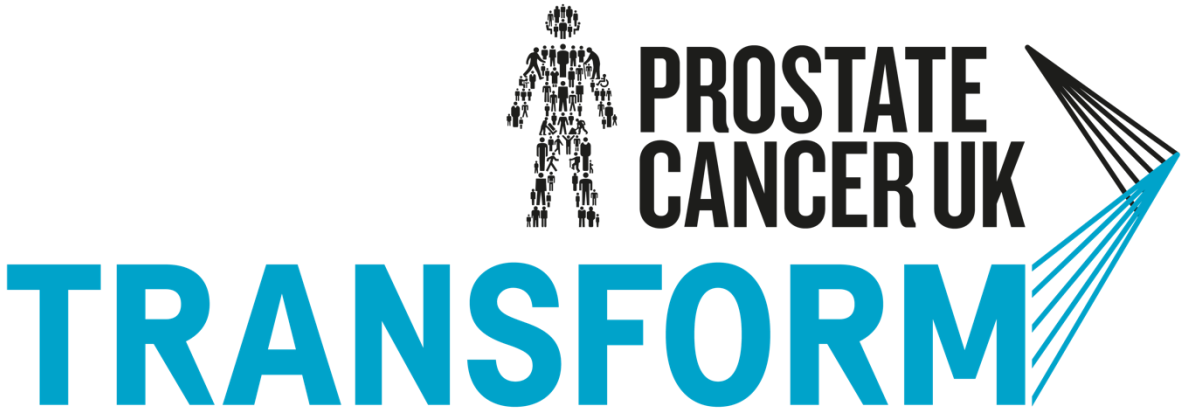
CLINICAL STUDY PROTOCOL



ICTU Adopted PROTOCOL

Trial of **R**andomised **A**pproaches for **N**ational Screening **FOR** **M**en

Sponsor:
Imperial College London

Version No:
1.0

Protocol Date:
30th July 2025

This protocol has regard for the HRA guidance

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

This trial will adhere to the principles outlined in the UK Policy Framework for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act 2018 and other regulatory requirements as appropriate.

ABBREVIATIONS

ADT	Androgen Deprivation Therapy
AE	Adverse Event
AI	Artificial Intelligence
ARI	Androgen Receptor Inhibitor
CAG	Confidentiality Advisory Group
CE	Cost-Effectiveness
CEAC	Cost-Effectiveness Acceptability Curves
cfRNA/DNA	Cell Free Ribonucleic Acid / Deoxyribonucleic Acid
CI	Chief Investigator
CLIA	Clinical Laboratory Improvement Amendments
CPA	Clinical Pathology Accreditation
CPG	Cambridge Prognostic Group
CRF	Case Report Form
CTC	Circulating Tumour Cell
CTCAE	The Common Terminology Criteria for Adverse Events
ctDNA	Circulating Tumour Deoxyribonucleic Acid
CUA	Cost-Utility Analysis
CWS	Cancer Worry Scale
DART	Data Asset Registration Tool
DICOM	Digital Imaging and Communications in Medicine
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DPIA	Dara Protection Impact Assessment
DSA	Deterministic Sensitivity Analysis
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ERSPC	European Randomised Study of Prostate Cancer
FDA	Food and Drug Administration
FFPE	Fresh and Formalin-Fixed Paraffin Embedded
GAD	Generalised Anxiety Disorder
GCP	Good Clinical Practice
GDPR	General Data Protection Regulations
GG	Grade Group
GLP	Good Laboratory Practice
GP	General Practitioner
GS	Gleason Score
GWAS	Genome-Wide Association Study
HES	Hospital Episodes Statistics

