. To evaluate the feasibility of undertaking a screening cohort study comparing the diagnostic performance of prostate MRI and/or US and/or serum prostate specific antigen (PSA) testing

2. To determine the recruitment rates to the study across different ethnic groups

3. To determine the eligibility rates across each screening test

4. To determine the compliance/retention of participants with study processes

5. To assess the acceptability of study processes and informational content.

6. To estimate the costs of undertaking a subsequent diagnostic paired cohort validating study

2.5 Reporting and CAD/AI Objectives

1. To evaluate the diagnostic performance of a CAD/AI algorithm as a standalone reader

2. To evaluate the effect of CAD/AI as a second reader on diagnostic performance of radiologists

3. To evaluate the effect of CAD/AI on interobserver variability of radiological interpretation of prostate MRI

4. To define a suitable threshold MAI score to detect clinically significant cancer

2.6 Other Objectives

1. To determine the health-related quality of life outcomes

2. To assess risk perception and prostate cancer worry and anxiety of prostate cancer during the study

3. To establish the prevalence of post-biopsy adverse events

4. To collect the long-term health outcomes of those men who consent to longitudinal follow-up

5. To build a databank of ultrasound and MRI meta-files matched with histopathology for future research and education

2.7 Primary Endpoint

The proportion of men with a screen-positive MRI defined by a score of 3 or greater.

2.8 Performance objectives (MRI and US)

1. The proportion of men with screen-positive prostate ultrasound defined by a score of 3 or greater

2. The proportion of participants within each MRI score or US score of 1, 2, 3, 4 or 5

3. An evaluation of proportion of participants across each MRI and US score with no cancer, insignificant cancer and significant cancer with each test.

4. A comparison of the proportion of participants with a positive result for each screening test. A comparison of the proportion of men subsequently diagnosed with a clinically significant prostate cancer as defined by pre-specified histological definitions

5. Comparison of different testing combinations in terms of biopsy rates, detection of insignificant cancer and significant cancers

6. The correlation between imaging findings and DRE

7. The proportion of men who go onto definitive local or systemic treatment. In men who undergo radical prostatectomy the proportion who are upgraded at final histology

2.9 Fluidic Biomarker objectives

1. The proportion of participants within a positive Episwitch biomarker panel and distribution of score
2. To establish a biobank of fluidic samples matched with histopathology for future research

2.10 Feasibility

1. Feasibility will be measured based on a point-estimate of recruitment rates across different recruitment strategies. Recruitment rates will be defined as the number of individuals who:
   i. Contact the study team with an expression of interest in participation
   ii. Attend the screening clinic
   iii. Offer informed consent and are enrolled into the study

These results will enable a prediction of number of General Practitioner (GP) practices and length of time needed to recruit the required number of patients for a future trial.

2. The proportion of men from different ethnic groups accepting the initial invitation to participate and subsequently participating within the study

3. Eligibility will be assessed against pre-defined eligibility criteria. The reasons for ineligibility will be recorded and compared across each screening test

4. The retention/compliance rate will be defined as the number of participants completing screening tests and any follow-up biopsy recommendation. The reasons for withdrawal will be documented with an optional survey offered to individuals.

5. The individual costs for recruitment and screening will be recorded in a resource utilisation log. These will be scaled up to provide an estimate of the cost for the subsequent study

2.11 MRI Reporting and CAD/AI Objectives

1. Sensitivity analysis of the CAD/AI system with histology and/or radiologist consensus as the reference standard
2. Comparison of radiologist diagnostic performance for detection of clinically significant cancer with and without the CAD/AI
3. The Intraobserver agreement with and without the use of CAD/AI as second reader
4. Receiver operating characteristic (ROC) to compare the diagnostic performance of CAD/AI at different MAI scores

2.12 Other

1. Changes in HRQOL measured by SF-12 and at baseline and follow-up
2. Changes in worry and anxiety scores measures by CWS and STAI.
3. Rates of biopsy related adverse events (infectious complications, urinary retention, and haematuria requiring admission)
4. Linkage to national database
5. An open access secure and quality controlled databank of ultrasound and MRI meta-files matched with histopathology for future research and education

2.13 Definition of clinically significant cancer

Clinically significant cancer will be defined across a range of histological thresholds including

i. Any length of Gleason >/=3+4
ii. Any length of Gleason >/=4+3
iii. UCL/Ahmed definition 1 (Gleason >/=4+3 and/or Maximum cancer core length >/=6mm).
iv. UCL/Ahmed definition 2: Gleason >/=3+4 and/or Maximum cancer core length >/=4mm
v. Gleason >/=3+4 and/or Maximum cancer core length (MCCL) >/=6mm

2.14 Specification of efficacy parameters

OBJECTIVES		EFFICACY PARAMETER	TIME POINT & TOOL
Primary Objectives			
To determine the prevalence of screen-positive prostate MRI scans in the general male population aged 50 to 69 years		The proportion of men with a screening MRI score of 3 or greater	Visit 1 MRI reporting form
Secondary Objectives			
OTHER TEST PERFORMANCE OBJECTIVES (MRI AND US)	To determine the prevalence of positive test rate of US	The proportion of men with a screening US score of 3 or greater	Visit 1: US reporting form
	To establish the distribution of MRI and US scores in a screened population	The proportion of men across each MRI score	Visit 1: MRI & US reporting form
	To establish a threshold score that defines positivity of MRI and US in a screened population	Comparison of false positives & false negatives across each MRI & US scores	Visit 1 & 2: MRI, US and biopsy reporting form
	The overall agreement between PSA, US and MRI in the proportion of men with a screen positive result.	The proportion with a positive result for each screening test	Visit 1 PSA, US and MRI reporting form
	The overall agreement between PSA, US & MRI in proportion of men diagnosed with clinically significant prostate cancer on biopsy.	The proportion diagnosed with a clinically significant prostate cancer as defined histologically	Visit 1 & 2: PSA, MRI and biopsy reporting form
	To explore combinations & sequences of MRI, US and PSA	Comparison of biopsy rates, detection of insignificant/significant cancer	Visit 1 PSA, MRI, US reporting form
	To estimate overall imaging findings and DRE	Correlation between imaging & DRE	Visit 1 & 2 MRI, US & DRE form
	To report the clinical outcomes of men with any positive test result	The proportion who undergo treatment. If RRP the proportion upgraded at final histology	Visit 1-3: PSA, MRI and biopsy reporting form. Treatment outcomes

