Statistical Analysis Plan (SAP)

Prostate Cancer Screening Trial using a Group of Radiological Approaches including MRI and ultrasound

IP1 – PROSTAGRAM

18HH4595

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Contents

1. Abbreviations

AE	Adverse Event
AI	Artificial Intelligence
AUROC	Area Under the ROC Curve
bp-MRI	Bi-parametric MRI
CAD	Computer Aided Detection
CAP	Cluster randomised trial of PSA testing for Prostate cancer
CDR	Cancer Detection Rate
CWS	Cancer Worry Scale
CRF	Case Report Forms
CCI	Charlson Co-Morbidity Index
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRN	Clinical Research Network
CWS	Cancer Worry Scale
DCE	Dynamic Contrast-Enhancement
DMEC	Data Monitoring and Ethic Committee
DRE	Digital Rectal Examination
DWI	Diffusion Weighted Imaging
EBQ	Expected Burden Questionnaire
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
GP	General Practitioner
HDP	Hypothetical Diagnostic Pathways
HRQoL	Health-Related Quality of Life
ICTU	Imperial Clinical Trials Unit
IMD	Index of Multiple Deprivation
IP	Imperial Prostate
IPSS	International Prostate Symptom Score
ISRCTN	International Standard Randomised Controlled Trial Number
MAI	Malignancy Attention Index
MCCL	Maximum Cancer Core Length

MCS-12	Mental Health Component Score (SF-12)
mp-MRI	Multi-parametric MRI
MRI	Magnetic Resonance Imaging
NIMP	Non Investigational Medicinal Product
NPV	Negative Predictive Value
PBQ	Perceived Burden Belief Questionnaire
PCPT	Prostate Cancer Prevention Trial
PCQ	Psychological Consequences Questionnaire
PCRMP	Prostate Cancer Risk Management Programme
PCS-12	Physical Health Component Score (SF-12)
PI	Principal Investigator
PIRADS	Prostate Imaging Reporting and Data System
PIS	Participant Information Sheet
PPV	Positive Predictive Value
PSA	Prostate-Specific Antigen
ROC	Receiver Operating Characteristic
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SF-12	12-item Short-Form Health Survey
SMS	Short Message Service
SOP	Standard Operating Procedure
STAI	State-Trait Anxiety Inventory
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TMG	Trial Management Group
TRUS-biopsy	Transrectal Ultrasound-guided biopsy
TSC	Trial Steering Committee
UCL	University College London
UK NSC	United Kingdom National Screening Centre
US	Ultrasound Score

This Statistical Analysis Plan (SAP) is structured in terms of the structure and content of the primary and secondary outcome papers agreed by the investigators on 17/06/2019. The primary and secondary outcome papers are listed below.

- Primary Outcome Paper

Secondary outcome papers:

- Feasibility and Recruitment Outcome Paper
- Fluidic Biomarker Outcome Paper
- MRI Reporting and CAD/AI Outcome Paper
- Health Related Quality of Life Outcome Paper
- Multivariable Analysis for Primary End Point and Correlation between DRE and Imaging Findings Outcome Paper.

The first version of the SAP will cover the analyses for the Primary Outcome Paper only. Amendments to the SAP will cover the subsequent analyses required for the secondary outcome papers.

2. Background and Rationale

We propose that prostate MRI has certain performance characteristics, which make it attractive as a potential screening test for prostate cancer. 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 (1).

The aim of a screening programme would be to detect clinically significant prostate cancer at a curable stage, prior to progression to metastatic disease, and thereby reduce cancer-specific mortality. 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 of the current screening process.

Currently, the UK National Screening Committee (UK NSC) have recommended against a universal screening programme due to the limitations of Prostate-Specific Antigen (PSA), the current first line test to diagnose prostate cancer. The summary report described PSA as “a poor test for prostate cancer and a more specific test is needed” (2). At present, the current guidelines 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 risks 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.

2.1. MRI

Prostate MRI has emerged as the dominant technique for diagnosis and staging of clinically localised prostate cancer. As an image-based screening test, prostate MRI has the potential to significantly reduce the problem of too many prostate biopsies and over-diagnosis of clinically insignificant cancers. Another advantage is that it allows suspicious areas to be visualised and targeted with biopsies, thus improving the detection of clinically significant cancers.

Image-based screening tests have been successfully adopted in other cancer screening programmes. Although MRI is the standard first-line investigation for men referred with a suspicion of prostate cancer, there have been a limited number of studies evaluating its role as a potential screening test.

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. Moreover, there has been growing interest in combining b-mode ultrasound

with additional modalities such as elastography, which is a technique used for cancer detection based on tissue stiffness.

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. There has been widespread interest in novel biomarkers as an alternative or adjunct to PSA screening.

2.4. CAD/AI

An image-based national screening programme requires a larger scanning capacity and produces many scans requiring interpretation by radiologists with the relevant experience and subspecialty training. Consistent results are important when prostate MRI will be performed across diverse centres and interpreted by different clinicians.

Computer-aided detection (CAD) or Artificial Intelligence (AI) systems can potentially be utilised to reduce interobserver variability and improve radiological reporting capacity. The CAD/AI system will act as a supplement to human readers and will mark potential areas of concern so the radiologist can decide if the area warrants further investigation.

CAD/AI application will be embedded in this study to evaluate the feasibility of using a CAD/AI system within the workflow of radiological interpretation.

2.5. Recruitment Strategies

This study will evaluate various recruitment pathways to establish the optimum recruitment strategy and identify potential barriers to recruitment. The recruitment strategies are:

- Letter from GP
- SMS/Text from GP
- Verbal from GP
- Stephen Fry Twitter
- Gamal Turawa Facebook
- Search engine/Other internet source
- Previous participant word of mouth
- PROSTAGRAM Team word of mouth
- Group messaging
- Other word of mouth
- Posters
- Newspaper adverts
- Radio
- Other.

In previous large screening trials there have been low screening uptake among certain ethnic groups, in particular African/African-Caribbean men, who are at double the risk of mortality from prostate cancer (3). Thus, there is need for further screening research in this population and this study aims to achieve a participant recruitment which is representative across ethnic risk groups, particularly African/African-Caribbean men.

2.6. Study Rationale

The UK National Screening Committee has recommended that further research is required into alternative screening tests before a population-based prostate cancer screening programme is considered for approval (1). We propose that prostate MRI has certain performance characteristics, which make it attractive as a potential screening test.

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 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.

3. Study Objectives

3.1. Primary Objective

The primary objective will be to determine the positive test rate of prostate MRI in the general male population aged 50 to 69 years.

3.2. Secondary Objectives

3.2.1. 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.

3.2.2. 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.

3.2.3. 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.

3.2.4. MRI 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.

3.2.5. 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.

4. Study End Points

4.1. Primary End Point

The proportions of men with a screen-positive MRI defined by a score of 3 or greater (Likert and PIRADS).

4.2. Secondary End Points

4.2.1. Other Test Performance End Points (MRI and US)

1. The proportions of men with a screen-positive MRI defined by a score of 4 or greater (Likert and PIRADS)
2. The proportion of men with screen-positive prostate ultrasound defined by a score of 3 or greater (US)
3. The proportion of men with screen-positive prostate ultrasound defined by a score of 4 or greater (US)
4. The proportion of men with raised PSA result defined by a recorded level of 3 ng/mL or greater
5. The proportion of participants within each MRI score or US score of 1, 2, 3, 4 or 5
6. An evaluation of proportion of participants across each MRI and US score with no cancer, insignificant cancer and significant cancer with each test
7. The proportion of participants across each PSA level (raised or normal) with no cancer, insignificant cancer and significant cancer
8. 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
9. Comparison of different testing combinations in terms of biopsy rates, detection of insignificant cancer and significant cancers
10. The correlation between imaging findings and DRE
11. The proportion of men who go onto definitive local or systemic treatment.

4.2.2. Fluidic Biomarker End Points

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.

4.2.3. Feasibility End Points

1. Feasibility will be measured based on a point-estimate of recruitment rates across different recruitment strategies (see Section 2.5). Recruitment rates will be defined as the number of individuals within each of the following recruitment stages:
   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. Assess the acceptability of each diagnostic test measured with EBQ, PBQ and time taken to complete each screening test.
6. 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*.

4.2.4. MRI Reporting and CAD/AI End Points

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 Interobserver 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.

4.2.5. Other End Points

1. Changes in HRQOL measured by SF-12 at baseline and follow-up
2. Changes in worry and anxiety scores measured by CWS, PCQ 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.

*The analyses of these end points will not be covered by the SAP.

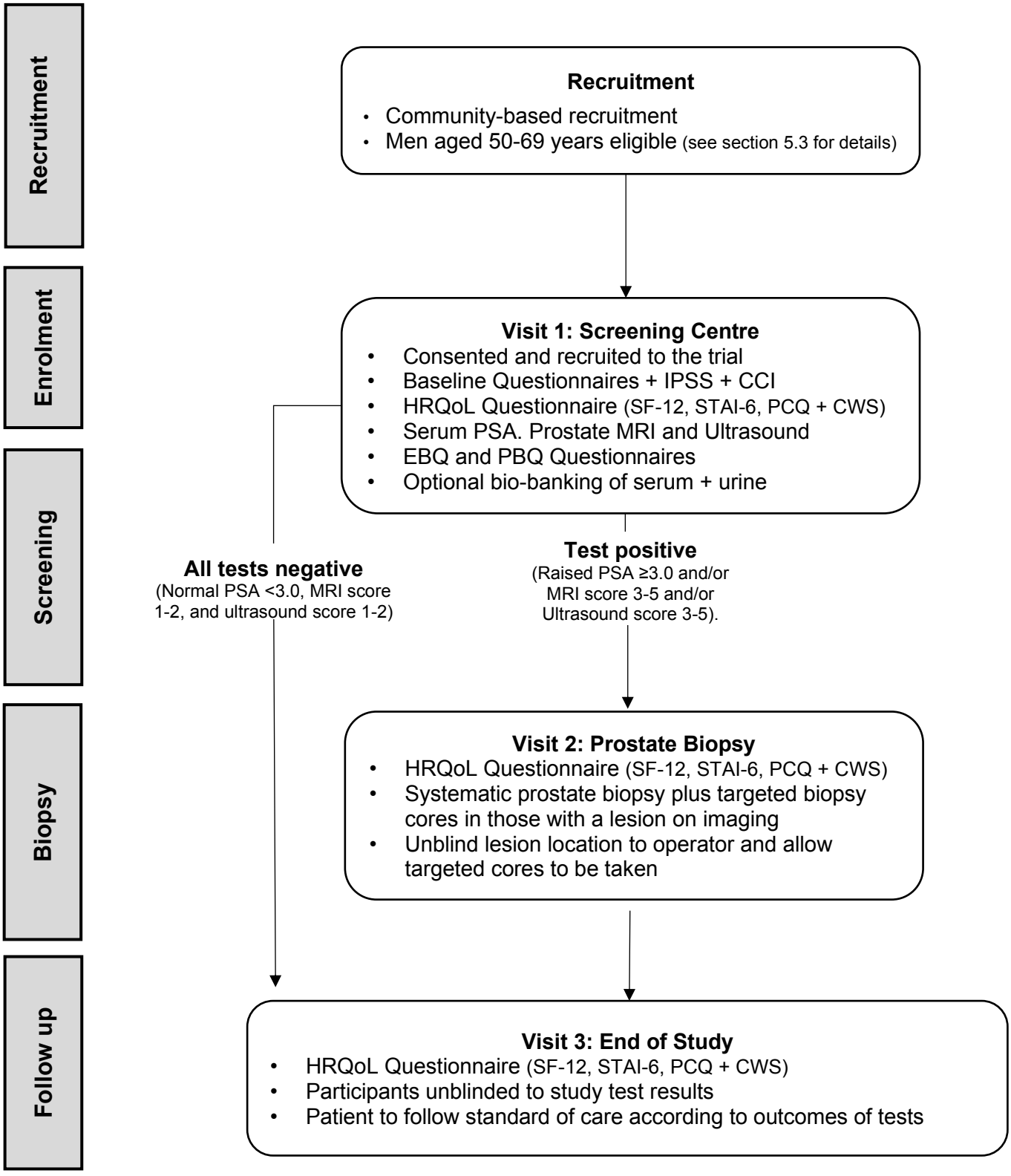
5. General Considerations

5.1. Study Design

A prospective cross-sectional screening study with 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 (4) and the Consolidated Standards of Reporting Trials (CONSORT) statement (5).

5.1.1. Trial Schema



5.2. Study Population

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

5.3. Eligibility Criteria

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.

Individuals who are not eligible for the study will have the reasons for ineligibility recorded within a screening log.

5.3.1. Inclusion Criteria

1. Men aged between 50 and 69 years inclusive at the time of consent
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.