HIS	Hospital Information System
HRA	Health Research Authority
HTA	Human Tissue Act
ICH	International Council for Harmonisation
ICHNT	Imperial College Healthcare NHS Trust
ICHOM	International Consortium for Health Outcomes
ICMJE	International Committee of Medical Journal Editors
ICTU	Imperial Clinical Trials Unit
IRAS	Integrated Research Application System
ISAG	Independent Scientific Advisory Group
ISO	Internation Organisation for Standardisation
ISUP	International Society of Urological Pathology
ITT	Intention to Treat
MAF	Minor Allele Frequency
MAMS	Multi Arm Multi Stage
MDT	Multidisciplinary Team
miRNA	Micro Ribonucleic Acid
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NCITA	National Cancer Imaging Translational Accelerator
NCRI	National Cancer Research Institute
NHSCR	National Health Service Care Register
NHSE	National Health Service England
NIHR	National Institute for Health and Care Research
NICE	National Institute for Health and Care Excellence
NRES	National Research Ethics Service
ONS	Office of National Statistics
PBQ	Perceived Burden Questionnaire
PACS	Picture Archiving and Communications System
PCRMP	Prostate Cancer Risk Management Programme
PCUK	Prostate Cancer UK
PHC	Prostate Health Check
PIC	Participant Identification Centre
PLOC	Prostate, Lung, Colorectal and Ovarian
PPIE	Patient and Public Involvement and Engagement
PROBE	Patient Reported Outcomes, Burdens and Experiences
PROMS	Patient Reported Outcome Measures
PRS	Polygenic Risk Score

PSA	Prostate Specific Antigen
QA	Quality Assurance
QALY	Quality Adjusted Life Year
QC	Quality Control
QMUL	Queen Mary – University of London
QOF	Quality Outcome Framework Register
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RIS	Radiology Information System
RNA	Ribonucleic Acid
RoPA	Record of Processing Activity
SABR	Strereotactic Ablative Radiotherapy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SILS	Single-Item Literacy Screener
SMACS	Sexual Minorities and Prostate Cancer Scale
SNP	Single Nucleotide Polymorphism
SOP	Standard Operating Procedure
SWAT	Study Within a Trial
TAF	Theoretical Framework of Acceptability
TMG	Trial Management Group
TSC	Trial Steering Committee
TWIC	Trial WithIn a Cohort
UCL	University College London
UKAS	United Kingdom Accreditation Service
WHO	World Health Organisation

TABLE OF CONTENTS

1. TRIAL SUMMARY 16
1.1. Lay Summary 22
1.2. TRANSFORM Stage 1 and Stage 2 22
1.3. TRANSFORM Discovery 23
1.4. Scientific Abstract 23
1.4.1. Background
1.4.2. Aims
1.4.3. Potential Impact
1.5. Plan 24
1.5.1. Stage 1: Pilot and Feasibility
1.5.2. Stage 2: Main Trial

2. BACKGROUND 25
2.1. Screening for Prostate Cancer 25
2.1.1. Chances in UK Secondary Care
2.1.2. Type of Screening Study Design – Pre-Consent or Post-Consent Randomisation
2.1.3. Comparator
2.1.4. Evaluating the Clinical Utility of Multiple Screening Strategies
2.2. Rationale for Screening Interventions to Test in TRANSFORM 28
2.2.1. Prostagram™
2.2.2. Polygenic Risk Scores
2.3. *Clinically Significant Prostate Cancer on Biopsy*

3. OBJECTIVES 30
3.1. Stage 1: Pilot and Feasibility 31
3.1.1. Trial Design Optimisation
3.1.2. Pilot Prostate Health Checks
3.1.3. TRANSFORM Discovery
3.2. Stage 2: Main Trial 31
3.2.1. Long Term Cancer Outcomes
3.2.2. Costs and Cost-Effectiveness
3.3. TRANSFORM Discovery 31

4. STUDY DESIGN 32
4.1. Flowcharts 32
4.1.1. Stage 1
4.1.2. Stage 1: Design 1
4.1.3. Stage 1: Design 2
4.1.4. Stage 2

5. STAGE 1: PARTICIPANT ENTRY 37
5.1. Study Setting and Population 37
5.1.1. GP Practice Setting and Population
5.1.2. Age Group for Recruitment