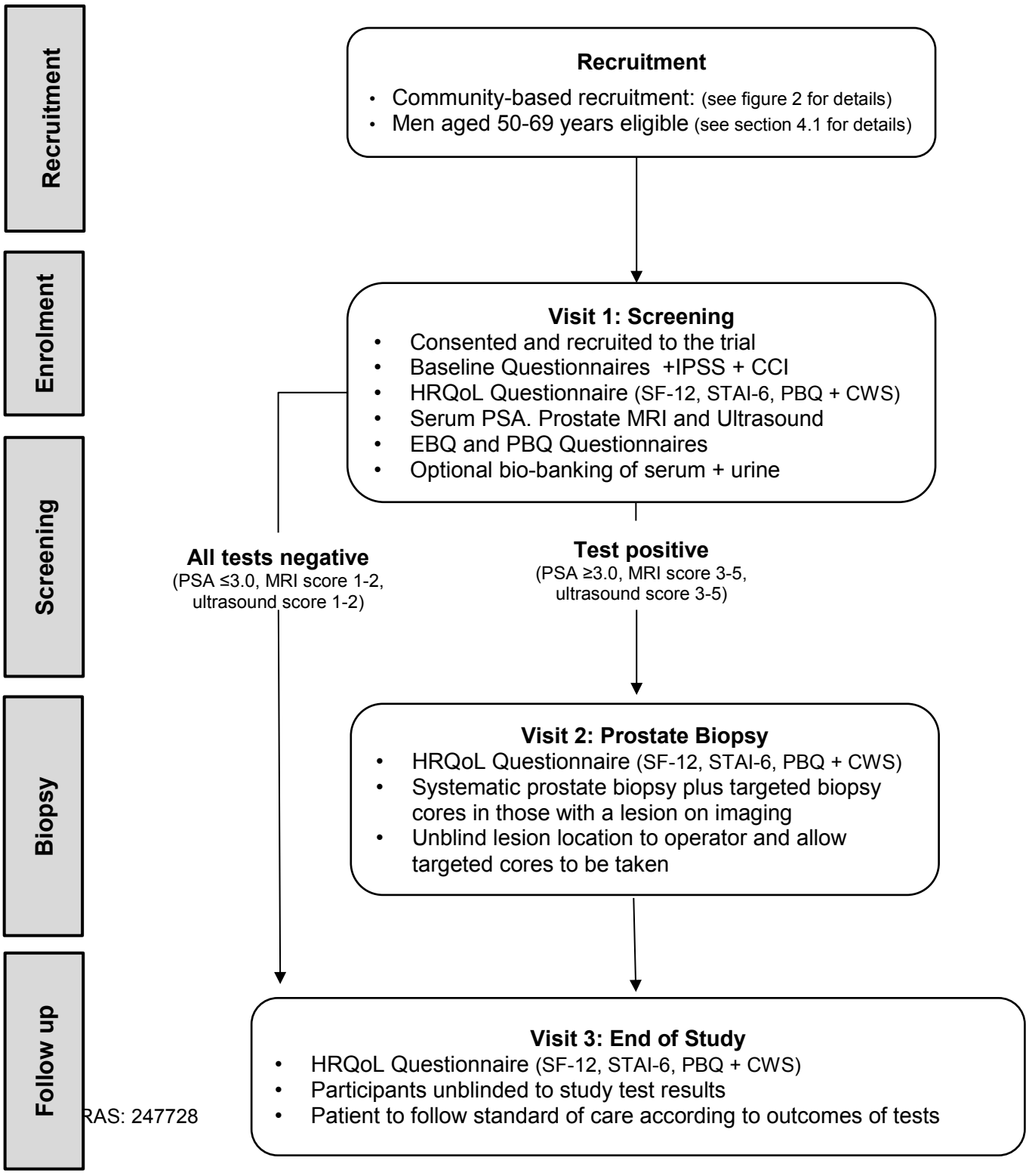
	OBJECTIVES	ENDPOINT	TIME POINT & TOOL
FLUIDIC BIOMARKERS	To establish the positive test rate and distribution of biomarker panel scores	The proportion of men with a positive Episwitch biomarker panel and score	Visit 1: Biomarker panel reporting form
	To establish a biobank of fluidic samples matched with histopathology for future research	Total number of men providing specimens to the tissue biomarker	Visit 1: Biobank entry log
FEASIBILITY	To evaluate the feasibility of a screening cohort study investigating the diagnostic performance of prostate MRI vs. PSA	Descriptive statistics of recruitment rates	Visits 1 & 2: Recruitment log/form
	To determine the recruitment rates across different ethnic groups	Proportion of men from different ethnic groups recruited to study	Visit 1 & 2: Recruitment log/form
	To determine the eligibility rate across each screening test	The number of men with reasons for ineligibility	Visit 1: Recruitment log
	To determine the compliance/ retention of participants with study processes	Number of men completing tests & follow up recommendations	Visits 1-3: Recruitment log/form
	The acceptability of study processes and informational content	Thematic analysis of interviews and free texts	Acceptability Questionnaires
	The costs of undertaking a diagnostic paired cohort validating study	Scaled up costs of recruitment & screening	Resource utilisation log

OBJECTIVES		ENDPOINT	TIME POINT & TOOL
CAD/AI	To evaluate diagnostic performance of a CAD/AI algorithm as a standalone reader to detect clinically significant prostate cancer on MRI	Sensitivity analysis of the CAD/AI system with biopsy or consensus as the reference standard	Visit 1 & 2: MRI, CAD and biopsy reporting form
	To evaluate the effect of CAD/AI as a second reader on diagnostic performance of the radiologist	Comparison of diagnostic performance of radiologists with and without CAD	Visit 1 & 2: MRI, CAD and biopsy reporting form
	To evaluate the effect of CAD/AI on interobserver variability of radiological interpretation of prostate MRI	Interoberver agreement quantified	Visit 1 & 2: MRI, CAD and biopsy reporting form
	To define a suitable threshold MAI score to detect clinically significant cancer	ROC comparing diagnostic performance of CAD/AI at different MAI scores	Visit 1 & 2: CAD output and biopsy reporting time
OTHER	To determine the health-related quality of life outcomes	Change to SF-12 at baseline and follow-up	Visit 1, 2 & 3: Questionnaires at baseline and follow-up
	To evaluate the risk perception and prostate cancer worry and anxiety	Change in risk perception, STAI, CWS at baseline & follow-up	Visit 1, 2 & 3 Questionnaires at baseline and follow up
	To determine the rates of biopsy related adverse events	Rates of biopsy related adverse events	Visit 3: Adverse events reporting form
	To collect the long-term health outcomes	Linkage via national database	Optional follow-up of consented
	To build a databank of ultrasound and MRI meta-files matched with histopathology for future research and education	Upload rate to databank	Visit 1: Databank entry log of mp-USS and mp-MRI meta-matched files

3. STUDY DESIGN

3.1 Design

A prospective cross-sectional screening study with a built-in feasibility assessment of a diagnostic cohort study.
The study design has been developed in accordance with STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (43) and the Consolidated Standards of Reporting Trials (CONSORT) statement (44).



4. PARTICIPANT ENTRY

4.1 Study setting and population

Men aged between 50 and 69 years at average risk of prostate cancer based in the community will be invited to participate

4.2 Inclusion and exclusion criteria

Inclusion criteria

1. Men aged between 50 and 69 years inclusive at the time of study entry
2. Participants must be fit to undergo all procedures listed in the protocol
3. Estimated life expectancy of 10 years or more
4. An understanding of the English language sufficient to understand written and verbal information about the trial and consent process
5. Participants must be willing and able to provide written informed consent

4.3 Exclusion criteria

1. Previous PSA test or prostate MRI within the prior two years of screening/consent visit
2. Evidence of a urinary tract infection or history of acute prostatitis within the last 6 months
3. Previous history of prostate cancer, prostate biopsy or treatment for prostate cancer (interventions for benign prostatic hyperplasia/bladder outflow obstruction is acceptable)
4. Any potential contraindication to MRI, including but not limited to:
    a. Devices or metallic foreign bodies such as pacemakers, implantable defibrillators, neurostimulators, cochlear implants, coronary stents, prosthetic heart valves, aneurysm clips and other intravascular devices
    b. Previous history of hip replacement surgery, metallic hip replacement or extensive pelvic orthopaedic metal
    c. Claustrophobia
5. Any potential contraindication to prostate biopsy
6. Dementia or altered mental status that would prohibit the understanding or rendering of informed consent.
7. Any other medical condition precluding procedures described in the protocol

4.4 Withdrawal criteria

Inability to conduct any one of the imaging tests, blood tests or biopsies according to protocol.