5.3.2. Exclusion Criteria

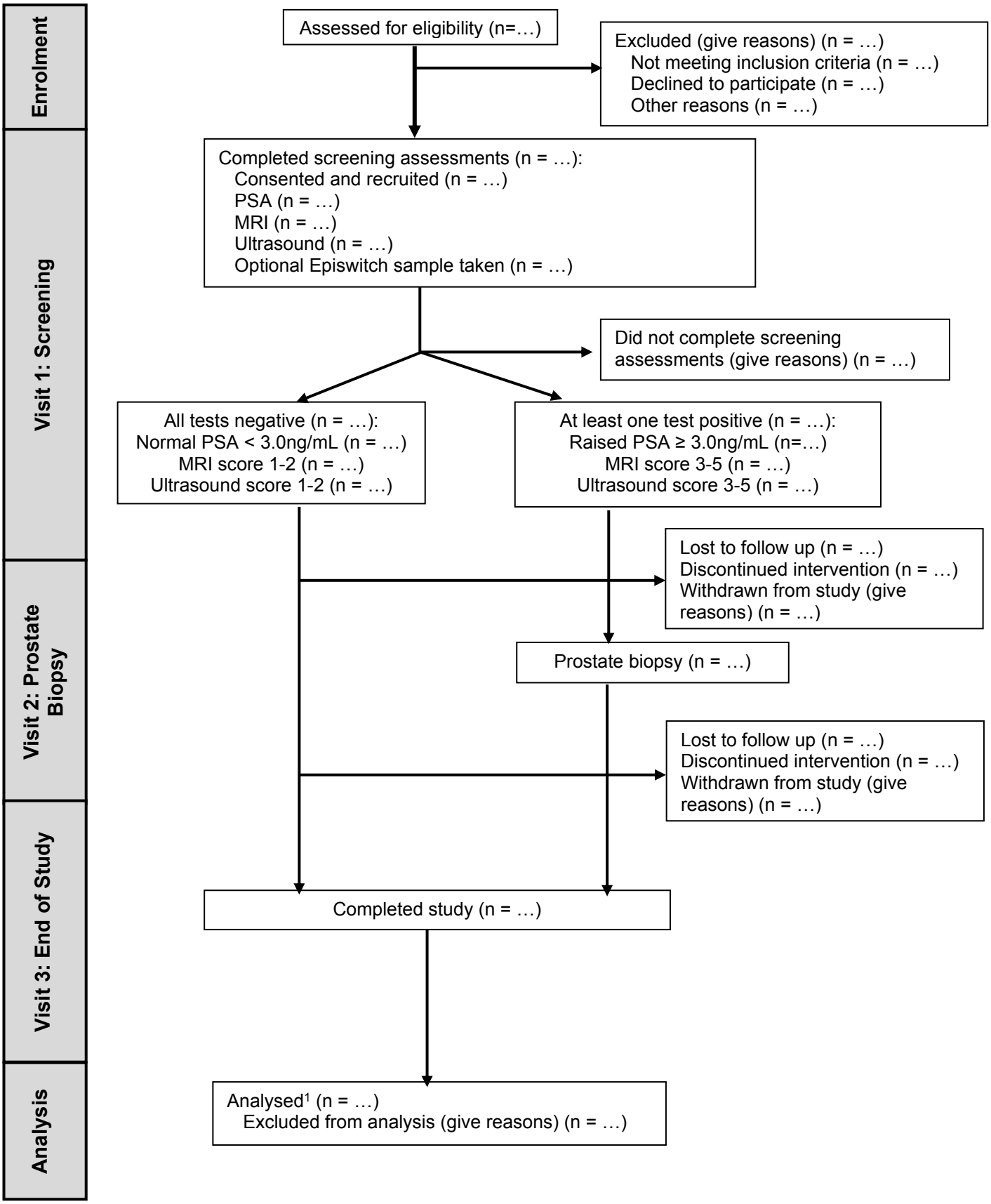
1. Previous PSA test or prostate MRI within the prior two years of screening/consent visit
2. Evidence of a urinary tract infection or history of acute prostatitis within the last 6 months
3. Previous history of prostate cancer, prostate biopsy or treatment for prostate cancer (interventions for benign 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.

5.4. Withdrawal Criteria

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

5.5. Schedule of Time and Events

5.5.1. Patient Flow (CONSORT) Diagram



[1]Providing participants meet the analysis population criteria outlined in Section 9.1 and Table 1 (Section 11.2.1).

5.5.2. Visit Schedule

	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, PCQ)			x	x	x	
PSA			x			
MRI			x			
Ultrasound			x			
Acceptability questionnaires (EBQ, PBQ)			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

This table includes the recommended schedule of events.

6. Sample Size Calculation

Screening tests are targeted at a large population of asymptotic individuals, the majority of whom are healthy and do not have the target disease. 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. The low prevalence of positive findings from screening necessitate a large sample size to evaluate performance characteristics of screening tests.

The null hypothesis is that there is no difference in the proportion of men with a screen-positive MRI between the treatment groups.

We have followed the formula recommended by Naing et al (6) 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.

With reference to the calculations of the prevalence of screen-positive MRI (protocol v1.2), and using the formula by Naing et al. (6) above, 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. The final, agreed, sample size was based on a prevalence of 61.1%, requiring 406 participants when allowing for a 10% dropout rate.

7. Randomisation and Blinding

7.1. 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.

A pseudo-randomisation was carried out by a random number generator in advance of the trial starting. Block randomisation was employed to keep the numbers in each group as similar as possible. A block size of 4 was 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.

7.2. Blinding of Screening Tests

In order to allow to limit reporter/reviewer bias all screening tests 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 is 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.

7.3. Randomisation and Blinding of Double MRI Reporting

To confirm the interobserver agreement of the MRI results assessed internally, 20% of the total MRI scans will be randomly selected to be double reported externally. The random selection will be stratified by PIRADS score: negative (a score of 1 or 2), intermediate (a score of 3), or positive (a score of 4 or 5). This double reporting will be undertaken by an independent radiology professor who will be blinded to the initial reading of the MRI scans.

8. Working Definitions

8.1. Definitions of the Types of Cancer Detected

8.1.1. Definition of Clinically Significant Cancer

There is no universally accepted histological definition of clinically significant prostate cancer. The definition has undergone significant changes over the years and it is expected that this dynamic process will continue. As there is no single agreed definition, clinically significant cancer will be defined across a range of thresholds.

At present, the definition which has general acceptance is (7):

i. Gleason ≥ 3 + 4 (Grade Group (GrG) ≥2).

Other definitions include:

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

8.1.2. Definition of Clinically Insignificant Cancer

The following definitions correspond directly to those in Section 8.1.1.

The definition with general acceptance is:

i. Gleason length of 3 + 3 (GrG 1).

Other definitions include:

ii. Gleason length of 3 + 3, 3 + 4, (GrG 1 + 2)
iii. Those participants who do not meet the criteria in definition (iii) for clinically significant cancer
iv. Those participants who do not meet the criteria in definition (iv) for clinically significant cancer

v. Those participants who do not meet the criteria in definition (v) for clinically significant cancer.

8.1.3. Definition of No Cancer

The definition of no cancer is “there exists no presence of any cores that contain cancer”.

Analyses which are focused on the detection and diagnosis of clinically significant cancer, clinically insignificant cancer or no cancer will be repeated for all stated sets of definitions (i – v) above.

8.2. Definition of a Positive Screening Test

Men will proceed to biopsy if any of the screening tests are positive. This includes:

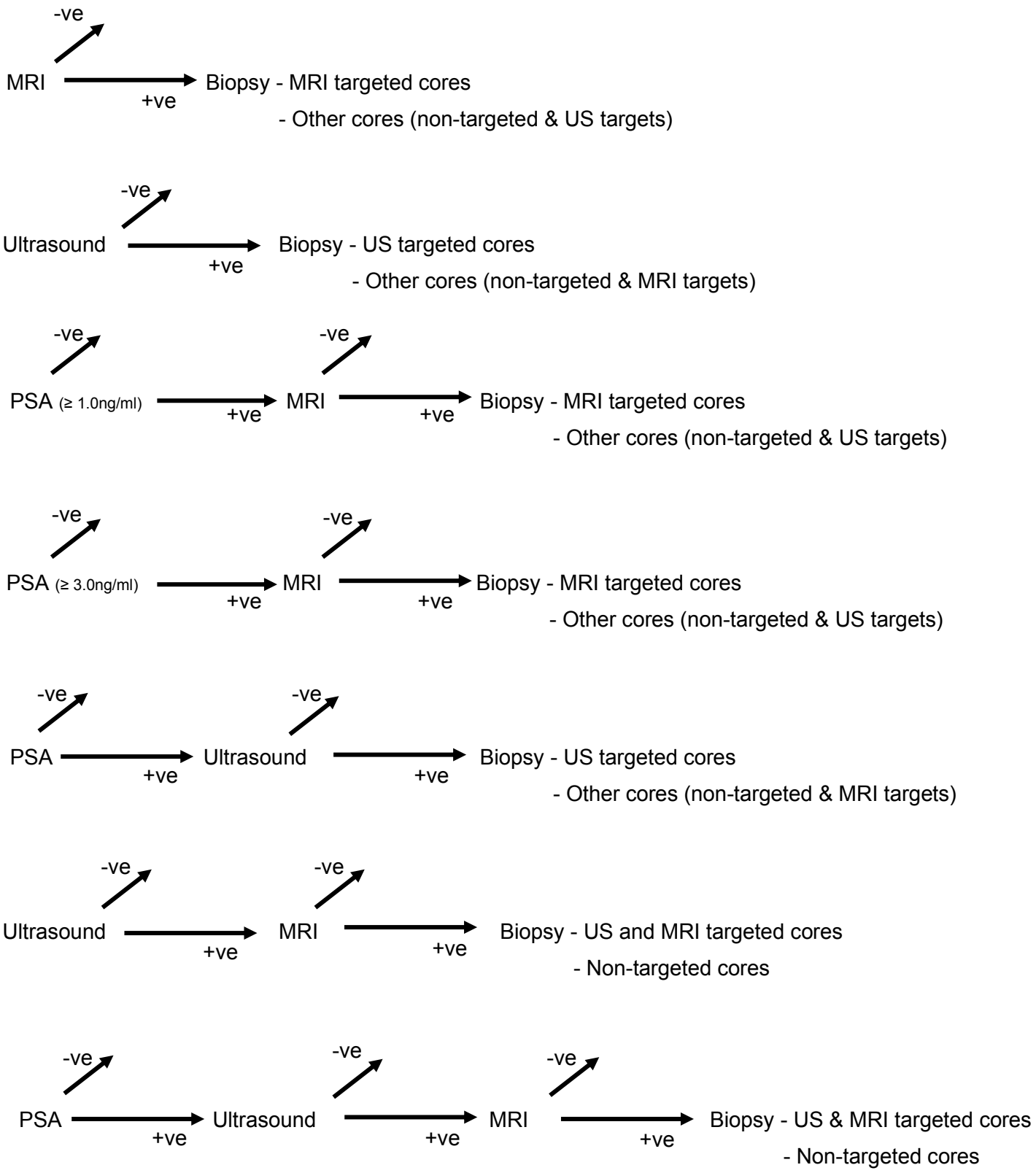
- PSA: A raised PSA is defined as PSA ≥ 3.0ng/ml as per UK screening guidelines.
- MRI: The presence of a discrete radiological score 3, 4 or 5 as scored by a radiologist or lesion on CAD/AI.
- Ultrasound: The presence of a discrete score of 3, 4 or 5 or prostate lesions on ultrasound.

Further threshold definitions for a screen-positive result for MRI and ultrasound will be analysed, as outlined in Sections 10.3.1 and 10.3.2.

8.3. Hypothetical Diagnostic Pathways

The following hypothetical diagnostic pathways (HDPs) correspond to the other test performance (MRI and US) end point “comparison of different testing combinations in terms of biopsy rates, detection of insignificant cancer and significant cancers”. To assess the different testing combinations of PSA, ultrasound and MRI, the HDPs, displayed in Figure 1, map the suggested specifications and order of the screening tests to biopsy.

Figure 1: Hypothetical diagnostic pathways (HDP) mapping suggested orders of screening tests (MRI, ultrasound and PSA) to biopsy



9. Analysis Set

9.1. Evaluable Population for Analysis

Analysis will be carried out for the evaluable population. This is defined as those individuals who meet the eligibility criteria and complete at least one of the screening assessments (MRI, ultrasound or PSA).

10. Variables of Analysis

10.1. Baseline Demographic Variables

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

- Demographics such as: age, Index of Multiple Deprivation (IMD) quintile, BMI, ethnicity, qualification level, marital status, employment status, frequency of GP visits, smoking status and history, how the patient heard about the prostate check and, Digital rectal examination (DRE) results.
- Specific family, medical and prostate history.
- CCI and IPSS questionnaires (see Appendix 1).

10.1.1. Recruitment Categories

The recruitment strategies listed in Section 2.5 will be grouped into 6 categories, as listed below, and then summarised:

- Letter from GP.
- GP Recruitment:
  - SMS/Text from GP
  - Verbal from GP.
- Traditional Recruitment:
  - Newspaper advert
  - Radio
  - Other.
- Social Media Recruitment:
  - Stephen Fry Twitter
  - Search engine/other internet source.
- Targeted Traditional Recruitment:
  - PROSTAGRAM team word of mouth/other word of mouth
  - Poster campaign.
- Targeted Social Media Recruitment:
  - Gamal Turawa Facebook
  - Group messaging (WhatsApp).

10.2. Combined Questionnaire Scores

Overall (combined) and component (question) scores for each patient at each visit, for the following questionnaires, are required as part of the feasibility end point analysis:

- EBQ (for each screening test) (Visit 1)
- PBQ (for each screening test) (Visit 1).

Details of the questionnaires are included in Appendix 1.

10.3. Primary and Secondary End Point Variables

For more detailed information on the variables used in the analysis, please refer to Appendix 2.