5.1.3. Diversity of Recruitment and Specific Targets for Recruiting Black Men
5.2. Eligibility Criteria 38
5.2.1. Eligibility Check 1
5.3. *Eligibility Check 2: Pre-Consent*

6. PROCEDURES AND MEASUREMENTS 39
6.1. Screening Interventions 39
6.2. Prostate Health Check 1 40
6.3. Prostate Health Check 2 41
6.4. Prostate Health Check 3 42
6.5. Prostate Health Check 4 43
6.6. Prostagram™ Magnetic Resonance Imaging 44
6.6.1. Prostagram™ MRI Conduct
6.6.2. Quality Assurance and Quality Control of Prostagram™ MRI
6.6.3. Radiology Expertise
6.6.4. Prostagram™ MRI Reporting Scheme
6.7. Targeted Only Transperineal Biopsy 44
6.7.1. Histology
6.8. Validated Patient Reported Outcome Measures 45
6.9. Health Economics and Main Trial Questionnaires (with Timepoints) 46
6.10. Process Evaluation on Study Screening Participation for Overall Study Population and Ethnic Group 46
6.11. Behavioural Questionnaires (with Timepoints) 47
6.12. Interviews with Participants and GPs 48
6.12.1. Invited Participants
6.12.2. General Practitioners, Urologists, Commissioners of Care
6.12.3. Mixed Methods Analysis
6.13. Health Economics 49
6.13.1. Economic Model
6.13.2. Model Structure
6.13.3. Assembly of Data

7. TRANSFORM DISCOVERY 51
7.1. Aims 51
7.2. Overview 52
7.2.1. Tissue and Multi-omic Digital Data Collection
7.3. Bio-Digital Twin 52
7.3.1. Prospective Tissue, Data Collections and Biomarker Testing
7.4. Scientific Reach 53
7.5. Adaptive Biomarker Testing in Real-Time 54
7.6. The TRANSFORM Discovery Laboratory 54
7.6.1. Robust Approaches to Generate High Quality Measures from the Tissue
7.6.2. Laboratory Standards
7.6.3. Processing for Tissue Archiving
7.6.4. Secure Storage
7.6.5. Data Laboratory
7.7. Tissue Specifications 55
7.8. Data Management 56
7.8.1. Clinical Meta-Data

7.8.2. Digital Imaging
7.8.3. Digital Pathology
7.9. Data Laboratory 57
7.9.1. State of the Art Computing Facilities
7.9.2. Secure Digital Data
7.10. AI Predictive Models of Health and Disease Status 57
7.10.1. Model Design
7.10.2. AI Prediction Model
7.10.3. Modelling Biomarker Performance
7.10.4. Integrative Analyses
7.11. Consent 58
7.11.1. Parallel Consent for Clinical and Translational Study
7.11.2. Detailing Tissue studies
7.11.3. Withdrawal Options for TRANSFORM Discovery after Consent has been Provided
7.11.4. Re-Contacting for Additional Studies or Linkage Across Other Studies
7.12. Stakeholder Engagement 59
7.12.1. Commercial and Academic Partnerships for Biomarker Development and Testing
7.12.2. Patient and Public Involvement and Engagement (PPIE)
7.13. Governance 60
7.13.1. Governance Structure
7.13.2. Strategy and Steering Board
7.13.3. Research Operations Board
7.13.4. Advisory Board
7.13.5. Contractual Basis of Collaborations
7.13.6. Intellectual Property
7.13.7. *Data and Tissue Access*