5 PROCEDURES AND MEASUREMENTS

5.1 Identification and recruitment of patients

5.1.1 GP Practice Recruitment

GP practices will be recruited from each individual study region. The initial recruitment will be from practices within the North West London study region in collaboration with the NIHR Clinical Research Network North West London (CRN NWL). The CRN NWL will approach GP practices, and the study team GP practices will continue to be added to ensure the sample size is achieved. Anonymised data will be extracted from all participating practice computer systems related to the demographics of the practice population. This data will be used to describe the general practice population and ensure that recruitment is representative across each practice.

5.1.2 Participant Recruitment

Figure 2 summarises the recruitment flow chart. A number of approaches will be used to inform potential participants about the trial and undertake recruitment:

Postal invitation
For practices using the postal invitation approach, potential participants will be identified from the GP practice registers. The practice database will be searched using pre-defined eligibility criteria including PSA results, history of prostate cancer and the presence of other co-morbidities. This data will be used to assess the patient's suitability to participate, including whether the patient's co-morbidity and/or frailty means that an individual's life expectancy would limit their benefit from screening or other reasons why it may be inappropriate for the patient to receive an invitation.
Participants deemed eligible will be sent an SMS or invitation letter with an enclosed leaflet depending on the GP practice policy. Research shows that the majority of participants make their informed decision on whether to participate in research based on shortened first level information(45). The participation postal recruitment procedures are detailed in a Standard Operating Procedure (SOP Postal Recruitment). Non-responders may be sent up to one reminder and/or telephone call or SMS message via the general practitioner depending on the services available in each surgery. The patient list will be used to provide basic, anonymised information regarding non-responders for comparison with the recruited cohort. This will enable some assessment of how representative the recruited cohort is for each GP Practice.

Opportunistic recruitment:
In practices using opportunistic recruitment, eligible individuals presenting to their GP for a routine consultation will be informed about the study and invited to participate. Potential participants may also be opportunistically approached by their GP during a home visit. The GP will check eligibility criteria and discuss the basic structure of the study. If the individual is interested, they will be offered an invitation letter directly along with the documents listed

above and asked to contact the study team. Posters and flyers may also be put on display at participating GP surgeries

Supplementary Recruitment strategies

We will publicise the study in the local area using posters and flyers. These may be displayed.

1. By Prostate Cancer Charities or organisations/individuals with an interest in prostate cancer. Examples of the organisation could include Prostate Cancer UK, Maggie's support group, Pelican Cancer Foundation, and other relevant organisations.

2. In select local areas frequented by our target group (e.g. community groups libraries, gyms) and in local newspapers

3. On the PROSTAGRAM website and social media pages.

Additional methods of recruitment will be via awareness meetings with community groups as well as media and press events.

Potential participants who contact the research team will discuss the trial in more detail over the telephone. The study co-ordinator will keep a screening and enrolment log of all participants being considered for the trial.
During the telephone discussion, the study team will explain more detail regarding the trial and check that the participants meets the inclusion criteria. If the person is interested in participating in the study the patient information sheet will be posted and/or emailed to them. A screening log will be kept and if a person does not wish to participate in the trial, the reasons for this should be recorded.
All potential participants who are interested in the study will be invited to the screening centre where the trial be re-discussed. Everyone will receive the Participant Information Sheet (PIS) at least 24 hours in advanced as per national standards to allow time to consider whether they want to participate in the study. The PIS will emphasise that if they do not want to participate in the study they are still eligible for a PSA screening test following discussion of the risks and benefits with their GP as part of the opportunistic PSA screening in the UK. The PIS will also contain contact details of the study co-ordinator who can be contacted if the participant has any additional questions about the study. The information pack may also include questionnaires for prior completion.
Individuals who are not eligible for the study will have the reasons for ineligibility recorded within a screening log. Individuals who express their interest in attending the initial screening clinic appointment will receive one reminder letter and a telephone call to confirm that they wish to participate in the trial, and will be able to rearrange the screening appointment, if needed.

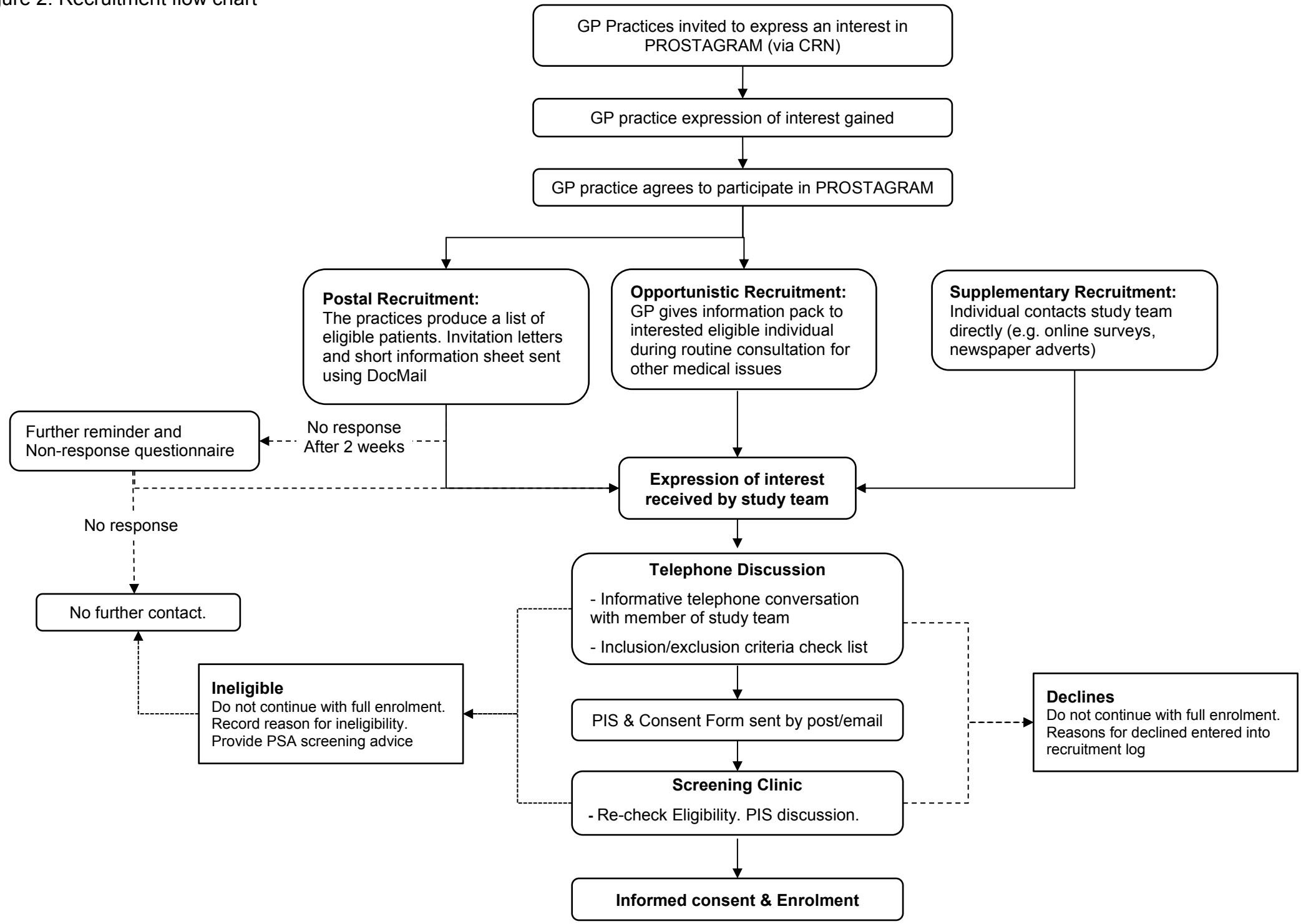
5.2 Screening and Pre-randomisation evaluations

A screening hub will be established. The screening visit and imaging studies will be held on a single day or split across more than one-day dependent on participant preference and availability of clinic and MRI time.