10.3.1. MRI Screening

MRI scores are recorded using two independent discrete scoring systems: Likert and PIRADS. Both of these are recorded on discrete scales from 1 to 5, and will be used in the analysis of MRI screening results. For each scoring system, two cut-offs defining a screen-positive MRI result will be evaluated.

Likert:

1. The presence of a discrete Likert score 3, 4 or 5 as scored by a radiologist.
2. The presence of a discrete Likert score 4 or 5 as scored by a radiologist.

PIRADS:

1. The presence of a discrete PIRADS score 3, 4 or 5 as scored by a radiologist.
2. The presence of a discrete PIRADS score 4 or 5 as scored by a radiologist.

Analysis of the primary end point will be repeated using each screen-positive cut-off definition, for both MRI scoring systems. Analyses of all other end points will be repeated for the two cut-offs defined by the PIRADS scoring system only. A biopsy will be carried out if at least one of the scores is screen-positive, even if there is disagreement between the scores.

The radiologist will report whether the MRI result was screen-positive or negative based on the PIRADS and Likert scores for each lesion.

If the question “Are there any lesions with an MRI score ≥ 3?” is recorded as “No”, on the MRI Reporting Form eCRF, then the MRI score (for both the Likert and PIRADS scoring systems) is classified as 1 or 2. This result would be categorised as a screen-negative result when using the first cut-offs for the two scoring systems above.

10.3.2. Ultrasound Screening

Discrete ultrasound scores are recorded using the Ultrasound Score (US) scoring system and range from 1 to 5. Two cut-offs defining a screen-positive ultrasound result will be evaluated.

1. The presence of a discrete score of 3, 4 or 5 or prostate lesions on ultrasound.
2. The presence of a discrete score of 4 or 5 or prostate lesions on ultrasound.

Analysis will be repeated for each screen-positive cut-off.

The operator will report whether the ultrasound result was screen-positive or negative based on the US score for each lesion.

If the question “Are there any lesions scoring US score ≥ 3?” is recorded as “No” on the Ultrasound Reporting Form eCRF, then the US score is classified as 1 or 2. This result would be categorised as screen-negative when using the first cut-off above.

10.3.3. PSA Screening

PSA levels will be recorded as a continuous level (ng/ml). This variable will be dichotomised, using established thresholds (see Section 8.2), into raised (≥ 3.0ng/ml) and normal (< 3.0ng/ml) PSA levels.

10.3.4. Clinically Significant/Insignificant and No Cancer

The thresholds for the type of cancer detected are calculated using the Gleason Score, maximum cancer core length (MCCL), and the definitions outlined in Section 8.1 separately.

10.3.5. Biopsy Rates

Biopsy rates will be the recorded number of patients who undergo the systematic prostate biopsy, and who undergo a targeted biopsy (MRI- and/or ultrasound-guided). The systematic biopsy will be carried out for any patient who attains at least one positive screening test (PSA, ultrasound or MRI). A MRI or ultrasound-guided biopsy will be carried out for patients who receive a positive screening result by the respective test.

10.3.6. Local or Systemic Treatment

Some patients may undergo definitive local or systemic treatment at follow-up. The procedures included are:

- Active surveillance
- Watchful waiting
- Focal treatment
- Radical prostatectomy
- Radical radiotherapy
- ADT.

10.3.7. Biopsy Related Adverse Events

Biopsy related adverse events refer to the recorded occurrences of:

- Infectious complications
- Urinary retention
- Haematuria requiring admission.

10.3.8. False Positive Results

The first definition of a false positive result, with histology as reference, is defined as a screen-positive result when prostate cancer is not present on biopsy. Prostate cancer not present on biopsy would indicate no cancer was found (using the definition in Section 8.1.3).

The second definition of a false positive result, with histology as reference, is defined as a screen-positive result when no prostate cancer or pathology grade of Gleason 3+3 is present on biopsy. Similarly to the above definition, prostate cancer not present on biopsy would indicate no cancer was found (using the definition in Section 8.1.3).

10.3.9. Screening Test Preference (PBQ)

Screening test preference, as measured by PBQ (see Appendix 1), will be dichotomised in four ways, to generate four preference variables:

- Prefer PSA vs any other response
- Prefer MRI vs any other response
- Prefer ultrasound vs any other response
- No preference vs any other response.

10.4. Safety Variables

The frequency and incidence of adverse events (AEs) and serious adverse events (SAEs) occurring through the course of the study will be assessed.

An adverse event (AE) is any untoward medical occurrence in a patient or clinical trial subject. AEs will be recorded as any unfavourable and unintended sign or symptom, whether or not they are considered to be related to the trial protocol.

Serious adverse events (SAEs) will be recorded throughout the study. 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).

Expected adverse events are listed in Appendix 3.

All protocol deviations and violations will be recorded throughout the study, and reported.

11. Statistical Analysis Plan for Primary Outcome Paper

11.1. Primary Outcome Paper End Points

Analyses of the following end points will be reported in the primary outcome paper.

11.1.1. Baseline Demographics

Patient characteristics will be summarised. Summaries of continuous variables will be presented as means and standard deviations if normally distributed, and as medians and inter-quartile ranges for skewed data; categorical variables will be presented as frequencies and percentages.

The CONSORT diagram (Section 5.5.1) will display subject disposition throughout the trial.

11.1.2. Primary End Point

The proportions of men with a screen-positive MRI defined by a score of 3 or greater (Likert and PIRADS).

11.1.3. Other Test Performance (MRI and US) End Points

- The proportions of men with screen-positive MRI defined by a score of 4 or greater (Likert and PIRADS)
- The proportion of men with screen-positive prostate ultrasound defined by a score of 3 or greater (US)
- The proportion of men with screen-positive prostate ultrasound defined by a score of 4 or greater (US)
- The proportion of men with raised PSA result defined by a recorded level of 3 ng/mL 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 for each test
- The proportion of participants across each PSA level (raised or normal) with no cancer, insignificant cancer and significant cancer
- 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 proportion of men who go onto definitive local or systemic treatment.

11.1.4. Feasibility End Point

- Assess the acceptability of each diagnostic test measured with EBQ, PBQ, and time taken to complete each screening test.

11.1.5. Other End Point

- Rates of biopsy related adverse events (infectious complications, urinary retention, and haematuria requiring admission).

11.2. Statistical Methodology

11.2.1. End Point Analysis Summary

All statistical tests will be two-tailed with 5% significance level.

Proportions will be reported as frequencies and percentages, along with the corresponding 95% confidence intervals. Continuous variables will be presented as means and standard deviations if

normally distributed, and as medians and inter-quartile ranges for skewed data; categorical variables will be presented as frequencies and percentages.

The primary end point analysis will be repeated for all cut-offs defining screen-positive MRI and ultrasound, as described in Sections 10.3.1 and 10.3.2.

Only the cut-offs for screen-positive MRI defined by PIRADS (see Section 10.3.1) will be used in the analyses of the other test performance (MRI and US) end points. These analyses will not be repeated for the cut-offs defined by the Likert scoring system.

Analysis of type of clinical cancer detected by the screening tests will be repeated for all definitions of the type of clinical cancer detected as outlined in Section 8.1, with the exception of the HDP analyses which will only be carried out for definitions (i) in Sections 8.1.1 & 8.1.2.

Table 1: Primary Outcome Paper End Point Analysis

	End Point	Analysis	Population
Primary End Point			
	Proportions of men with a screen-positive MRI defined by a score of 3 or greater (PIRADS and Likert)	Proportion with positive MRI score defined by a cut-off ≥ 3 (PIRADS cut-off [1] and Likert cut-off [1] in Section 10.3.1)	Participants with MRI results[1]
Other Test Performance (MRI and US)			
	Proportions of men with a screen-positive MRI defined by a score of 4 or greater (PIRADS and Likert)	Proportion with positive MRI score defined by a cut-off ≥ 4 (PIRADS cut-off [2] and Likert cut-off [2] in Section 10.3.1)	Participants with MRI results[1]
	Proportion of men with a screen-positive prostate ultrasound defined by a score of 3 or greater (US)	Proportion with positive ultrasound score defined by a cut-off ≥ 3 (US cut-off [1] in Section 10.3.2)	Participants with ultrasound results[1]
	Proportion of men with a screen-positive prostate ultrasound defined by a score of 4 or greater (US)	Proportion with positive ultrasound score defined by a cut-off ≥ 4 (US cut-off [2] in Section 10.3.2)	Participants with ultrasound results[1]
	Proportion of men with raised PSA level (defined as PSA ≥ 3.0ng/mL)	Proportion with raised PSA level (Section 10.3.3)	Participants with PSA results[1]
	Proportion of participants within each MRI score or US score of 1, 2, 3, 4 or 5	• Proportion within each value of Likert score • Proportion within each value of PIRADS score • Proportion within each value of US score • Histograms of distribution of each score (Likert, PIRADS and US) (Sections 10.3.1 & 10.3.2)	Participants who completed the relevant test for the respective analyses[1]
	Proportion of participants across each MRI and US score with no cancer, insignificant cancer and significant cancer for each test	• Proportion within each value of Likert score detected to have each type of clinical cancer (Sections 8.1 & 10.3.1) • Proportion within each value of PIRADS detected to have each type of clinical cancer (Sections 8.1 & 10.3.1)	Participants biopsied, and who completed the relevant test for the

		• Proportion within each value of US score detected to have each type of clinical cancer (Sections 8.1 & 10.3.2) • Histograms of distribution of type of cancer detected across scoring systems	respective analyses[1]
	Proportion of participants with raised and normal PSA level with no cancer, insignificant cancer and significant cancer	Proportion with raised and normal PSA result detected to have each type of clinical cancer (Sections 8.1 & 10.3.3)	Participants biopsied, and who have PSA results[1]
	Comparison of the proportion of participants with a positive result for each screening test	Comparisons of proportions of results (positive/negative) between pairs of screening tests: • MRI & ultrasound • MRI & PSA • Ultrasound & PSA using McNemar chi square tests	Participants who completed both tests in each pair[1]
	Comparison of the proportion of men subsequently diagnosed with a clinically significant prostate cancer (as defined by pre-specified histological definitions)	• Sensitivity and specificity of screening results (MRI, ultrasound and PSA) with histology results as reference standard (Sections 10.3.1, 10.3.2 and 10.3.3) • Graph displaying proportions of results for each screening test compared to histology results • Proportions of false positive results by each screening test (MRI, ultrasound and PSA), using histology (no cancer) as the reference • Proportions of false positive results by each screening test (MRI, ultrasound and PSA), using histology (no cancer or Gleason 3+3) as the reference	Participants biopsied, and who completed the relevant test for the respective analysis[1]
	Comparison of different testing combinations in terms of biopsy rates, detection of clinically insignificant cancer and significant cancers	• Hypothetical diagnostic pathways (HDP) of the different testing combinations being analysed (Section 8.3): • MRI • Ultrasound • PSA (≥ 1.0ng/ml) & MRI • PSA (≥ 3.0ng/ml) & MRI • PSA & ultrasound • Ultrasound & MRI • PSA & ultrasound & MRI • For each HDP, summary statistics for the population of patients with all positive tests, in terms of: • Total number biopsied (Section 10.3.5) • Total number detected to have clinically insignificant cancer	Participants biopsied, and who completed the relevant test for the respective analysis[1]

		(Section 8.1.2), in targeted and non-targeted cores • Total number detected to have clinically significant cancer (Section 8.1.1), in targeted and non-targeted cores	
	Proportion of men who go onto definitive local or systemic treatment.	Proportion who undergo each treatment: • Active surveillance • Watchful waiting • Focal treatment • Radical prostatectomy • Radical radiotherapy • ADT	Participants with positive screening results, by each screening test[1]
Feasibility			
	Assess the acceptability of each diagnostic test measured with EBQ, PBQ and time taken to complete each screening test	• EBQ and PBQ Questionnaires (see Appendix 1 for details): • Summary statistics for overall scores for EBQ and PBQ, for each screening test • Paired t-tests comparing mean overall scores between pairs of screening tests (MRI & PSA, MRI & ultrasound, ultrasound & PSA), for EBQ and PBQ separately • Paired t-tests comparing mean difference between pre- and post-screening test scores, for each screening test • Proportions within each value of the Likert score, for each EBQ component, for each screening test (Appendix 1) • Mean score for each EBQ component, for each screening test • Paired t-tests comparing mean component scores between pairs of screening tests (MRI & PSA, MRI & ultrasound, ultrasound & PSA) • Proportions within each value of the Likert score, for each PBQ component, for each screening test (Appendix 1) • Mean score for each PBQ component, for each screening test • Paired t-tests comparing mean component scores between pairs of screening tests (MRI & PSA, MRI & ultrasound, ultrasound & PSA)	Participants who completed the relevant test for the respective analyses[1] For the paired tests, participants who completed both tests in each pair

		• Bar charts displaying the proportions of participants who selected each Likert score, compared between screening tests, for each EBQ & PBQ component • Paired t-tests comparing mean difference between pre- (EBQ) and post- (PBQ) screening test component scores, for each screening test • Proportion of preference for each test as measured by EBQ (expected preference) and PBQ (final preference) • Multivariable logistic regression on dichotomised test preference, for each screening test, controlling for patient related factors • Summary statistics for the time taken for each test to be completed • Proportion who undergo repeat screening assessments (MRI, ultrasound & PSA) • Summary statistics of incidental findings	
Other			
	Rates of biopsy related adverse events (infectious complications, urinary retention, and haematuria requiring admission)	Table of biopsy related adverse events (Section 10.3.7)	Participants who were biopsied[1]
Subgroup Analysis			
	Proportion of men with a screen-positive MRI defined by a score of 3 or greater (PIRADS)	• Logistic regression model for MRI result (defined using PIRADS cut-off [1], see Section 10.3.1) on age • Ordinal logistic regression model for PIRADS score on age • Boxplots displaying the distribution of age across PIRADS scores	Participants with MRI results[1]
	Proportion of men with a screen-positive MRI defined by a score of 4 or greater (PIRADS)	Logistic regression model for MRI result (defined using PIRADS cut-off [2], see Section 10.3.1) on age	Participants with MRI results[1]
	Proportion of men with a screen-positive prostate ultrasound defined by a score of 3 or greater (US)	• Logistic regression model for ultrasound result (defined by US cut-off [1], see Section 10.3.2) on age • Ordinal logistic regression model for US score on age • Boxplots displaying the distribution of age across US scores	Participants with ultrasound results[1]
	Proportion of men with a screen-positive prostate ultrasound defined by a score of 4 or greater (US)	Logistic regression model for ultrasound result (defined by US cut-off [2], see Section 10.3.2) on age	Participants with ultrasound results[1]
Interobserver Agreement for MRI			

	Interobserver agreement for double reported MRI scans	• Agreement of PIRADS scores for MRI scans between local and central readers • Cohen's Kappa statistic	Participants whose MRI results were double reported[1] Double reported MRI scans

[1]This population will satisfy the definition in Section 9.1

The use of parametric methods of analysis require stronger distributional assumptions. These can be evaluated for robustness using non-parametric methods. Firstly, an appropriate transformation will be considered if the assumption of normality is not met. This may involve a log transformation which provides transparent interpretation of effects in relative terms. Then, non-parametric methods will be considered and implemented if after an appropriate transformation the assumption of normality is still not met.