8. IDENTIFICATION AND RECRUITMENT OF PARTICIPANTS 61
8.1. Pre-Randomisation Evaluations 61
8.1.1. Stage 1
8.1.2. Stage 2
8.2. Randomisation and Blinding 61
8.2.1. Stage 1
8.2.2. Stage 1: Design 1
8.2.3. Stage 1: Design 2
8.3. Schedule 62
8.4. Schedule of Events 63
8.5. Behavioural Questionnaires 66
8.6. Health Economics and Main Trial Questionnaires 68
8.7. Participant Pathway 69
8.8. Follow-Up 70
8.8.1. Stage 1 (Control Arms)
8.8.2. Intervention Arms
8.8.3. Health Status
8.9. Laboratory Evaluations 71
8.10. Intervention 72

8.10.1. Permanent Discontinuation of Study Intervention and Withdrawal from Study

9. SAFETY REPORTING 72
9.1. Overview 73
9.2. Adverse Events (AE) 73
9.3. Serious Adverse Events (SAE) 74
9.4. Harms (Post-PHC Follow-Up) 76

10. STATISTICAL ANALYSES 76
10.1. Stage 1: Feasibility 76
10.1.1. Primary Outcomes
10.1.2. Secondary Outcomes
10.2. Stage 1: Prostate Health Checks Intervention Pilot Outcomes 77
10.2.1. Primary Outcomes
10.2.2. Secondary Outcomes
10.2.3. Detection
10.2.4. Biopsy-Related Harms
10.2.5. Treatment
10.2.6. Treatment-Related Harms
10.2.7. Patient Reported Measures
10.2.8. Health Economics
10.2.9. TRANSFORM Discovery
10.3. Stage 2: Main Trial 80
10.3.1. Primary Outcomes
10.3.2. Secondary Outcomes
10.3.3. Cancer Control Outcomes
10.3.4. Demographics and Recruitment
10.3.5. Screening Interventions
10.3.6. Cancer Detection and Management
10.3.7. Biopsy-Related Harms
10.3.8. Treatment
10.3.9. Treatment-Related Harms
10.3.10. Participant Reported Measures
10.3.11. Health Economics
10.3.12. NHS Dissemination and Healthcare Resource Impact
10.3.13. TRANSFORM Discovery
10.4. Sample Size and Power Considerations 83
10.4.1. Stage 1: Pilot and Feasibility
10.4.2. Stage 2: Main Trial
10.5. Interim Analysis 84
10.6. Planned Recruitment Rate 85
10.7. Statistical Analysis 85
10.7.1. Stage 1: Trial Design Optimisation
10.7.2. Stage 1: Pilot Prostate Health Checks
10.7.3. *State 2*

11. REGULATORY 86
11.1. Declaration of Helsinki 86
11.2. Good Clinical Practice 87

11.3. Research Ethics Committee (REC) Approval 87
11.4. HRA Approval 87
11.5. Other Required Approvals 87
11.6. Non-Compliance and Serious Breaches 87
11.7. Insurance and Indemnity, Sponsor and Funding 88
11.8. Trial Registration 88
11.9. Informed Consent 88
11.10. Contact with General Practitioner 88
11.11. Participant Confidentiality 89
11.12. Data Protection and Participant Confidentiality 89
11.13. End of Trial 90
11.14. Study Documentation and Data Storage 90

12. DATA MANAGEMENT 90
12.1. Source Data 90
12.2. Language 90
12.3. Database 90
12.4. Data Collection 90
12.5. Archiving 91

13. STUDY MANAGEMENT STRUCTURE 91
13.1. Trial Steering Committee 91
13.2. Trial Management Group 91
13.3. Data Monitoring Committee 91
13.4. Early Discontinuation of the Study 91
13.5. Risk Assessment 91
13.6. Monitoring 91
13.7. Quality Control and Quality Assurance 92
13.8. Peer Review 92
13.9. Ongoing Involvement 92
13.10. Publication and Dissemination Policy 93