At the clinical screening appointment, the inclusion and exclusion criteria will be verified and eligible patients who wish to proceed will then provide informed written consent and will be enrolled in the study. Written informed consent will be obtained before any further procedures are undertaken and only once the potential participant is satisfied that all their questions have been addressed. A trained member of staff will obtain written informed consent and a unique study number will be assigned to the participant. The original signed consent form will be filed in the investigator's site file and a copy given to the participant.

The baseline visit case report form (CRF) and baseline assessment will be completed and signed by the investigator as outlined in section 6.1. The participant is then deemed as being registered into the study and the GP will be informed.

Figure 2: Recruitment flow chart



5.3 Randomisation and Blinding

5.3.1 Randomisation of Biopsy Lesion

If both the MRI and ultrasound are scored as suspicious by the relevant scoring system, these men will be randomised to have their ultrasound or MRI targeted biopsies first in order to reduce incorporation bias. This can occur as the biopsy tracts from the first lesion may influence the tracts of the second lesion.

Therefore, a pseudo-randomisation will be carried out by a random number generator in advance of the trial starting. Block randomization will be employed to keep the numbers in each group as similar as possible. A block size of 4 has been chosen to reduce the chances that the biopsy order is inadvertently guessed by the operators. Allocation will be held by the Imperial Clinical Trials Unit and the order for lesions to be biopsied passed to the operating surgeon before the procedure begins. No provision for out-of-hours randomization will be required for this study of elective procedures. Occasional audit of the demographic and other characteristics of the groups produced during the study will ensure a balance between the two groups.

5.3.2 Randomisation of screening tests

In order to allow to limit reporter/reviewer bias all screening test will be interpreted by an independent assessor blinded to the results of the other tests. In particular, the MRI and US report will be issued prospectively prior to any prostate biopsy. The pathologist will be blinded to the results of imaging/PSA.

It is not practical to fully blind the biopsy surgeon to the results of the screening tests, as the procedure will vary dependent on whether there is a lesion on the image-screening test. Therefore, the study team will inform the biopsy surgeon whether targeting needs to be incorporated into the biopsy strategy and the location of any areas suspicious on imaging.

This need for biopsy also means that it will not be feasible to fully blind participants to their screening result. However, if participants are informed of all their results this a potential source of attrition bias if participants selectively withdraw from undergoing biopsy based on the results of a single test. Participants may place undue emphasis on the image based screening tests at the expense of the PSA or biomarker test. To reduce the risk of selective withdrawal men who are recommended for biopsy will be informed that one or more of their screening test is positive. However, the specific test indicating a biopsy will not be made available to participants until after the prostate biopsy. Men who have a complete set of negative screening tests will be informed that no biopsy is required.

Men will be unblinded to the screening test results after having a biopsy or on exiting the trial due to negative screening tests. If a participant withdraws from the trial, they will be unblinded to their screening test result. There should be no other reasons for unblinding during the study.

5.4 Visit Schedule

The table below includes the recommended schedule of events.

	RECRUITMENT		FOLLOW UP			
	Invitation	Telephone screening	Screening Visit	Biopsy Visit	Final Visit (primary end point)	Long Term Follow up
Invitation, and flyer	x					
Screen for eligibility		x				
Explain screening procedures		x				
Informed consent			x			
Demographics, medical history, concomitant meds, clinical assessment			x			
Physical examination and DRE			x			
Questionnaires (SF-12, STAI, CWS)			x	x	x	
PSA			x			
MRI			x			
Ultrasound			x			
Acceptability questionnaires			x			
Episwitch and biobank samples (optional)			x			
Prostate Biopsy				x		
Adverse Event assessments and subject compliance			x	x	x	
Resource utilisation data					x	
Long term follow up data (optional)						x

5.5 Study Follow up

Linkage to National databases
The recruitment period will end once 366 (406 with dropouts) participants have been entered into the study, and the last participant has attended the screening clinic. The recruitment period is expected to last 24 months. The follow-up phase of the study will be complete when the last patient has had their final follow-up visit, which should take place approximately one month after any biopsy procedure.
The long-term outcomes of the PROSTAGRAM cohort will be important for evaluating any effect on survival of this group.
The study will include optional consent to allow the use of patient identifiers to link our patients to national databases so that we might derive long-term outcomes in future if further downstream funding is gained to do this. We do not transfer any new data to these existing national databases. This allows the potential to determine the rates of interval prostate cancers. The term interval cancer denotes a cancer diagnosed after a negative screening examination. The rate of interval cancers arising following a screening test is an important performance indicator for a population based screening test.

Collection of partial postcodes
In order to get an area-based estimate of deprivation, the participants' partial postcodes will be converted into an Index of Multiple Deprivation (IMD) score. The IMD is the established index of deprivation for England Wales and has been adopted widely in studies across local and national government. Partial postcodes will not be stored in the InForm Database only IMD rank, which is based on detailed ward-level index of deprivation based on severe separate domains.

5.6 Laboratory Evaluations

5.6.1 Urinalysis

Urinalysis will be performed locally to evaluate for evidence of urinary tract infection.
The urine samples will be stored for 7 days post analysis and then auto disposed in tiger stripe (offensive waste) bag as per the Trust Clinical Waste Management Policy.
The urine samples might be collected and stored for Biobanking and may in future undergo further analysis if new biomarkers are discovered that may be of clinical use in diagnosing prostate cancer (optional consent). Urine samples for biobanking will be stored in -80' C freezers within approved biobank facilities at Imperial College Healthcare Tissue Bank for a period of 10 years.

5.6.2 PSA

Collection of five millilitres of blood via peripheral venepuncture and place in a plastic tube containing SST (serum separating tube). This will be processed in a local laboratory.
The blood samples will be stored for 4 days post analysis and then auto disposed to bio-bins and incinerated off site according to the Trust Clinical Waste Management Policy.
The blood samples might be collected and stored for Biobanking and may in future undergo further analysis if new biomarkers are discovered that may be of clinical use in diagnosing prostate cancer (optional consent). Blood samples for biobanking will be stored in -80' C freezers within approved biobank facilities at Imperial College Healthcare Tissue Bank for a period of 10 years.

5.6.3 Episwitch biomarker panel

Collect six millilitres of blood via peripheral venepuncture using a 22 gauge or larger bore needle and place in a plastic tube containing EDTA (for options see below).
The tube filled with blood is then thoroughly mixed by repeated gentle inversion between 10 to 12 times immediately after collection. The mixed blood should be placed in a –20 to -80^{o}C freezer within 60 minutes of collection and stored at that temperature until shipping. This is an optional test.