11.2.2. Primary End Point Analysis

The primary end point is the proportion (frequency and percentage) of men with a screen-positive MRI defined by a score of 3 or greater. The proportion of men with a positive radiological score will be reported along with the corresponding 95% confidence intervals. This analysis will be repeated for PIRADS cut-off [1] and Likert cut-off [1], as defined in Section 10.3.1.

11.2.3. Other Test Performance (MRI and US) End Point Analysis

The proportion of men with a screen-positive MRI defined by a score of 4 or greater will be reported. This analysis will be repeated for PIRADS cut-off [2] and Likert cut-off [2], as defined in Section 10.3.1.

The proportion of men with a screen-positive prostate ultrasound score (US), using the two US cut-offs for a screen-positive result defined in Section 10.3.2, will be reported. Similarly, the proportion of patients with a raised PSA level, using the definition in Section 10.3.3, will be reported.

The proportions of patients within each discrete score of the Likert, PIRADS and US scoring systems (see Sections 10.3.1 & 10.3.2) will be reported. The distribution of patients across the discrete scores will be displayed using a histogram for each scoring system.

The proportions of patients across the discrete values of the scoring systems for MRI and ultrasound detected to have clinically significant cancer, clinically insignificant cancer or no cancer, by each screening test (repeated for each of the thresholds defined in Section 8.1 separately) will be reported. The distribution of the type of cancer detected by each test, using each definition ((i)-(v), Section 8.1), will be displayed using histograms for each scoring system. Similarly, the proportions of patients with raised and normal PSA (see Section 10.3.3) detected to have clinically significant cancer, clinically insignificant cancer or no cancer (repeated for each of the thresholds defined in Section 8.1 separately) will be reported.

Comparisons of proportions of screening results (positive/negative), between pairs of screening tests, (MRI & ultrasound, MRI & PSA, ultrasound & PSA) will be conducted using McNemar chi square tests. McNemar chi square tests will be used to assess whether there is marginal homogeneity of results between pairs of screening tests. The McNemar chi square test statistic and p-value will be reported for each pair of screening results. This analysis will use the screen-positive MRI cut-offs defined by the PIRADS scoring system (see Section 10.3.1), and the screen-positive ultrasound cut-offs defined by the US scoring system (see Section 10.3.2).

Sensitivity and specificity analysis will be conducted between screening test results and histology results (reference standard). Histology results will be dichotomised into "clinically significant cancer" and "absence of clinically significant cancer" (repeated for each of the threshold definitions in Section 8.1). The following measures of test accuracy will be reported, along with

their 95% confidence intervals: negative predictive value (NPV), positive predictive value (PPV), sensitivity and specificity. Results will be displayed using graphs for each screening test.

The proportions of false positive results will be reported, with histology as reference. This analysis will be repeated for each of the definitions of false positive results outlined in Section 10.3.8.

For each HDP (see Section 8.3) the proportion of participants with all positive tests, along that pathway, will be reported. For each HDP, we will take the population of participants with all positive tests along each pathway and provide summary statistics. Screen-positive results for MRI are defined by PIRADS cut-off [2] in Section 10.3.1. Similarly, screen-positive results for ultrasound are defined by US cut-off [2] in Section 10.3.2. A “positive” PSA result is defined by a raised PSA level (≥ 3.0ng/ml) (see Section 10.3.3). The summary statistics will be in terms of: the total number of patients who were biopsied (see Section 10.3.5), the total number of patients who were detected to have clinically insignificant cancer in targeted and non-targeted cores, separately, and, the total number of patients who were detected to have clinically significant cancer in targeted and non-targeted cores, separately. This analysis will be limited to the generally accepted definitions for the detection of clinically significant and insignificant cancers (definitions (i) in Sections 8.1.1 & 8.1.2) (7), only.

The proportions of patients, with positive test results by each screening test, who go onto local or systemic treatment for prostate cancer (see Section 10.3.6) will be reported. Positive screening test results will be defined using the PSA cut-off in Section 10.3.3, and both PIRADS and US cut-offs in Sections 10.3.1 & 10.3.2.

11.2.4. Feasibility End Point Analysis

Summary statistics will be presented for the overall (combined) EBQ and PBQ scores for each screening test. The overall scores will be calculated using the method described in Appendix 1. Paired t-tests will be conducted to compare the mean overall scores between pairs of screening tests (MRI & PSA, MRI & ultrasound, and ultrasound & PSA), for EBQ and PBQ scores separately. Pre-screening test scores are measured using the EBQ, and post-screening test scores are measured using the PBQ. Paired t-tests will also be used to compare the mean difference between pre- and post-screening test scores, for each screening test separately.

Each component of EBQ and PBQ is represented by a single question. EBQ has a total of four components (four questions), and PBQ has a total of five components (five questions) (see Appendix 1 for further details). Both EBQ and PBQ share four common components (embarrassment, pain, burden, anxiety).

Summary statistics will be presented for the separate components for the EBQ. These will be reported as the proportions within each value of the Likert score, for each EBQ component, measured for each screening test (PSA, ultrasound and MRI). The mean scores of each EBQ component, measured for each screening test (PSA, ultrasound and MRI) will also be calculated and reported. Paired t-tests will compare the mean EBQ component scores between pairs of screening tests (MRI & PSA, MRI & ultrasound, and ultrasound & PSA). A similar analysis will be conducted for the PBQ component scores.

Paired t-tests will compare the mean difference between pre- and post-screening test scores, for each common component of EBQ and PBQ (embarrassment, pain, burden and anxiety).

The proportions of preference for each screening test, as measured by EBQ (“Expected preference) and PBQ (“Final preference”) separately, will be reported.

Further analysis will be conducted on screening test preference, as measured by PBQ, after the screening tests. Screening test preference will be dichotomised in four ways, as outlined in Section 10.3.9. A multivariable logistic regression model will be fit to each of these newly generated dichotomous variables, separately, controlling for pre-specified baseline patient factors. If any of the factors have more than 10% missing data then we will not include the factor in the multivariable logistic regression. The number of pre-specified baseline patient factors to be included in the

models is to be determined based on the number of cases in each of the categories of the dichotomised screening test preference variables (see Section 10.3.9) (approximately one variable per 10 cases of the smaller category). The pre-specified factors have been ranked in order of importance for inclusion in the described models. The ranked pre-specified patient factors are:

1. Age: < 60 years vs ≥ 60 years
2. Previous PSA: Yes vs No
3. Previous DRE: Yes vs. No
4. Ethnicity: Black vs. All other ethnicities
5. Any first degree relative (brother/father) with a history of prostate cancer: Yes vs. No
6. IMD quintile
7. Highest level of qualification: University degree vs All other responses
8. Length of relevant procedure, excluding set up time: (Phlebotomy (PSA)/US/MRI) – as measured for the screening test in the dichotomised preference variable
9. IPSS score: Mild vs. Moderate/Severe
10. Charlson Co-morbidity Index: Severe (≥2) vs. Not severe (< 2)
11. BMI: < 30kg/m^2 vs ≥ 30kgm^2
12. EBQ pain of relevant test (PSA/US/MRI): Not at all vs. All other categories – as measured by the EBQ for the screening test in the dichotomised preference variable
13. EBQ anxiety of relevant test (PSA/US/MRI): Not at all vs All other categories – as measured by the EBQ for the screening test in the dichotomised preference variable
14. EBQ embarrassment of relevant test (PSA/US/MRI): Not at all vs All other categories – as measured by the EBQ for the screening test in the dichotomised preference variable
15. EBQ burden of relevant test (PSA/US/MRI): Not at all vs All other categories – as measured by the EBQ for the screening test in the dichotomised preference variable

Odds ratios, their corresponding 95% confidence intervals, and p-values will be reported for each patient factor in each multivariable analysis.

Summary statistics will also be reported for the time taken to complete each test. Time taken will be recorded using two measurements: the length of procedure, and the length of procedure and set up.

The proportion of participants who undergo a repeat screening assessment for MRI, ultrasound and/or PSA will be reported. Summary statistics of incidental findings detected by MRI and ultrasound screening tests will also be reported.

11.2.5. Other End Point Analysis

Biopsy related adverse events (see Section 10.3.7) will be summarised. Proportions of patients who experience each symptom, patients in whom the symptom caused a problem, and patients who had contact with healthcare will be reported.

11.3. Safety Analysis

At the final visit, the adverse and serious adverse events should be reconciled on the eCRF. Reported adverse events (AEs) and serious adverse events (SAEs) will be listed and summarised separately. A separate table will summarise study-related adverse events (see Appendix 3). Expected adverse events are listed in Appendix 3.

All other safety variables will be summarised by time point in the form of frequency tables for categorical variables or descriptive statistics for continuous variables.

11.4. Subgroup Analysis

11.4.1. Subgroup Analysis End Points

Subgroup analysis will focus on the other test performance (MRI and US) end points relating to positive test rates for MRI and ultrasound, namely:

- The proportion of men with a screen-positive MRI defined by a score of 3 or greater (PIRADS only)
- The proportion of men with a screen-positive MRI defined by a score of 4 or greater (PIRADS only)
- The proportion of men with screen-positive prostate ultrasound defined by a score of 3 or greater (US)
- The proportion of men with screen-positive prostate ultrasound defined by a score of 4 or greater (US).

The subgroup analysis will be limited to the continuous age variable. The other variables required for the analysis of the end points above are described in Sections 10.3.1 and 10.3.2.

11.4.2. Subgroup Analysis Methodology

The analysis with respect to screen-positive MRI will use the PIRADS cut-offs (see Section 10.3.1). The primary subgroup analysis of this end point is concerned with whether age is significantly associated with the probability of attaining a screen-positive MRI result. The distribution of the age variable will be evaluated. From this we will consider whether it is necessary to centre the age variable on the median for improved interpretation of the model. The screening results will be dichotomised into screen-positive and negative results using the PIRADS cut-offs defined in Section 10.3.1. A logistic regression model will be fitted to screening results on the continuous age variable. This analysis will be repeated for each of the PIRADS cut-offs (Section 10.3.1). Odds ratios and their corresponding 95% confidence intervals will be presented. The distribution of age over screen-positive and negative results (using both cut-offs defined in Section 10.3.1) will be displayed using boxplots. A similar analysis will be carried out for screen-positive ultrasound, using the US cut-offs defined in Section 10.3.2.

A secondary subgroup analysis of MRI screening results is concerned with whether age is significantly associated with PIRADS score. The distribution of the age variable will be evaluated. From this we will consider whether it is necessary to centre the age variable on the median for improved interpretation of the model. This will be evaluated by fitting an ordinal logistic model for PIRADS score on the continuous age variable. The proportional odds assumption will be tested and verified. Cumulative odds ratios and the corresponding 95% confidence intervals will be presented. The distribution of age across PIRADS scores will be displayed using boxplots. A similar analysis will be carried out to evaluate whether age is significantly associated with US score.

11.5. Interobserver Agreement for MRI

The reproducibility of MRI will be an important aspect of future use of MRI in the diagnostic pathway for prostate cancer. It is felt that interobserver agreement is more important than intraobserver agreement as in general practice, scans will be assessed once by a locally based radiologist.

Given that it takes approximately 30-60 minutes for a radiologist to assess a scan and complete the CRF, the workload on the central reporter will be unfeasible if all the scans are to be double reported. Thus, the interobserver agreement will be assessed on a random sample of 20% of the total MRI scans. The random sample will be stratified by PIRADS score: negative (a score of 1 or 2), intermediate (a score of 3), or positive (a score of 4 or 5). The central reader for Prostagram is Prof. Anwar Padhani, the Clinical Lead in MRI and Head of Imaging Research at Paul Strickland Scanner Centre, Mount Vernon Cancer Centre, London.