1. TRIAL SUMMARY

Master Protocol	
Title	**TRANSFORM** **T**rial of **R**andomised **A**pproaches for **N**ational **S**creening **FOR** **M**en
Version	0.1
Date	06-JUN-2025
NCT	NCTXXXXXXXX
Objectives	**Stage 1: Pilot and Feasibility** • Trial design optimisation: Evaluate feasibility of design options for a trial estimating effectiveness and cost-effectiveness of screening for prostate cancer • Pilot Prostate Health Checks (PHCs) • TRANSFORM Discovery: Develop, optimise and operationalise a trial-related bio-digital twin incorporating a repository of biospecimens and digital data **Stage 2: Main Trial** • Conduct a trial designed to evaluate effectiveness and cost-effectiveness of prostate screening using one or more Prostate Health Checks (PHCs) • Evaluate NHS delivery of the intervention • Expand data and biospecimen banking into TRANSFORM Discovery and deliver (i) biomarker testing and (ii) translational and discovery science
Design	Multi-arm multi-stage randomised platform trial
Participants	Men 50-74 years of age (45-74 if Black ethnicity or with learning disability) Ineligible if history of prostate cancer (clinical diagnosis or histological) or underwent previous PSA test, prostate MRI scan, prostate biomarker test or prostate biopsy in the preceding 5 years
Settings	Community, primary and secondary care
Interventions	Various - see Intervention Evaluations table below

Primary Outcomes	**Stage 1**
	• Proportion in each randomised group:
	  ○ Diagnosed with intermediate risk prostate cancers (NCCN)
	  ○ Diagnosed with low-risk prostate cancers (NCCN)

	○ Having a prostate biopsy • Costs and cost-effectiveness modelling • Uptake of invitation to participate • Compliance to randomised intervention, contamination with prostate cancer testing in control groups **Stage 2** • Defined per Intervention Evaluation (after Stage 1)
Planned Number of Participants	To be defined for each stage of trial and per intervention evaluation
Duration	See Intervention Evaluation tables below for details

Stage 1: Pilot and feasibility	
Design 1: Feasibility of a randomised-controlled trial of Prostate Health Checks in those registered to the TRANSFORM Research Cohort	
Participants	As defined in master protocol table
Design	Participants consenting to the TRANSFORM Research Cohort will be randomised between standard of care (post-consent control) and multiple PHC interventions
Intervention	Invitation to participate in the TRANSFORM Research Cohort
Control 1	Approached to participate and expressing interest in a PHC study and randomised to no invitation to a PHC (post-consent control)
Evaluation	• Feasibility of expression of interest • Feasibility of randomisation process • Evaluation of multiple PHCs
Allocation Ratio	Adapts to achieve target number of participants completing each PHC **Randomisation** Post-consent Control: PHC1 : PHC2 : PHC3 : PHC4 **Initial Randomisation Ratio** 7 : 10 : 10 : 10 : 10 N.B. The randomisation ratio may be adjusted to achieve the target number of participants completing each PHC.

	Ratio to be Achieved 1 : 1 : 1 : 1 : 1
Primary Outcomes	• Proportion of those invited who provide Stage 1 consent to express interest • Proportion undergoing the PHC in each of the intervention arms after invitation following expression of interest • Post consent control • Proportion known to have had a PSA test within the stage 1 timeframe after randomisation • Proportion known to have had an MRI of the prostate within the Stage 1 timeframe after randomisation • Prostate Health Checks: see Intervention Evaluations table below
Planned Number of Participants	2500 participants completing the PHC per intervention arm and 2500 in post-consent control
Duration	3 years (in parallel to Design 2)

Design 2: Feasibility of a randomised-controlled invitation to undergo a Prostate Health Check	
Participants	As defined in master protocol table
Design	Randomise between control and invitation to undergo Prostate Health Checks
Control 2	Not approached to undergo the PHCs (pre-consent control)
Intervention	Invitation to undergo one of the 4 PHCs, four groups, each representing one PHC
Evaluation	Feasibility of randomisation process
Allocation Ratio	**Randomisation** Pre-consent control: PHC1 : PHC2 : PHC3 : PHC4 **Randomisation Ratio** 10 : 1 : 1 : 1 : 1
Primary Outcomes	Proportion undergoing the PHC in each of the intervention arms Proportion in pre-consent control with a PSA test within the Stage 1 timeframe after randomisation Proportion known to have had an MRI of the prostate within the Stage 1 timeframe after randomisation