The Episwitch biomarker panel will be stored within the biobank facilities. Shipments of samples in groups of 100 to be provided to Oxford Biodynamics (OBD) ISO-certified (9001) Processing Reference Facility in full accordance with OBS HTA license and Quality Management System. Address: Reference Laboratory (UK): First Floor, Building 7600 C2, The Quorum, Oxford Business Park North, Garsington. These samples will be identifiable only by anonymised study ID. The company will not receive any study related data and will not be involved in outcome analysis. The contractual agreement is that they only provide an analysis of anonymised samples for the study.
Samples sent for Episwitch biomarker testing will be destroyed at the end of the study in accordance with the Human Tissue Authority's Code of Practice and Oxford Biodynamics Clinical Waste Management Policy.

6. INTERVENTION *(IF APPLICABLE)*

6.1 Baseline Assessments

After obtaining informed consent and registering the patient in the study the following clinical and baseline assessments will be undertaken:

- A clinical history and review of concomitant medications.
- Specific history related to family history of prostate cancer and urinary symptoms.
- Ethnicity will be recorded.
- Physical examination including digital rectal examination (DRE)
- IPSS, SF-12, CWS and STAI questionnaire

6.2 Laboratory assessments

The participant will undergo venous blood sampling for:

- PSA - collected prior to rectal exam.
- Biobanking of urine/blood
- Episwitch biomarker panel

The specific collection procedures for each these samples are detailed in a Standard Operating Procedure (SOP Serum and Urine Samples).

6.3 BP-MRI and CAD/AI

All men will undergo a screening prostate MRI. It is not necessary for participants to have a renal function performed prior to MRI as the scan is performed without contrast. Specifics of MRI protocol, sequences and reporting employed will be detailed in a Standard Operating Procedure (SOP MRI). An antispasmodic agent such as Hyoscine butylbromide should be administered prior to the scan. If there are contra indication then Glucagon can be administered. The presence of a discrete radiological score 3, 4 or 5 lesion recorded by radiologist or a lesion on CAD/AI leads to a targeted biopsy. All MRIs will be reported by experienced uro-radiologists who are compliant with the standards laid down by the British Society of Uro-Radiology (BSUR).

6.4 Prostate USS

Participants will be offered to undergo an ultrasound prior to MRI. The technique for image acquisition and reporting will be standardised in a Standard Operating Procedure (SOP MP-USS). Participants who have identified prostate lesions on ultrasound scored as 3 or greater by the relevant scoring system will be offered a prostate biopsy.

6.5 Questionnaires

Participants will complete the following validated questionnaires during the study in additional to questionnaires at baseline

1. **SF-12**
   It consists of 36 items to derive eight profiles of functional health and well-being.
   This will be completed at baseline (T0), following receiving test results (T1) and in those with a positive test requiring a biopsy after the biopsy result (T2)

2. **The Spielberger state-trait anxiety inventory(STAI)**
   This has been widely used to evaluate the impact of the screening process on healthy participants. It is designed to assess the changes in transitory anxiety such as might be experienced in a screening programme.
   This will be completed at baseline (T0), following receiving test results (T1) and in those with a positive test requiring a biopsy after the biopsy result (T2)

3. **The Cancer Worry Scale (CWS)**
   The CWS was originally created to assess breast cancer worry and has been adapted for other malignancies including colon and prostate cancer. The revised CWS scale consists of three questions, one question regarding the frequency of cancer worry and two questions regarding the impact of worry about prostate cancer on mood, and daily functioning, respectively.
   This will be completed at baseline (T0), following receiving test results (T1) and in those with a positive test requiring a biopsy after the biopsy result (T2)

4. **Modified Expected burden questionnaire (EBQ) and perceived bur-den questionnaire (PBQ)**
   The EBQ and PBQ evaluate information on the expected embarrassment, pain and burden of a diagnostic test. They have been validated in FOBT and CT colonoscopy screening and modified for this population. The EBQ will be completed prior to each test and the PBQ following each test.

6.6 Prostate biopsy

Men will proceed to biopsy if any screening test is positive. This includes

- PSA: A raised PSA is defined as PSA ≥ 3.0ng/ml as per UK screening guidelines
- MRI: The presence of a discrete radiological score 3, 4 or 5 as scored by a radiologist or lesion on CAD/AI
- Ultrasound: The presence of prostate lesions on ultrasound

If there is a lesion detected on an image based screening test men will have image-fusion guided biopsies for each lesion detected under local anaesthetic or sedation. The targeted

biopsy procedure will follow a Standard Operating Procedure (SOP Prostate Biopsies). Men will have been randomised by means of random number generator result to have either their MRI or ultrasound derived lesions biopsies first in order to overcome incorporation bias affecting the biopsy procedure.

If no lesion is identified, men will have a systematic prostate biopsy as per the local centre standard of care pathway. Prostate biopsy tissues samples will be preserved in formalin as soon as they are taken. All biopsy samples will be transported to Imperial College Healthcare NHS Trust for processing. No additional samples will be taken beyond what is required for a clinical diagnosis as outlined in the biopsy SOP.

The prostate biopsy samples will be stored in Imperial College Healthcare NHS Trust pathology department for a period of 30 years of and destroyed as per the standard operating regulations of the NHS laboratories.

The prostate biopsy samples will be stored in Imperial College Healthcare NHS Trust pathology department for a period of 30 years of and destroyed as per the standard operating regulations of the NHS laboratories.

7. SAFETY REPORTING

7.1 Specification of safety parameters

Safety parameters will include the following:

1. Urinalysis: Testing for both nitrite and leukocyte esterase as indicators of bacteriuria
2. Blood tests for PSA: Values outside the reference range will be flagged and the abnormal values will be presented
3. The frequency and incidence of serious adverse events (SAE) occurring through the course of the study

7.2 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical trial subject. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, whether or not considered related to the trial protocol.

7.3 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. Serious adverse Events (SAE) will be recorded throughout the study.

7.4 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

7.5 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 a study procedure). 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 conducting a study procedure). 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.

7.6 Serious Adverse Events

7.6.1 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.

7.7 Expected Study-Related Adverse Events

The following AEs that could be reasonably expected during the course of the study for each procedure.

Expected Adverse Events Associated with Venepuncture Procedure

- Haematomas and ecchymoses around venepuncture site
- Minor discomfort
- Infection

7.8 Expected Adverse Events Associated with MRI

The following Adverse Events are associated with MRI:

- Claustrophobia
- Anxiety/Stress
- Discomfort

Note: No contrast agent is used in the study prostate MRI protocol

The MRI is a non-contrast scan and equipped with monitoring methods that allow conversation with the participants and identification of any anxiety or discomfort. A detailed history for absolute and relative contraindications for a non-contrast MRI will be taken as set out in MRI SOP.

7.9 Expected Adverse Events Associated with Prostate M-P US

Minimal rectal discomfort during the procedure

An antispasmodic agent such as Hyoscine butylbromide should be administered prior to the scan. If there are contra-indication then glucagon maybe used. These are standard injections used during MRI scans. Side effects include blurred vision, dry mouth, dizziness, increased heart rate, constipation and pain at the injection site.