A 5x5 contingency table will present the agreement in PIRADS scores (see Section 10.3.1) for MRI scans between the local reader and the central reader, Prof. Padhani. The Cohen's kappa statistic and corresponding 95% confidence interval will be reported to assess the level of agreement.

The kappa statistic ranges from -1 to 1. Unity represents perfect agreement between the two reviewers. A score of zero indicates agreement is no better than that expected by chance. A negative kappa indicates agreement is worse than that expected by chance.

11.6. Tables to Present

11.6.1. Baseline Characteristics

Table 1.1. 1: Baseline Characteristics

Demographic	Variable	Statistics	Total
Age	Age (years)	50-54 – n (%)	xxx (xx%)
		55 – 59 – n (%)	xxx (xx%)
		60-64 – n (%)	xxx (xx%)
		65 – 69 – n (%)	xxx (xx%)
		N	xxx
		Mean (SD)	xx.xx (xx.xx)
		Median (IQR)	xx.xx (xx.xx, xx.xx)
		Missing from eCRF – n (%)	xx (xx%)
IMD	IMD Quintiles (n (%))	Quintile 1 (1 – 6496)	xxx (xx%)
		Quintile 2 (6497 – 12993)	xxx (xx%)
		Quintile 3 (12994 – 19489)	xxx (xx%)
		Quintile 4 (19490 – 25986)	xxx (xx%)
		Quintile 5 (25987 – 32482)	xxx (xx%)
		Missing from eCRF	xxx (xx%)
BMI	BMI (Kg/m^2)	N	xxx
		Mean (SD)	xx.xx (xx.xx)
		Median (IQR)	xx.xx (xx.xx, xx.xx)
		Missing from eCRF – n (%)	xx (xx%)
Ethnicity	Ethnicity (n (%))	White	xxx (xx%)
		Asian	xxx (xx%)
		Black	xxx (xx%)
		Mixed Race	xxx (xx%)
		Other	xxx (xx%)
		Missing from eCRF	xxx (xx%)
Qualification level	Highest qualification level (n (%))	No formal qualifications	xxx (xx%)
		GCSEs/O-Levels/CSEs/Other	xxx (xx%)
		A-levels/Higher education below degree	xxx (xx%)
		University degree	xxx (xx%)
		Missing from eCRF	xxx (xx%)
Marital status	Marital status (n (%))	Married/Civil partnership/Co-habiting	xxx (xx%)
		Single/Divorced/Widowed	xxx (xx%)
		Missing from eCRF	xxx (xx%)
Employment status	Employment status (n (%))	Employed	xxx (xx%)
		Unemployed	xxx (xx%)

		Retired	xxx (xx%)
		Unable to work	xxx (xx%)
		Other (Student/Homemaker)	xxx (xx%)
		Missing from eCRF	xxx (xx%)
Visit to GP	Visits to GP in last 12 months (n (%))	0	xxx (xx%)
		≥ 1	xxx (xx%)
		Missing from eCRF	xxx (xx%)
Smoking status	Smoking status (n (%))	Current smoker	xxx (xx%)
		Former smoker	xxx (xx%)
		Never smoked	xxx (xx%)
		Missing from eCRF	xxx (xx%)
Smoking history	Age started smoking	N	xxx
		Mean (SD)	xx.xx (xx.xx)
		Median (IQR)	xx.xx (xx.xx, xx.xx)
		Missing from eCRF – n (%)	xx (xx%)
	Age stopped smoking[1]	N	xxx
		Mean (SD)	xx.xx (xx.xx)
		Median (IQR)	xx.xx (xx.xx, xx.xx)
		Missing from eCRF – n (%)	xx (xx%)
	Pack years[1, 2]	N	xxx
		Mean (SD)	xx.xx (xx.xx)
		Median (IQR)	xx.xx (xx.xx, xx.xx)
		Missing from eCRF – n (%)	xx (xx%)
Heard about prostate check	How they heard about the prostate health check (n (%))	Letter from GP	xxx (xx%)
		GP Recruitment	xxx (xx%)
		Traditional Recruitment	xxx (xx%)
		Social Media Recruitment	xxx (xx%)
		Targeted Traditional Recruitment	xxx (xx%)
		Targeted Social Media Recruitment	xxx (xx%)
		Missing from eCRF	xxx (xx%)
Prostate history	Previous PSA test (n (%))	No (and < 2 years ago)	xxx (xx%)
		Yes (and > 2 years ago)	xxx (xx%)
		2-3 years ago	xxx (xx%)
		3-5 years ago	xxx (xx%)
		> 5 years ago	xxx (xx%)
		Unknown	xxx (xx%)
		Missing from eCRF	xxx (xx%)

	Previous DRE (n (%))	Yes	xxx (xx%)
		No	xxx (xx%)
		Missing from eCRF	xxx (xx%)
Family history	Family history of prostate cancer (n (%))	Any family history of prostate cancer	xxx (xx%)
		Any first degree relative (brother/father)[3]	xxx (xx%)
		3 or more affected relatives OR at least two relatives who have developed early-onset PCa (<55 years)[4]	xxx (xx%)
		Missing from eCRF	xxx (xx%)
Medical history	Is the patient taking 5-alpha reductase inhibitors? (n (%))	Yes	xxx (xx%)
		No	xxx (xx%)
		Missing from eCRF	xxx (xx%)
	Is the patient taking an alpha blocker? (n (%))	Yes	xxx (xx%)
		No	xxx (xx%)
		Missing from eCRF	xxx (xx%)
Physical examination	Digital rectal examination result (n (%))	No nodule	xxx (xx%)
		Nodule	xxx (xx%)
		Evidence of locally advanced disease	xxx (xx%)
		Missing from eCRF	xxx (xx%)

[1]Former smokers only

[2]Calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked (former smokers only)

[3]See reference (8) for details

[4]See reference (9) for details

Table 1.1. 2: Summary of IPSS[1] Questionnaire at Baseline (Visit 1)

IPSS – urinary symptoms	Statistics	Total
Severity – n (%)	Mild = ≤ 7	xxx (xx%)
	Moderate = 8-19	xxx (xx%)
	Severe = 20-35	xxx (xx%)
Summary statistics	N	xxx
	Mean (SD)	xx.xx (xx.xx)
	Median (IQR)	xx.xx (xx.xx, xx.xx)
	Missing from eCRF – n (%)	xx (xx%)

[1]See Appendix 1 for details

Table 1.1. 3: Summary of CCI[1] at Baseline (Visit 1)

CCI	Statistics	Total
Severity – n (%)	None = 0	xxx (xx%)
	Mild = 1	xxx (xx%)
	Severe ≥ 2	xxx (xx%)
Summary statistics	N	xxx
	Mean (SD)	xx.xx (xx.xx)
	Median (IQR)	xx.xx (xx.xx, xx.xx)
	Missing from eCRF – n (%)	xx (xx%)

[1]See Appendix 1 for details

11.6.2. Other Test Performance (MRI and US) End Points

Table 1.2. 1: Number of patients completing the screening tests (MRI, ultrasound and/or PSA)

	N
All three screening tests: MRI, ultrasound & PSA	 xxx
Two screening tests, only: MRI & Ultrasound MRI & PSA Ultrasound & PSA	**xxx** xxx xxx xxx
One screening test, only: MRI Ultrasound PSA	**xxx** xxx xxx xxx
Total	xxx

Table 1.2. 2: Proportion of men with a screen-positive MRI, screen-positive ultrasound and/or raised PSA level[1]

Screen-positive results	**Positive MRI (≥ 3)*** (Cut-off [1])		**Positive MRI (≥ 4)** (Cut-off [2])		**Positive ultrasound (≥ 3)** (Cut-off [1])	**Positive ultrasound (≥ 4)** (Cut-off [2])	**Raised PSA (≥ 3.0ng/ml)**
Scoring system	Likert	PIRADS	Likert	PIRADS	US	US	PSA
Proportion – n (%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
95% confidence interval	x.xx to x.xx	x.xx to x.xx	x.xx to x.xx	x.xx to x.xx	x.xx to x.xx	x.xx to x.xx	x.xx to x.xx
Missing from eCRF[2] – n (%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)

*Primary end point.
[1]See Sections 10.3.1, 10.3.2 and 10.3.3 for definitions of thresholds
[2]Proportion who did not undergo the screening test out of the total number of patients recruited

Table 1.2. 3: Proportion within each value of the discrete LIKERT score (MRI scoring system)

LIKERT score	1-2	3	4	5
Proportion – n (%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
95% confidence interval	x.xx to x.xx	x.xx to x.xx	x.xx to x.xx	x.xx to x.xx
Missing from eCRF – n (%)	xx (xx%)			

Table 1.2. 4: Proportion within each value of the discrete PIRADS score (MRI scoring system)

See output in Table 1.2. 3**Error! Reference source not found.**, but for discrete values of the PIRADS scoring system.

Table 1.2. 5: Proportion within each value of the discrete ultrasound score (US)

See output in Table 1.2. 3, but for discrete values of the US scoring system.

Table 1.2. 6: Proportion of men within each value of the discrete LIKERT score (MRI scoring system) and corresponding type of clinical cancer detected

		Likert score			
Definition[1]	**Type of clinical cancer**	**1 - 2**	**3**	**4**	**5**
i	Clinically significant cancer	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx
	Clinically insignificant cancer	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx
	No cancer	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx
ii	Clinically significant cancer	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx
	Clinically insignificant cancer	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx
	No cancer	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx
iii	Clinically significant cancer	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx
	Clinically insignificant cancer	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx
	No cancer	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx
iv	Clinically significant cancer	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx
	Clinically insignificant cancer	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx
	No cancer	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx
v	Clinically significant cancer	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx

	Clinically insignificant cancer	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx
	No cancer	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx

[1]See Section 8.1 for definitions.

Table 1.2. 7: Proportion of men within each value of the discrete PIRADS score (MRI scoring system) and corresponding type of clinical cancer detected

See Table 1.2. 6, but for discrete values of the PIRADS scoring system.

[1]See Section 8.1 for definitions.

Table 1.2. 8: Proportion of men within each value of the discrete ultrasound score (US) and corresponding type of clinical cancer detected

See Table 1.2. 6, but for discrete values of the US scoring system.

[1]See Section 8.1 for definitions.

Table 1.2. 9: Proportion of men within each PSA level (raised and normal[2]) and corresponding type of clinical cancer detected

		PSA Level	
Definition[1]	**Type of clinical cancer**	**Raised (≥ 3.0 ng/ml)**	**Normal (< 3.0 ng/ml)**
i	Clinically significant cancer	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx
	Clinically insignificant cancer	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx
	No cancer	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx
ii	Clinically significant cancer	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx
	Clinically insignificant cancer	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx
	No cancer	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx
iii	Clinically significant cancer	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx
	Clinically insignificant cancer	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx
	No cancer	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx
iv	Clinically significant cancer	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx

	Clinically insignificant cancer	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx
	No cancer	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx
v	Clinically significant cancer	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx
	Clinically insignificant cancer	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx
	No cancer	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx

[1]See Section 8.1 for definitions.
[2]See Section 10.3.3 for definitions.

Table 1.2. 10: Comparisons of proportions of results between pairs of screening tests (MRI & ultrasound, MRI & PSA and ultrasound & PSA[2]) using McNemar chi square tests

McNemar's test statistic		**MRI**		**Ultrasound**		**PSA**
		Positive MRI (PIRADS ≥ 3) (Cut-off [1])	**Positive MRI** (PIRADS ≥ 4) (Cut-off [2])	**Positive ultrasound** (US ≥ 3) (Cut-off [1])	**Positive ultrasound** (US ≥ 4) (Cut-off [2])	**Raised PSA** (≥ 3.0 ng/ml)
MRI	**Positive MRI** (PIRADS ≥ 3) (Cut-off [1])			McNemar's chi2(1) = xx.xx p-value = x.xxx	McNemar's chi2(1) = xx.xx p-value = x.xxx	McNemar's chi2(1) = xx.xx p-value = x.xxx
	Positive MRI (PIRADS ≥ 4) (Cut-off [2])			McNemar's chi2(1) = xx.xx p-value = x.xxx	McNemar's chi2(1) = xx.xx p-value = x.xxx	McNemar's chi2(1) = xx.xx p-value = x.xxx
Ultrasound	**Positive ultrasound** (US ≥ 3) (Cut-off [1])	McNemar's chi2(1) = xx.xx p-value = x.xxx	McNemar's chi2(1) = xx.xx p-value = x.xxx			McNemar's chi2(1) = xx.xx p-value = x.xxx
	Positive ultrasound (US ≥ 4) (Cut-off [2])	McNemar's chi2(1) = xx.xx p-value = x.xxx	McNemar's chi2(1) = xx.xx p-value = x.xxx			McNemar's chi2(1) = xx.xx p-value = x.xxx
PSA	**Raised PSA** (≥ 3.0 ng/ml)	McNemar's chi2(1) = xx.xx p-value = x.xxx	McNemar's chi2(1) = xx.xx p-value = x.xxx	McNemar's chi2(1) = xx.xx p-value = x.xxx	McNemar's chi2(1) = xx.xx p-value = x.xxx	

[1]See Section 10.3.1, 10.3.2 and 10.3.3 for definitions
[2]Screen-positive vs screen-negative results by each threshold definition