7.10 Expected Adverse Events Associated with Prostate Biopsy

The expected risks of the biopsy procedure include:

- Blood in the urine (Haematuria) is common for up to 48 hours
- Pain passing urine (Dysuria) is common for up to 24 hours
- Blood in the semen is common (Haematospermia) for up to 3-4 months
- Temporary pain/discomfort in the perineal area
- Temporary problems with erections for up to 6-8 weeks (less than 1 in 20, <4-6 weeks)
- Retention of urine requiring a temporary catheter (1 in 100)
- Prostatitis (inflammation or infection of the prostate (1 in 100)
- Infection requiring admission and intravenous antibiotics (0.5-4%)

The majority of biopsies will be performed under local anaesthetic and/or sedation. A small proportion might be offered a general anaesthetic for technical reasons and patient preference as per local standard practice. The expected risks from undergoing the local anaesthetic and conscious sedation procedure include:

- Nausea and vomiting (1 in 10).
- Minor bruises from intravenous catheters (drips) are common.
- Occasionally extensive bruising, temporary hardening of the vein (phlebitis) or infection can occur from intravenous catheters (1 in 20).
- Dizziness/Vertigo

- Confusion/Disorientation
- Respiratory depression and apnoea (rare)
- Anaphylaxis to Local Anaesthetic (1 in 200 000)

There are expected risks associated with the procedure under general anaesthetic including:

- Nausea and vomiting (1 in 10).
- Most men will have a dry cough for an hour or two and may experience a sore throat for 24 hours. This occurs because a mask and /or tube are placed in the throat during the anaesthetic.
- Minor bruises from intravenous catheters (drips) are common.
- Occasionally extensive bruising, temporary hardening of the vein (phlebitis) or infection can occur from intravenous catheters (1 in 20).
- Death. The known risk of death under anaesthesia in the UK is 1 in 150,000 anaesthetics.

7.11 Reporting of SAEs

Rapid reporting of all SAEs i.e. within 24 hours, 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).

7.12 Related SAEs

Related: resulted from administration of any of the research procedures

7.13 Unexpected SAEs

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

7.14 Reporting of SAEs that are related and unexpected

An SAE form should be completed and faxed to the Chief Investigator within 24 hours. However, relapse, death and/or hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the relevant REC where in the opinion of the Chief Investigator, the event was:

- 'Related', i.e. resulted from the administration of any of the research procedures; and
- 'Unexpected', i.e. an event that is not listed in the protocol as an expected occurrence

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. Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs are as follows:

Joint Research Compliance Office
Imperial College London and Imperial College Healthcare NHS Trust
E-mail: jrco@imperial.ac.uk

Chief Investigator
Professor Hashim Uddin Ahmed
Imperial College London, Charing Cross Campus
E-mail: hashim.ahmed@imperial.ac.uk
Tel: 0 20 7589 5111 (Mon to Fri 09.00 – 17.00)

7.15 Annual reporting of Serious Adverse Events

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

7.16 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. DISCONTINUATION & WITHDRAWAL FROM STUDY

8.1 Study Discontinuation by the sponsor

The Sponsor may terminate the study at any time if the following occur, and the investigator is unable to take corrective action in any of these cases:

- The investigator is non-compliant with the protocol
- The investigator is non-compliant with the regulatory requirements

- The investigator is non-compliant with the principles of Good Clinical Practice as outlined in the Declaration of Helsinki and the Research Governance Framework
- The CRF completion is inadequate

8.2 Study Discontinuation by the Chief Investigator

If an unwanted effect is considered severe by the Chief Investigator and endangers the health of all patients, the study will be discontinued after agreement with the Sponsor.

8.3 Study Discontinuation for an individual patient

The criteria for discontinuing the study in the case on individual patients are:

- Intercurrent illness: Any illness, which in the judgment of the investigators would affect the assessments of clinical status to a significant degree
- Request by the patient: It is the patients right to request discontinuation of their participation in the study. If this request is made, it will be respected and will not affect the patient's ability to receive medical care from the investigators now or in the future.
- Discontinuation of attendance at the investigating site: Efforts should be made to maintain the investigations schedule and continue follow-up, even if patients no longer attend the participating institution.

8.4 Withdrawal from Study

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

- Participant decision
- Inability to conduct any one of the imaging tests, blood tests or biopsies according to protocol.
- Loss to follow-up

8.4.1 Procedures for Withdrawal from Study

Each participant has the right to withdraw from the study at any time. Withdrawal may be complete (i.e. from further study procedures and any follow up), or partial (e.g. from study procedures but allowing the possibility of further follow up). All communication surrounding the withdrawal should be noted in the patient's records, and where withdrawal is complete, no further CRFs should be completed for that patient. Data up to the time of withdrawal can be included in the study if anonymised.

Participants who withdraw will be replaced to maintain the accrual of patients.

All participants who withdraw will remain eligible for follow-up via standard of care prostate cancer screening which is available through informed discussion of the risks and benefits with their GP.

9. STATISTICAL ANALYSES

9.1 Sample Size and power considerations

The study is powered for the primary objective to determine the prevalence of screen-positive MRIs in the general male population aged 50-69 years. We have followed the formula recommended by Naing et al(46) to determine an adequate sample size to estimate the prevalence of screen positive MRIs with a precision of +/- 5%

$$n = \frac{Z^2 P(1-P)}{d^2}$$

Z = Z statistics for a level of confidence
P = expected prevalence or proportion
d = precision.

The sample size calculation requires an estimate of the prevalence of screen-positive MRI (p). There are no previous studies that provide a reliable estimate of this figure in 50-69 years at average risk of prostate cancer. We have estimated this figure based on a number of assumptions, which are listed below. We have split the population into 2 groups depending on PSA level, as there are different levels of evidence for each group.

GROUP 1: PSA raised (PSA ≥ 3.0):

We have assumed this to be 73% based on a combination of studies.

- The PROMIS study has shown that in a group of biopsy-naïve men referred with a suspicion of prostate cancer, the prevalence of positive MRI (Likert ≥ 3) was 72.6%(7).
- The PRECISION study which used PI-RADS v2 and found a prevalence of 71.1% (47) for PIRADS ≥ 3.
- A recent review, which did not include PROMIS and PRECISION, categorising PI-RADS threshold across different groups of men confirmed that 73% of biopsy-naïve men have a positive scan defined as PI-RADS score(48).

GROUP 2: PSA normal (PSA ≤ 3.0):

There is limited data on the number of positive MRIs in this group so we have combined previous research estimating

1. The prevalence of expected significant cancers
2. The performance characteristics of MRI:

1. The prevalence of clinically significant disease in men with normal PSA

In the Prostate Cancer Prevention Trial (PCPT), this estimated that the prevalence of clinically significant disease in a normal PSA population is 2.20% (49, 50). The reference test was a 6-core (sextant) biopsy, which is known to underestimate the presence of cancer

and has been replaced with a 10-12 core approach. However, we do not have any reference to estimate by how much the 6-core biopsy underestimates the clinically significant disease in a normal PSA population. Therefore, we hypothesise that the prevalence of undiagnosed clinically significant disease in this group is 2.20%.

2. The performance characteristics of MRI:
    a. We will assume that the performance characteristics (sensitivity and specificity) of mp-MRI to detect clinically significant disease are the same in a normal and raised PSA population.
    b. These performance characteristics are variable across the literature.
        i. A meta-analysis by Rooij et al 2014(51) reported a sensitivity and specificity of 74% and 88% respectively.
        ii. The recent PROMIS study(7) (not included in Rooij et al) reported a sensitivity and specificity of 93% and 41% respectively.
    c. We have calculated the assumed prevalence of a positive MRI in a normal PSA population using both these performance characteristics using the following 2x2 table.

		Clinically significant prostate cancer		
MRI		Diseased	Non-diseased	Total
	Positive	a	b	**P Normal PSA**
	Negative	c	d	
	Total	2.20%	97.80%	

    d. Based on the performance characteristics in <u>Rooij et al 2014:</u>
        i. Sensitivity: 74%

a/ (a+c) = 0.74
a/0.022 = 0.74
a = 0.0163 c = 0.0057

        ii. Specificity: 88%

d/(b+d) = 0.88
d/0.978 = 0.88
b = 0.1174 d = 0.8606

ROOIJ ET AL 2014		Clinically significant prostate cancer		
MRI		Diseased	Non-diseased	Total
	Positive	1.63%	11.74%	**13.37%**
	Negative	0.57%	86.06%	**86.63%**
	Total	2.20%	97.80%	

Based on the performance characteristics in Ahmed et al 2017:

iii. Sensitivity: 93%

a/(a+c) = 0.93
a/0.022 = 0.93
a = 0.0205 c = 0.0015

iv. Specificity: 41%

d/(b+d) = 0.41
d/0.978 = 0.41
b = 0.5770 d = 0.4010

AHMED ET AL 2017		Clinically significant prostate cancer		
MRI		Diseased	Non-diseased	Total
	Positive	2.05%	57.70%	**59.75%**
	Negative	0.15%	40.10%	**40.25%**
	Total	2.20%	97.80%	

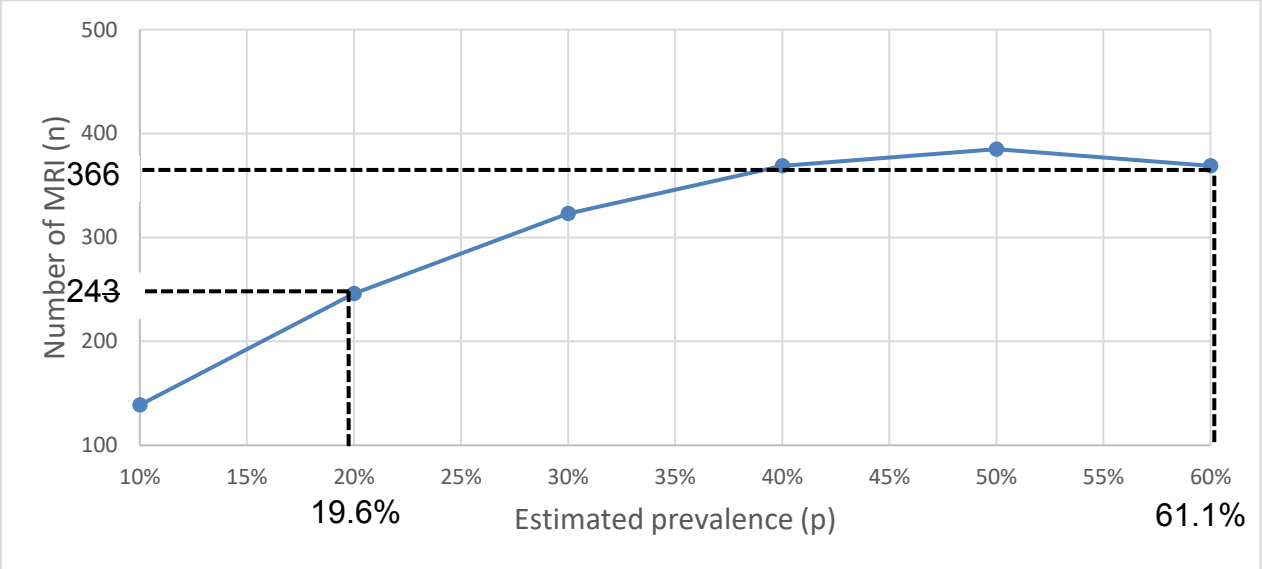
e. Therefore given these performance characteristics the prevalence of a positive MRI in a normal PSA population will be either
   i. 13.37% based on Rooij et al 2014(51)
   ii. 59.75% based on Ahmed et al 2017 (7).

The final part of the calculation is to combine the assumed prevalence of positive MRI in the normal and raised PSA groups to estimate the prevalence of positive MRI in a mixed population. There is high quality evidence for the expected percentage of normal and raised PSA from the Cluster randomised trial of PSA testing for Prostate cancer (CAP)(52), namely:-

- Raised PSA: 10.4%
- Normal PSA: 89.6%.

Therefore, using our estimates above for the prevalence of positive MRIs in a normal PSA population, we expect 11.98% (13.37% of 89.6%) (Rooij et al) and 53.54% (59.75% of 89.6%) (Ahmed et al). The positive prevalence in a raised PSA population is 7.59% (73% of 10.4%).

This produces an assumed prevalence of positive MRI in both groups of 19.6% (Rooij et al) or 61.1% (Ahmed et al). Based on 95% confidence interval (z = 1.96) and precision (d) 0.05, these sample sizes can be represented on the below graph at different prevalence estimates.



Using the formula by Naing et al. (46), assuming a prevalence of 19.6% requires a sample size of 243 participants. While assuming a prevalence of 61.1% will require a sample size of 366 participants. Allowing for a 10% dropout this requires a sample size of 270 and 406 participants respectively.

9.2 Recruitment rates

The estimated postal response rate is 10-20% based on the experience of the CAP study. Given an expected 10% response rate, we will need to post 4,800 letters to reach recruitment targets with postal recruitment alone. It is unknown the recruitment rates for opportunistic and other forms of recruitment. The recruitment rates will be monitored to ensure a stable recruitment rate given MRI and biopsy capacity.

9.3 Data Analysis

A statistical analysis plan will be prepared and finalised prior to database lock.

10. REGULATORY, ETHICAL AND LEGAL ISSUES

10.1 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.

10.2 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).

10.3 Independent Ethics Committee Approval

10.3.1 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.

10.3.2 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.

10.4 Annual Progress Reports

The REC will be sent annual progress reports in accordance with national requirements.

10.5 Annual Progress Reports and End of Trial Notification

The REC will be sent Annual Progress updates in order to facilitate their continuing review of the study (reference. ICH GCP E6 Section 3.1.4) and will be informed about the end of the trial, within the required timelines. The Annual Progress Report will detail all SAEs recorded.

10.6 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.

10.7 Other Required Approvals

None required as no ionising radiation or administration of radioactive substances are required in the protocol.

10.8 Non-Compliance and Serious Breaches

All protocol deviations and protocol violations will be reported via the eCRF/CRF 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.

10.9 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 study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

10.10 Trial Registration

The study will be registered on an International Standard Randomised Controlled Trial Number (ISRCTN) database in accordance with requirements of the International Committee of Medical Journal Editors (ICMJE) regulations.

10.11 Informed Consent

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.

10.12 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 medical notes.

10.13 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained. On the CRF or other documents submitted to the Sponsors, 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 and regulatory authorities.

10.14 Data Protection and Patient Confidentiality

The investigator will preserve the confidentiality of all participants taking part in the study, which will be conducted in accordance with the Data Protection Act.

10.15 End of Trial

The end of trial will be when all participants have completed their final follow-up visit (Visit 3) or at the request of the Trial Steering Committee. The final visit should take place within approximately one month of the biopsy procedure.