Table 1.2. 11: Sensitivity and specificity of screening results (screen-positive or screen-negative) with histology results (clinically significant cancer vs absence of clinically significant cancer) as reference standard

	Screening results[1]

		Positive MRI (PIRADS ≥ 3) (Cut-off [1])	**Positive MRI** (PIRADS ≥ 4) (Cut-off [2])	**Positive ultrasound** (US ≥ 3) (Cut-off [1])	**Positive ultrasound** (US ≥ 4) (Cut-off [2])	**Raised PSA** (≥ 3.0 ng/ml)
Prevalence		xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
Definitions of clinically significant cancer[2]	**i**	Sens = Spec = PPV = NPV =	Sens = Spec = PPV = NPV =	Sens = Spec = PPV = NPV =	Sens = Spec = PPV = NPV =	Sens = Spec = PPV = NPV =
	ii	Sens = Spec = PPV = NPV =	Sens = Spec = PPV = NPV =	Sens = Spec = PPV = NPV =	Sens = Spec = PPV = NPV =	Sens = Spec = PPV = NPV =
	iii	Sens = Spec = PPV = NPV =	Sens = Spec = PPV = NPV =	Sens = Spec = PPV = NPV =	Sens = Spec = PPV = NPV =	Sens = Spec = PPV = NPV =
	iv	Sens = Spec = PPV = NPV =	Sens = Spec = PPV = NPV =	Sens = Spec = PPV = NPV =	Sens = Spec = PPV = NPV =	Sens = Spec = PPV = NPV =
	v	Sens = Spec = PPV = NPV =	Sens = Spec = PPV = NPV =	Sens = Spec = PPV = NPV =	Sens = Spec = PPV = NPV =	Sens = Spec = PPV = NPV =

[1]Screen-positive vs screen-negative using definitions in Sections 10.3.1, 10.3.2 and 10.3.3

[2]Clinically significant cancer vs absence of clinically significant cancer. See Section 8.1 for threshold definitions

Table 1.2. 12: Proportions of false positive results[1] by each screening test (MRI, ultrasound and PSA) with histology (no cancer) as reference

False positive results (histology as reference)	**MRI (PIRADS)[2]**		**Ultrasound (US)[2]**		**PSA[2]**
	Cut-off [1] (≥ 3)	Cut-off [2] (≥ 4)	Cut-off [1] (≥ 3)	Cut-off [2] (≥ 4)	Raised (≥ 3.0ng/ml)
Proportion – n (%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
95% confidence interval	x.xx to x.xx	x.xx to x.xx	x.xx to x.xx	x.xx to x.xx	x.xx to x.xx

[1]False positive results are defined as a screen-positive result when prostate cancer is not present on biopsy (no cancer found on biopsy) (see Section 10.3.8)

[2]See Section 10.3.1, 10.3.2 and 10.3.3

Table 1.2. 13: Proportions of false positive results[1] by each screening test (MRI, ultrasound and PSA) with histology (no cancer or Gleason 3+3) as reference

See Table 1.2. 12, but for false positive results, with histology as reference, defined as a screen-positive result when no prostate cancer or Gleason 3+3 is present on biopsy.

[1]False positive results are defined as a screen-positive result when prostate cancer is not present on biopsy or Gleason 3+3 is present on biopsy

[2]See Section 10.3.1, 10.3.2 and 10.3.3

Table 1.2. 14: Comparison of different testing combinations[5] in terms of biopsy rates, detection of clinically insignificant cancer, in targeted and non-targeted cores, and clinically significant cancer, in targeted and non-targeted cores

			Hypothetical Diagnostic Pathways[6]					
		MRI[3]	**Ultrasound[4]**	**PSA (≥ 1.0ng/ml) & MRI[3]**	**PSA (≥ 3.0ng/ml) & MRI[3]**	**PSA & Ultrasound[4]**	**Ultrasound[4] & MRI[3]**	**PSA & Ultrasound[4] & MRI[3]**
All screen-positive results[3,4]		xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx
Biopsied[1]		xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx
Clinically significant cancer[2]	**Targeted cores**	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx
	Non-targeted cores	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx
Clinically insignificant cancer[2]	**Targeted cores**	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx
	Non-targeted cores	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx

[1]See Section 10.3.5 for definition
[2] Definitions (i) from Sections 8.1.1 & 8.1.2 to defined the detection of clinically significant and insignificant cancers
[3]A screen-positive MRI result is defined by PIRADS cut-off [2] in Section 10.3.1
[4]A screen-positive ultrasound result is defined by US cut-off [2] in Section 10.3.2
[5]See Section 8.3 for Hypothetical Diagnostic Pathways (HDPs)

Table 1.2. 15: Proportion of men, with positive screening results by each screening test[1], who undergo each type of definitive local or systemic treatment

Screen-positive results by each screening test	Total	Definitive local or systemic treatment					
		Active surveillance	Watchful waiting	Focal treatment	Radical prostatectomy	Radical radiotherapy	ADT
PSA (≥ 3.0 ng/ml)	xxx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx
MRI (PIRADS Cut-Off [1])	xxx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx
MRI (PIRADS Cut-Off [2])	xxx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx
Ultrasound (US Cut-Off [1])	xxx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx
Ultrasound (US Cut-Off [2])	xxx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx

[1]See Sections 10.3.1, 10.3.2 and 10.3.3 for definitions

11.6.3. Feasibility End Point

Table 1.3. 1: Mean overall EBQ and PBQ scores[1], and the output of corresponding paired t-tests comparing mean difference between pre- (EBQ) and post (PBQ)-screening test scores, for each screening test

	MRI	Ultrasound	PSA
EBQ (Expected)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
PBQ (Perceived)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Difference*	xx.xx (xx.xx) x.xx to x.xx	xx.xx (xx.xx) x.xx to x.xx	xx.xx (xx.xx) x.xx to x.xx

*From EBQ to PBQ

[1]See Appendix 1 for details

Table 1.3. 2: Output of paired t-tests comparing mean overall EBQ scores[1] between pairs of screening tests (MRI & PSA, MRI & ultrasound, and ultrasound & PSA)

EBQ	N	Mean (SD)	Standard error	95% confidence interval
MRI & PSA	xxx	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
MRI & ultrasound	xxx	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
Ultrasound & PSA	xxx	xx.xx (xx.xx)	xx.xx	x.xx to x.xx

[1]See Appendix 1 for details

Table 1.3. 3: Output of paired t-tests comparing mean overall PBQ scores[1] between pairs of screening tests (MRI & PSA, MRI & ultrasound, and ultrasound & PSA)

PBQ	N	Mean (SD)	Standard error	95% confidence interval
MRI & PSA	xxx	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
MRI & ultrasound	xxx	xx.xx (xx.xx)	xx.xx	x.xx to x.xx

Ultrasound & PSA	xxx	xx.xx (xx.xx)	xx.xx	x.xx to x.xx

[1]See Appendix 1 for details

Table 1.3. 4: Proportions within each value of the Likert score, for each EBQ component[1], for each screening test

EBQ – n (%) (95% CI)		Not at all	Slightly	Somewhat	Rather	Extremely
MRI	**Embarrassment**	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)
	Burden	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)
	Pain	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)
	Anxiety	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)
Ultrasound	**Embarrassment**	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)
	Burden	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)
	Pain	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)
	Anxiety	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)
PSA	**Embarrassment**	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)
	Burden	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)
	Pain	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)
	Anxiety	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)

[1]See Appendix 1 for details

Table 1.3. 5: Mean scores, for each EBQ component[1], for each screening test

	PSA	Ultrasound	MRI
Embarrassment	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Pain	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Burden	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Anxiety	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)

[1]See Appendix 1 for details

Table 1.3. 6: Output of paired t-test comparing mean EBQ component scores[1] between pairs of screening tests (MRI & PSA, MRI & ultrasound, and ultrasound & PSA)

EBQ	N	Mean (SD)	Standard error	95% confidence interval
Embarrassment				
MRI & PSA	xxx	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
MRI & ultrasound	xxx	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
Ultrasound & PSA	xxx	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
Burden				
MRI & PSA	xxx	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
MRI & ultrasound	xxx	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
Ultrasound & PSA	xxx	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
Pain				
MRI & PSA	xxx	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
MRI & ultrasound	xxx	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
Ultrasound & PSA	xxx	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
Anxiety				
MRI & PSA	xxx	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
MRI & ultrasound	xxx	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
Ultrasound & PSA	xxx	xx.xx (xx.xx)	xx.xx	x.xx to x.xx

[1]See Appendix 1 for details

Table 1.3. 7: Proportions within each value of the Likert score, for each PBQ component[1], for each screening test

PBQ – n (%) (95% CI)		Not at all	Slightly	Somewhat	Rather	Extremely
MRI	**Embarrassment**	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)
	Burden	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)
	Pain	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)
	Anxiety	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)
	Repeat test	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)
Ultrasound	**Embarrassment**	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)
	Burden	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)
	Pain	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)

	Anxiety	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)
	Repeat test	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)
PSA	**Embarrassment**	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)
	Burden	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)
	Pain	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)
	Anxiety	xx (xx%) (x.xx to x.xx))	xx (xx%) (x.xx to x.xx))	xx (xx%) (x.xx to x.xx))	xx (xx%) (x.xx to x.xx))	xx (xx%) (x.xx to x.xx))
	Repeat test	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)	xx (xx%) (x.xx to x.xx)

[1]See Appendix 1 for details

Table 1.3. 8: Mean scores, for each PBQ component[1], for each screening test

	PSA	Ultrasound	MRI
Embarrassment	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Pain	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Burden	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Anxiety	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Repeat test	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)

[1]See Appendix 1 for details

Table 1.3. 9: Output of paired t-test comparing mean PBQ component scores[1] between pairs of screening tests (MRI & PSA, MRI & ultrasound, and ultrasound & PSA)

PBQ	N	Mean (SD)	Standard error	95% confidence interval
Embarrassment				
MRI & PSA	xxx	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
MRI & ultrasound	xxx	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
Ultrasound & PSA	xxx	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
Burden				
MRI & PSA	xxx	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
MRI & ultrasound	xxx	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
Ultrasound & PSA	xxx	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
Pain				
MRI & PSA	xxx	xx.xx (xx.xx)	xx.xx	x.xx to x.xx

MRI & ultrasound	xxx	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
Ultrasound & PSA	xxx	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
Anxiety				
MRI & PSA	xxx	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
MRI & ultrasound	xxx	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
Ultrasound & PSA	xxx	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
Repeat test recommendation				
MRI & PSA	xxx	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
MRI & ultrasound	xxx	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
Ultrasound & PSA	xxx	xx.xx (xx.xx)	xx.xx	x.xx to x.xx

[1]See Appendix 1

Table 1.3. 10: Output of paired t-test comparing mean difference between pre- and mean post-screening test scores, as measured by EBQ and PBQ[1], respectively

	N	Pre (EBQ)	Post (PBQ)	Mean difference*	Standard error	95% confidence interval
MRI						
Embarrassment	xxx	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
Burden	xxx	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
Pain	xxx	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
Anxiety	xxx	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
Ultrasound						
Embarrassment	xxx	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
Burden	xxx	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
Pain	xxx	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
Anxiety	xxx	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
PSA						
Embarrassment	xxx	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
Burden	xxx	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
Pain	xxx	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx	x.xx to x.xx
Anxiety	xxx	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx	x.xx to x.xx

*From EBQ to PBQ

[1]See Appendix 1

Table 1.3. 11: Proportion of preference for each test as measured by EBQ ("Expected preference") and PBQ ("Final preference")[1]

	Expected preference (EBQ)	Final preference (PBQ)
No preference	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx
PSA preferred	xxx (xx%)	xxx (xx%)

	x.xx to x.xx	x.xx to x.xx
Ultrasound preferred	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx
MRI preferred	xxx (xx%) x.xx to x.xx	xxx (xx%) x.xx to x.xx

[1]See Appendix 1

Table 1.3. 12: Overview of multivariable logistic regression model fitted to dichotomised test preference (as measured by PBQ[1]), and pre-specified patient related factor variables

Multivariable logistic regression model	**Prefer PSA vs any other response**		**Prefer MRI vs any other response**		**Prefer ultrasound vs any other response**		**No preference vs any other response**	
Patient Factors[2]	**Odds ratio (95% CI)**	**P-value**	**Odds ratio (95% CI)**	**P-value**	**Odds ratio (95% CI)**	**P-value**	**Odds ratio (95% CI)**	**P-value**
Age (< 60 vs ≥ 60 years)	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx
Previous PSA (Yes vs No)	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx
Previous DRE (Yes vs No)	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx
Ethnicity (Black vs Other)	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx
Any first degree relative with history of prostate cancer (Yes vs No)	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx
IMD quintile (Lowest quintiles vs Higher quintiles)	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx
Qualification level (University degree vs Other)	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx
Length of relevant procedure	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx
IPSS score[3]	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx

(Mild vs Moderate/Severe)	(x.xx to x.xx)		(x.xx to x.xx)		(x.xx to x.xx)		(x.xx to x.xx)	
CCI[3] (Severe (≥ 2) vs Not Severe (< 2))	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx
BMI (< 30kg/m^2 vs ≥ 30kg/m^2)	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx
Expected pain (Not at all vs Other)	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx
Expected anxiety (Not at all vs Other)	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx
Expected embarrassment (Not at all vs Other)	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx
Expected burden (Not at all vs Other)	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx	x.xxx (x.xx to x.xx)	x.xxx