During this final visit, the study team will discuss the results of all screening study tests and biopsy results with the patient. Any side effects of the tests experienced by the patient can be discussed. This consultation marks the end of the study for participants.

10.16 Study Documentation and Data Storage

The study 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.

All research documentation and information will undergo a process of pseudonymisation where possible. Whilst within the study, patients will be identified by a unique study number, and the data in the CRF will be linked to this number. Research data will be entered onto a dedicated, secure, encrypted trial database, specifically constructed for the purpose. The study team will maintain the confidentiality of all patient data and will not disclose information by which patients may be identified to any third party other than those directly involved in the treatment of the patient and organisations for which the patient has given explicit consent for data transfer. Data within the NHS system such as patient notes, MRI reports and histopathology reports will remain confidential in accordance with NHS confidentiality code of practice.

Paper enrolment logs, including patients' names, NHS numbers and dates of birth, will be kept in the Investigator Site File, stored in a secure, code-locked store room within the designated Imperial College London facilities. Electronic enrolment logs will be kept on the Trust Computers stored in a locked office space within Imperial College London and Imperial College Healthcare NHS Trust premises. Access to these documents will be highly restricted and only be available to the relevant study team members.

Contact details

Contact details collected using online survey providers, will be encrypted during transit and at rest. All data collected from online surveys will be stored in the UK. Online survey used must remain fully compliant with GDPR legislation and European Privacy Laws. The list of online-responders will be exported to excel file and stored on Trust Computers. The GDPR transparency wording will be utilised to ensure online responders about their data being secured for a 2-year period and destroyed thereafter.

MRI and US files

All MRI will be stored in a secure and password-protected databank (XNAT: https://www.xnat.org/about/) held in Imperial College London Clinical Imaging Facility under university research governance protocols and standard operating procedures. All the US scans will be kept on the Ultrasound Machine used and backed-up onto an external hard-drive on regular basis. The US machine and the external hard-drive will be kept at a code-locked, secure room within Imperial College Clinical Imaging Facility.

The anonymised MRI images will be transferred to a university computer/laptop to allow the AI/CAD reporting. This computer/laptop is encrypted and password protected using high levels of security in accordance with the University protocols. On completion of the study, this data will be transferred to the University servers and the laptop hard-drive wiped.

11. DATA MANAGEMENT

11.1 Source Data

Source documentation is defined as the first time data appear, and may include original document, data and records (hospital records, clinical reports, MRI and Ultrasound reports, other procedure reports, laboratory notes, other data recorded at the pathology and biochemistry laboratories, etc.). Information in source documents (e.g. medical history) dated prior to the Informed Consent Form signature date may be used to verify patient suitability for the study.

Clinical records must be marked to indicate a subject has been enrolled into the clinical study.

The Investigator must ensure the availability of source documents from which the information on the eCRF was obtained. Where printouts and electronic medical records are provided as source documents, they should be signed and dated by a member of the adequately trained research team, to indicate that the data provided is a true reproduction of the original source document.

All study data may be inspected by sponsor and regulatory authorities by people working on behalf of the Sponsor, and by representatives of Regulatory Authorities, where it is relevant to this research.

11.2 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.

11.3 Database

The principal means of data collection from participant visits will be Electronic Data Capture (EDC) via the internet using the InForm database. Data is entered into the EDC system via site personnel. All source data recorded in the CRF will be signed by the Investigator or his/her appropriate designee. All changes made following the electronic signing will have an electronic audit trail with a signature and date. Specific instructions and further details will be outlined in the CRF manual.

11.4 Data Collection

All study data will be entered into electronic Case Report (eCRFs) in a database provided by the Sponsor (InForm). All eCRFs will be completed using de-identified data.
CRF completion may be delegated by the Principal Investigator (documented on the Delegated Task List) to other study personnel u the Principal Investigator remains responsible for the accuracy and integrity of the of all data entered to eCRFs.
Further details of procedures for CRF/eCRF completion, including data review, database cleaning, issuing and resolving data queries, and identification of steps or creation, modification, maintenance and archiving of source data via any computerised systems will be provided in the study specific Data Management Plan (CRF manual).

11.5 Archiving

The investigator must retain essential documents until notified by the Sponsor, and for 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 later. 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.

Storage and handling of confidential trial data and documents will be in accordance with the Data Protection Act 2018 (UK)

Contact details collected using online survey providers will be encrypted during transit and at rest. All data collected from online surveys will be stored in the UK. Online survey used must remain fully compliant with GDPR legislation and European Privacy Laws.

The list of online-responders will be exported to excel file and stored on Trust Computers. Imperial College London will contact online responders about the research study, and make sure that relevant information about the study is recorded with care.

The GDPR transparency wording will be utilised to ensure online responders about their contact details being secured for a 2-year period after study completion and destroyed thereafter.

12. STUDY MANAGEMENT STRUCTURE

12.1 Trial Steering Committee

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 the TSC Charter. A TSC meeting will be held at the start of the trial prior to patient recruitment, and then annually as a minimum.

12.2 Trial Management Group

The study team will meet regularly throughout the study to co-ordinate the project with other collaborators as deemed appropriate. When necessary, decisions will be referred to the TSC. Meetings will be scheduled in a risk-adapted manner to allow for the review of events during the trial.

12.3 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.

12.4 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.

12.5 Quality Control and Quality Assurance

Quality Control will be performed according to ICTU’s 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 NHS Research Governance Framework for Health and Social Care (2nd Edition).

12.6 Peer review

This study has been peer reviewed by the study funders; the Wellcome Trust and the Urology Foundation.

12.7 Publication and Dissemination policy

The results of the PROSTAGRAM trial will be submitted for publication in peer-reviewed scientific journals. Findings will be presented at relevant national and international scientific conferences. The work may also be included in theses and dissertations. Any submissions for publication using data from this study to undertake original analyses must have authorisation from the TSC.

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.

The results will be disseminated to participating GPs and to relevant organisations as their involvement will be critical in the subsequent larger studies. Participants who consent to receive a copy of the findings will receive a lay summary of the findings by post or email after the main report has been published

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.

The results may be published or presented by the investigator(s), but the Sponsor will be given the opportunity to review and comment on any such results for up to 1 month before any presentations or publications are produced. The funders' terms and conditions do not require review of manuscripts or abstracts or posters prior to submission.

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

12.8 Authorship

There are expected to be a number of resulting publications and the authorship will be determined on a per paper basis by the Trial Management Group and Chief Investigator. All publications will acknowledge individual authors in accordance with normal academic practice. Individual authors are likely to include relevant members of the TSC listed individually or in the name of the 'PROSTAGRAM Study Group'.

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SIGNATURE PAGE 1 (CHIEF INVESTIGATOR)

The signature below constitutes approval of this protocol by the signatory 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: PROSTAGRAM

Protocol Number: 18HH4595

Signed:

Professor Hashim Ahmed

Date:

SIGNATURE PAGE 2 (SPONSOR)

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

Study Title: PROSTAGRAM

Protocol Number: 18HH4595

Signed: _____

Becky Ward
Research Governance Manager
Imperial College London

Date:

SIGNATURE PAGE 3 (STATISTICIAN)

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

Study Title: PROSTAGRAM

Protocol Number: 18HH4595

Signed: _____

Francesca Fiorentino
Imperial College Trials Unit & Division of Surgery

Date: _____

Study Title: PROSTAGRAM

Protocol Number: 18HH4595

Signed: _____

Ms Emily Day
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