[1]See Appendix 1 and Section 10.3.9

[2]See Section 11.2.4

[3]See Appendix 1

Table 1.3. 13: Summary statistics for time taken for each screening test to be completed

Screening test	Statistics	Length of procedure (minutes)	Length of procedure and set up (minutes)
MRI	N	xxx	xxx
	Mean (SD)	xx.xx (xx.xx)	xx.xx (xx.xx)
	Median (IQR)	xx.xx (xx.xx)	xx.xx (xx.xx)
	Missing from eCRF – n (%)	xx (xx%)	xx (xx%)
Ultrasound	N	xxx	xxx
	Mean (SD)	xx.xx (xx.xx)	xx.xx (xx.xx)
	Median (IQR)	xx.xx (xx.xx)	xx.xx (xx.xx)
	Missing from eCRF – n (%)	xx (xx%)	xx (xx%)
PSA	N	xxx	xxx
	Mean (SD)	xx.xx (xx.xx)	xx.xx (xx.xx)
	Median (IQR)	xx.xx (xx.xx)	xx.xx (xx.xx)
	Missing from eCRF – n (%)	xx (xx%)	xx (xx%)

Table 1.3. 14: Proportion of participants who undergo a repeat screening assessment for MRI, Ultrasound and/or PSA

Repeat screening assessments	MRI	Ultrasound	PSA	Total[1]
Proportion – n (%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)
95% confidence interval	x.xx to x.xx	x.xx to x.xx	x.xx to x.xx	x.xx to x.xx

[1]Total number of participants who underwent at least one repeat screening assessment

Table 1.3. 15: Proportion of incidental findings for MRI and Ultrasound screening tests

Type of Incidental Finding	MRI	Ultrasound
None	xx (xx%)	xx (xx%)
Bladder Tumour	xx (xx%)	xx (xx%)
Rectal Tumour	xx (xx%)	xx (xx%)
Other (please specify):	xxx (xx%)	xxx (xx%)
…	xx (xx%)	xx (xx%)
…	xx (xx%)	xx (xx%)
…	xx (xx%)	xx (xx%)

11.6.4. Other End Point

Table 1.4. 1: Rates of biopsy related adverse events (infectious complications, urinary retention, and haematuria requiring admission)

Biopsy related adverse events (subjects*)	Proportion – n (%)

Infectious complications:	xxx (xx%)
Presence	xxx (xx%)
Experienced complications	xxx (xx%)
Healthcare contact	xxx (xx%)
Urinary retention:	xxx (xx%)
Presence	xxx (xx%)
Experienced complications	xxx (xx%)
Healthcare contact	xxx (xx%)
Haematuria requiring admission:	xxx (xx%)
Presence	xxx (xx%)
Experienced complications	xxx (xx%)
Healthcare contact	xxx (xx%)
Total	xxx (xx%)

*Table note: Where subjects have more than one AE the highest relationship has been used

11.6.5. Safety Analysis

Table 1.5. 1: Listing of all adverse events

Subject ID	Diagnosis	Onset Date	Recovery Date	Duration (days)	Relationship	Severity	Expectedness	Serious

Table 1.5. 2: Incidence of expected adverse events (see Appendix 3)

Event class	**Total** - n (%)
Expected study-related adverse events:	xx (xx%)
Haematomas and ecchymoses around venepuncture site	xx (xx%)
Minor discomfort	xx (xx%)
Infection	xx (xx%)
Expected adverse events associated with MRI:	xx (xx%)
Claustrophobia	xx (xx%)
Anxiety/Stress	xx (xx%)
Discomfort	xx (xx%)
Expected adverse events associated with Prostate M-P US:	xx (xx%)
Minimal rectal discomfort during the procedure	xx (xx%)
Expected adverse events associated with Prostate Biopsy:	xx (xx%)
	xx (xx%)

Blood in urine (Haematuria)	xx (xx%)
Pain passing urine (Dysuria)	xx (xx%)
Blood in semen (Haematospermia)	xx (xx%)
Temporary pain/discomfort in the perineal area	xx (xx%)
Temporary problems with erections for up to 6-8 weeks	xx (xx%)
Retention of urine requiring a temporary catheter	xx (xx%)
Prostatitis	xx (xx%)
Infection requiring admission and intravenous antibiotics	xx (xx%)
Expected risks from undergoing local anaesthetic:	xx (xx%)
Nausea and vomiting	xx (xx%)
Minor bruises for intravenous catheters	xx (xx%)
Extensive bruising, temporary hardening of vein (phlebitis) or infection	xx (xx%)
Dizziness/Vertigo	xx (xx%)
Confusion/Disorientation	xx (xx%)
Respiratory depression and apnoea	xx (xx%)
Anaphylaxis to local anaesthetic	xx (xx%)
Expected risks from undergoing general anaesthetic:	xx (xx%)
Nausea and vomiting	xx (xx%)
Dry cough	xx (xx%)
Minor bruises from intravenous catheter	xx (xx%)
Extensive bruising, temporary hardening of the vein (phlebitis) or infection	xx (xx%)
Death	xx (xx%)
Other adverse event (specify):	
...	xx (xx%)
Total	xx (xx%)

Table 1.5. 3: Listing of all new unexpected adverse events

Subject ID	Diagnosis	Onset Date	Recovery Date	Duration (days)	Relationship	Severity	Expectedness	Serious

Table 1.5. 4: Summary of adverse events by severity

Total subjects (N)	Severity	No. adverse events	No. subjects AEs – n (%)	No. serious AEs	No. subjects SAEs – n(%)
	Mild	xx	xx (xx%)	xx	xx (xx%)

	Moderate	xx	xx (xx%)	xx	xx (xx%)
	…	xx	xx (xx%)	xx	xx (xx%)
	All	xx	xx (xx%)	xx	xx (xx%)

Table 1.5. 5: Number of adverse events by causality relationship

Subjects with AEs*						
No relationship	**Unlikely**	**Possible**	**Probable**	**Definitely**	**Not Yet Defined**	**Total**
xx	xx	xx	xx	xx	xx	xxx
Total AEs						
No relationship	**Unlikely**	**Possible**	**Probable**	**Definitely**	**Not Yet Defined**	**Total**
xx	xx	xx	xx	xx	xx	xxx

*Table note: Where subjects have more than one AE the highest relationship has been used.

Table 1.5. 6: Listing of all serious adverse events

Subject ID	AE Diagnosis	Details	Relation to study	Severity	Start date	Days from baseline	Recovery date	Expectedness	Outcome	Event frequency

Table 1.5. 7: Summary of serious adverse events by category

Subjects with SAEs*							
Resulted in death	**Life threatening**	**Require inpatient hospitalisation or prolongation of existing hospitalisation**	**Result in persistent or significant disability or incapacity**	**Resulted in congenital anomaly/birth defect**	**Other medically important event**	**Other**	**TBC**
xx	xx	xx	xx	xx	xx	xx	xx
All SAEs							
Resulted in death	**Life threatening**	**Require inpatient hospitalisation or prolongation of existing hospitalisation**	**Result in persistent or significant disability or incapacity**	**Resulted in congenital anomaly/birth defect**	**Other medically important event**	**Other**	**TBC**
xx	xx	xx	xx	xx	xx	xx	xx

*Table note: Where subjects have more than one SAE the highest category has been used.

Table 1.5. 8: Number of serious adverse events by category and causality relationship

	Subjects with SAEs*						
Category	**No relationship**	**Unlikely**	**Possible**	**Probable**	**Definitely**	**Not Yet Defined**	**Total**
Resulted in death	xx	xx	xx	xx	xx	xx	xx
Life-threatening	xx	xx	xx	xx	xx	xx	xx
Required inpatient hospitalisation or prolongation of existing hospitalisation	xx	xx	xx	xx	xx	xx	xx
Resulted in persistent or significant disability/incapacity	xx	xx	xx	xx	xx	xx	xx
Other medically important event	xx	xx	xx	xx	xx	xx	xx
Other	xx	xx	xx	xx	xx	xx	xx
TBC	xx	xx	xx	xx	xx	xx	xx
	All SAEs						
Category	**No relationship**	**Unlikely**	**Possible**	**Probable**	**Definitely**	**Not Yet Defined**	**Total**
Resulted in death	xx	xx	xx	xx	xx	xx	xx
Life-threatening	xx	xx	xx	xx	xx	xx	xx
Required inpatient hospitalisation or prolongation of existing hospitalisation	xx	xx	xx	xx	xx	xx	xx
Resulted in persistent or significant disability/incapacity	xx	xx	xx	xx	xx	xx	xx
Other medically important event	xx	xx	xx	xx	xx	xx	xx
Other	xx	xx	xx	xx	xx	xx	xx
TBC	xx	xx	xx	xx	xx	xx	xx

*Table note: Where subjects have more than one SAE, the SAE with the highest relationship has been used.

11.6.6. Subgroup Analysis

Table 1.6. 1: Output of logistic regression analysis[1] of the probability of a screen-positive[2] MRI result on age

Variable	N	Odds Ratio	Standard Error	z	p-value	95% confidence interval
Age	xxx	x.xx	xx.xx	x.xx	x.xxx	x.xx to x.xx
Intercept	xxx	x.xx	xx.xx	x.xx	x.xxx	x.xx to x.xx

[1]Logistic regression model: MRI screening result = intercept + age

[2]Repeat analysis for both screen-positive MRI cut-offs defined by PIRADS scoring system in Section 10.3.1

Table 1.6. 2: Output of logistic regression analysis[1] of the probability of a screen-positive[2] ultrasound result on age

See output in Table 1.6. 1, but for screen-positive ultrasound results.

[1]Logistic regression model: ultrasound screening result = intercept + age

[2]Repeat analysis for both screen-positive ultrasound cut-offs defined by US scoring system in Section 10.3.2

Table 1.6. 3: Output of ordinal regression analysis[1] of PIRADS score[2] on age

Variable	N	Cumulative Odds Ratio	Standard Error	z	p-value	95% confidence interval
Age	xxx	x.xx	xx.xx	x.xx	x.xxx	x.xx to x.xx
Intercept	xxx	x.xx	xx.xx	x.xx	x.xxx	x.xx to x.xx

[1]Proportional odds model: PIRADS score = intercept + age

[2]See Section 10.3.1.

Table 1.6. 4: Output of ordinal regression analysis[1] of US score[2] on age

See output in Table 1.6. 3, but for US score.

[1]Proportional odds model: US score = intercept + age

[2]See Section 10.3.2.

11.6.7. Interobserver Agreement for MRI

Table 1.7. 1: Agreement[1] in PIRADS score[2] for MRI scans between local reader and central reader, and Cohen's Kappa statistic

		Central reader					
		1	2	3	4	5	Total
Local reader	1	xxx	xxx	xxx	xxx	xxx	xxx
	2	xxx	xxx	xxx	xxx	xxx	xxx
	3	xxx	xxx	xxx	xxx	xxx	xxx
	4	xxx	xxx	xxx	xxx	xxx	xxx
	5	xxx	xxx	xxx	xxx	xxx	xxx
	Total	xxx	xxx	xxx	xxx	xxx	xxx

Agreement (%)	Expected agreement (%)	Kappa statistic	Standard error	95% confidence interval	Z	Pr > Z
xx.xx%	xx.xx%	x.xxx	x.xxx	x.xx to x.xx	x.xxx	x.xxx

[1]Red indicates agreement between PIRADS scores

[*]Green shading indicates concordant scores, where management decision to perform biopsy would not have changed. Blue shading indicates discordant scores, where management decision to perform biopsy would have changed.

[2]See Section 10.3.1

11.7. Figures to Present

11.7.1. Other Test Performance (MRI and US) End Points

- Histogram to present the distribution of men across discrete values of Likert score (MRI scoring system)
- Histogram to present the distribution of men across discrete values of PIRADS (MRI scoring system)
- Histogram to present the distribution of men across discrete values of ultrasound score (US)
- Histogram to present distribution of the type of cancer detected across discrete values of Likert score (MRI scoring system) (repeated for each of the thresholds defined in Section 8.1 separately)
- Histogram to present distribution of the type of cancer detected across discrete values of PIRADS (MRI scoring system) (repeated for each of the thresholds defined in Section 8.1 separately)
- Histogram to present distribution of the type of cancer detected across discrete values of ultrasound score (US) (repeated for each of the thresholds defined in Section 8.1 separately)
- Graph displaying proportions of results for MRI compared to histology results for detection of clinically significant cancer
- Graph displaying proportions of results for ultrasound compared to histology results for detection of clinically significant cancer
- Graph displaying proportions of results for PSA compared to histology results for detection of clinically significant cancer.

11.7.2. Feasibility End Point

- Bar charts displaying the proportions of participants who selected each Likert score, compared between screening tests (PSA, ultrasound and MRI), for each EBQ component (embarrassment, pain, burden, anxiety) (10)
- Bar charts displaying the proportions of participants who selected each Likert score, compared between screening tests (PSA, ultrasound and MRI), for each PBQ component (embarrassment, pain, burden, anxiety, repeat test recommendation) (10).

11.7.3. Subgroup Analysis

- Boxplots to present distribution of age over screen-positive and negative MRI results (repeated using both PIRADS cut-offs in Section 10.3.1)
- Boxplots to present distribution of age over screen-positive and negative ultrasound results (repeated using both US cut-offs in Section 10.3.2)
- Boxplots to present distribution of age across PIRADS scores
- Boxplots to present distribution of age across US scores

12. Missing Data

Follow up time will be calculated as the time from enrollment. As the period of follow-up is relatively short, there should be minimal problems with loss to follow-up in this study. Circumstances and reasons why a patient is lost to follow-up will be summarised using the CONSORT diagram, and characteristics of patients with missing data or those lost to follow up will be described. Given the thorough nature of our follow-up procedure we expect the issue of missing data to be relatively minimal and therefore it is unlikely that imputation of data will be required.

12.1. Missing Questionnaire Responses

Every effort should be made by the clinical team to ensure questionnaires are completed in full. If this is not possible, missing values may be present in patient responses to these questionnaires.

Patients with missing item responses for EBQ and PBQ will be excluded from the final analysis, as an overall questionnaire score cannot be computed for these patients.

13. Outliers

No formal method will be used for handling outliers in the data. If outlier(s) are found, then the source data will be checked firstly. If the source data is verified as correct, then the outlier(s) will be retained in the analysis. A sensitivity analysis will be considered for analysis that includes that variable.

14. Safety Analysis

At the final visit, the adverse and serious adverse events should be reconciled on the eCRF. Reported adverse events (AEs) and serious adverse events (SAEs) will be listed and summarised separately. A separate table will summarise study-related adverse events (see Appendix 3). Expected adverse events are listed in Appendix 3.

All other safety variables will be summarised by time point in the form of frequency tables for categorical variables or descriptive statistics for continuous variables.

15. Interim Analysis

No interim analysis will be carried out for this study.

16. Protocol Deviations

Protocol deviations, and violations, are to be listed and summarised, if necessary, by category.

16.1. Tables to Present Protocol Deviations/Violations

Table 2. 1: Listing of protocol deviations and violations

Subject ID	Site	Deviation or violation	Interval	Date reported	How identified

Table 2. 2: Number of protocol deviations and violations

Type of Deviation/Violation	Total
Inclusion/exclusion criteria	xx (xx%)
Study drug administration	xx (xx%)
Sampling/laboratory measurements	xx (xx%)
Consent issue	xx (xx%)
Study visit windows	xx (xx%)
NIMP administration	xx (xx%)
Study drug prescription	xx (xx%)
Dispensing	xx (xx%)
Accountability	xx (xx%)
Compliance	xx (xx%)
Missed study visit	xx (xx%)

Study measurements/assessments	xx (xx%)
Primary outcome measure	xx (xx%)
Secondary outcome measure	xx (xx%)
Safety outcome	xx (xx%)
Device	xx (xx%)
Equipment	xx (xx%)
Prohibited medication/substance(s)	xx (xx%)
AE/SAE reporting	xx (xx%)
Blinding/unblinding	xx (xx%)
Randomisation	xx (xx%)
Implementation of document prior to research approval	xx (xx%)
Licence/certification/calibration/servicing (labs and equipment)	xx (xx%)
Delegation log/authorisation	xx (xx%)
Dose interruptions/modifications not specified in protocol	xx (xx%)
Variation in clinical management of participant	xx (xx%)
Withdrawal issue	xx (xx%)
Falsifying research or medical records	xx (xx%)
Repeated protocol deviations (of same type)	xx (xx%)
Other	xx (xx%)
Total deviations/violations	**xx (xx%)**
Total patients with at least one deviation/violation	**xx (xx%)**

17. Imperial Prostate Trial Steering Committee

A combined TSC and DMEC is in place to provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of Good Clinical Practice (GCP) and the relevant regulations. The TSC should agree the trial protocol and any protocol amendments and provide advice to the investigators and the Trial Management Group (TMG), via Imperial Clinical Trials Unit (ICTU) on all aspects of the trial.

The TSC should meet at least annually, although there may be periods when more frequent meetings are necessary.

18. Amendments to Version 1.0

19. References

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20. Appendix

20.1. Appendix 1 – Baseline Questionnaires

20.1.1. IPSS

The International Prostate Symptom Score (I-PSS) is based on the answers to seven questions concerning urinary symptoms and one question concerning quality of life. The responses to the questions concerning urinary symptoms range from 0 to 5, indicating increasing severity of the particular symptom. Thus, the overall score can range from 0 (asymptomatic) to 35 (very symptomatic). The total score for the questions concerning urinary symptoms can be categorised as follows (11):

- Mild – symptom score less than or equal to 7
- Moderate – symptom score range 8-19
- Severe – symptom score range 20-35.

The answers to the question concerning the patient's quality of life ranges from 0 "delightful" to 6 "terrible".

20.1.2. CCI

The Charlson Co-Morbidity Index (CCI) is used to assess the number of comorbidities per patient. The questionnaire has seven questions, each with various sub-questions (12). Weights are assigned for each condition. The total score equals the sum of the weights for the comorbidities the patient has. The weights are defined below (13).

Assigned weights for diseases	Conditions
1	Myocardial infarction Congestive heart failure Peripheral vascular disease Cerebrovascular disease Dementia Chronic pulmonary disease Connective tissue disease Ulcer disease Mild liver disease[1] Diabetes
2	Hemiplegia Moderate or severe renal disease Diabetes with end organ damage Any tumour Leukaemia Lymphoma
3	Moderate of severe liver disease[1]
6	Metastatic solid tumour AIDS

[1]Note: that since we do not distinguish between mild and serious liver disease, we assign two points to patients who endorsed the question about liver disease (12).

The total score ranges from 0 to 29.

20.1.3. EBQ and PBQ

The Expected Burden Questionnaire (EBQ) and Perceived Burden Questionnaire (PBQ) have been developed for use in bowel cancer screening. It has been used in studies investigating the acceptance of CT Colonography/FOBT (10) and has been adapted for the tests used in this study.

EBQ is comprised of four questions addressing the expected extent of embarrassment, pain, burden and anxiety caused by each test. This is followed up by a question summarising which test the patient expects to prefer. The EBQ is completed at visit 1, before the screening tests. The

responses to the first four questions are coded as a 5-point Likert score, 1 = not at all, 2 = slightly, 3 = somewhat, 4 = rather and 5 = extremely (14). Each question, representing each component, will be reported separately. An overall burden score will also be calculated for each screening test by summing the response scores to the first four questions. Lower overall scores represent lower expected overall burden for that particular screening test.

Similarly, PBQ is comprised of five questions addressing the embarrassment, pain, burden and anxiety experienced from each test, and how likely the patient is to have the test again, if recommended. This is followed up by a question summarising which test the patient preferred. The PBQ is completed at visit 1, after each screening test. The responses to the first five questions will be coded as 1 = not at all, 2 = slightly, 3 = somewhat, 4 = rather and 5 = extremely (14). Each question, representing each component, will be reported separately. An overall burden score will be calculated for each screening test by summing the response scores to the first four questions, excluding the question relating to repeat test recommendation. Lower overall scores represent lower perceived overall burden for that particular screening test.

20.2. Appendix 2 – Primary and Secondary End Point Variables

20.2.1. Primary Outcome Paper End Point Variables

Table 2: Primary Outcome Paper End Point Variables

End Point		Variables	Time point & tool
Primary End Point			
Proportion of men with a screen-positive MRI defined by a score of 3 or greater		• Likert and PIRADS scores • Binary recorded overall MRI score	**Visit 1** MRI reporting form
Secondary End Points			
	Proportion of men with a screen-positive MRI defined by a score of 4 or greater	• Likert and PIRADS scores	**Visit 1** MRI reporting form
Performance Objectives (MRI and US)	Proportion of men with screen-positive prostate ultrasound defined by a score of 3 or greater	• Ultrasound Score (US) • Binary recorded overall US score	**Visit 1** US reporting form
	Proportion of men with screen-positive prostate ultrasound defined by a score of 4 or greater	• Ultrasound Score (US)	**Visit 1** MRI reporting form
	Proportion of men with raised PSA level (defined as PSA ≥ 3.0ng/mL)	Dichotomised PSA level	**Visit 1** PSA reporting form
	Proportion of participants within each MRI score and US score of 1, 2, 3, 4 or 5	• Likert and PIRADS scores • Ultrasound Score (US)	**Visit 1** MRI & US reporting forms
	Proportion of participants across each MRI and US score with no cancer, insignificant cancer and significant cancer with each test	• Likert and PIRADS scores • Ultrasound Score (US) • Type of clinical cancer detected (all definitions in Section 8.1 using variables in Section 10.3.4) Definition	**Visit 1** MRI & US reporting forms **Visit 2** Biopsy reporting form

	Proportion of participants with raised and normal PSA level with no cancer, insignificant cancer and significant cancer	• Dichotomised PSA level • Type of clinical cancer detected (all definitions in Section 8.1 using variables in Section 10.3.4)	**Visit 1** PSA reporting form **Visit 2** Biopsy reporting form

	Comparison of the proportion of participants with a positive result for each screening test	• MRI score:
		  • PIRADS score
		  • Binary recorded overall MRI score
		• Ultrasound score:
		  • US score
		  • Binary recorded overall US score
		• Dichotomised PSA level
			Visit 1
			PSA, MRI & US reporting forms

	Comparison of the proportion of men subsequently diagnosed with a clinically significant prostate cancer (as defined by pre-specified histological definitions).	• MRI score:
		  • PIRADS score
		  • Binary recorded overall MRI score
		• Ultrasound score:
		  • US score
		  • Binary recorded overall US score
		• Dichotomised PSA level
		• Type of clinical cancer diagnosed on biopsy (using all definitions in Section 8.1 using variables in Section 10.3.4)
		• Pathology score (Gleason score) on biopsy
			Visit 1
			PSA, MRI & US reporting forms
			Visit 2
			Biopsy reporting form

	Comparison of different testing combinations in terms of biopsy rates, detection of clinically insignificant cancer and significant cancers	• MRI score:
		  • PIRADS score
		  • Binary recorded overall MRI score
		• Ultrasound score:
		  • US score
		  • Binary recorded overall US score
		• PSA level
		• For each of the screening test combinations:
		  • Biopsy rates: recorded number of patients who undergo recommended biopsy (systematic and targeted) (Section 10.3.5)
			Visit 1
			PSA, MRI & US reporting forms
			Visit 2
			Biopsy reporting form

		• Type of clinical cancer diagnosed (using all definitions in Section 8.1 using variables in Section 10.3.4) for targeted and non-targeted cores	

	Proportion of men who go onto definitive local or systemic treatment.	• MRI score:
		  • PIRADS score
		  • Binary recorded overall MRI score
		• Ultrasound score:
		  • US score
		  • Binary recorded overall US score
		• Dichotomised PSA level
		• Number of men who undergo definitive local or systemic treatment (Section 10.3.6)
			Visit 3
			Treatment outcomes

Feasibility	Assess the acceptability of each diagnostic test with EBQ, PBQ and time taken to complete each screening test	• Recorded responses to EBQ at visit 1, for all screening tests
		• Recorded responses to PBQ at visit 1, for all screening tests
		• Dichotomised test preference as measured by PBQ
		• Patient factors:
		  • Age: < 60 years vs ≥ 60 years
		  • Previous PSA: Yes vs No
		  • Previous DRE: Yes vs No
		  • Ethnicity: Black vs All other ethnicities
		  • Any first degree relative with history of prostate cancer: Yes vs No
		  • IMD quintiles
		  • Highest level of qualification: University degree vs All other responses
		  • Length of relevant procedure in minutes, excluding set up time, (Phlebotomy (PSA)/US/MRI)
		  • IPSS score: Mild vs Moderate/Severe
		  • CCI: Severe (≥ 2) vs Not severe (< 2)
		  • BMI: < 30kg/m^2 vs ≥ 30 kg/m^2
		  • EBQ component scores for each screening test.
		• Time taken to complete each screening test procedure
		• Time taken to complete each screening test procedure and set up
		• Number of assessments by each screening test (MRI, ultrasound & PSA)
		• Incidental findings reported for MRI & ultrasound screening tests
			Visit 1
			Questionnaires at baseline
			PSA, ultrasound and MRI reporting forms

Other	Rates of biopsy related adverse events	Recorded biopsy related adverse events (Section 10.3.7)	**Visit 3** Adverse events

Subgroup Analysis	Proportion of men with a screen-positive MRI defined by a score of 3 or greater (PIRADS)	• PIRADS score • Binary recorded overall MRI score • Age	**Visit 1** MRI reporting form
	Proportion of men with a screen-positive MRI defined by a score of 4 or greater (PIRADS)	• PIRADS score • Age	**Visit 1** MRI reporting form
	Proportion of men with a screen-positive prostate ultrasound defined by a score of 3 or greater (US)	• US score • Binary recorded overall US score • Age	**Visit 1** US reporting form
	Proportion of men with a screen-positive prostate ultrasound defined by a score of 4 or greater (US)	• US score • Age	**Visit 1** US reporting form
Interobserver agreement for MRI	Interobserver agreement for double reported MRI scans	• PIRADS score (scored by local reader) • PIRADS score (scored by central reader)	**Visit 1** MRI reporting form

20.3. Appendix 3 – 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.

20.3.1. Expected Study-Related Adverse Events

Expected Adverse Events Associated with Venepuncture Procedure

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

20.3.2. Expected Adverse Events Associated with MRI

The following Adverse Events are associated with MRI:

- Claustrophobia
- Anxiety/Stress
- Discomfort.

20.3.3. Expected Adverse Events Associated with Prostate M-P US

- Minimal rectal discomfort during the procedure

20.3.4. 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