Planned Number of Participants	2500 in pre-consent control arm, 250 invited per PHC arm
Duration	3 years (in parallel with Design 1)

Evaluation of Prostate Health Checks in Stage 1	
Interventions	**PHC1:** PSA ≥ 3 followed by community-based Prostagram™ MRI, or if Black ethnicity/first degree family history of Prostate Cancer then PSA ≥ 2.5 followed by community-based Prostagram™ MRI **PHC2:** PSA ≥ 1 followed by community-based Prostagram™ MRI **PHC3:** Community-based Prostagram™ MRI in all **PHC4:** PRS followed by community-based Prostagram™ MRI if PRS-risk eligible

Primary Outcomes	• Proportion in each randomised group:
	  ○ diagnosed with intermediate risk prostate cancers (NCCN)
	  ○ diagnosed with low-risk prostate cancers (NCCN)
	  ○ having a prostate biopsy
	• Costs and cost-effectiveness modelling of each PHC intervention (from first visit to diagnosis/treatment)

Stage 2.1: Main Trial	
Prostate Health Check – Optimal (PHC-Optimal) evaluation for long term cancer control *[to be defined through substantial amendment]*	
Participants	As defined in master table above
Design	To be determined from findings of Stage 1
Interventions	Prostate Health Check as determined from findings of Stage 1 (PHC-Optimal)
Allocation Ratio	To be determined following Stage 1 outcomes
Aim	To determine whether a PHC-Optimal, compared to standard care, will lead to an improved balance of benefits, harms and costs in men from the general population
Primary Outcomes	**To be decided but outcomes of interest include:** • Time to metastatic prostate cancer or prostate cancer death • Time to death from prostate cancer • Costs and cost-effectiveness to the NHS

Target Number of Participants	To be determined following findings of Stage 1
Duration	To be determined following findings of Stage 1

Stage 2.2: Further prostate health checks that could be added as additional intervention arm(s) as PHC(x)	
Such future novel screening strategies will be reviewed by all relevant trial oversight committees and funders and then submitted to sponsor, REC and HRA through a substantial amendment mechanism	
Participants	As defined in master table above
Design	To be determined from findings of Stage 1
Interventions	Prostate Health Check(s) using strategies that are developed in the future To be determined
Allocation Ratio	To be determined
Aims	**Pilot of PHC(x)** To determine whether the use of a novel PHC(x), compared to standard care, will lead to an improved balance of benefits, harms and costs in terms of biopsy and cancer detection rates, to justify an assessment of medium, long term cancer control and cost to the NHS? If a PHC qualifies for medium and long-term assessment of cancer control, it will continue to be evaluated against the control for long-term outcomes. **Main Trial of PHC(x)** To determine whether the use of a novel PHC(x), compared to standard care, will lead to an improved balance of benefits, harms and costs in terms of prostate cancer mortality, time to prostate cancer metastases or mortality, biopsy rates and biopsy- and treatment-related harms, cancer detection rates and costs and cost-effectiveness to the NHS?

Primary Outcomes	**Pilot of PHC(x)**
	• Proportion in each randomised group,
	  ○ diagnosed with intermediate risk prostate cancers (NCCN)
	  ○ diagnosed with low-risk prostate cancers (NCCN)
	  ○ having a prostate biopsy
	• Costs and cost-effectiveness modelling of chosen PHC (from first visit to diagnosis/treatment)
	
	Main Trial of PHC(x)
	• Time to metastatic prostate cancer or prostate cancer death
	• Time to death from prostate cancer
	• Costs and cost-effectiveness to the NHS

Target Number of Participants	To be determined
Duration	To be determined

1.1. LAY SUMMARY

Each year in the UK, nearly 50,000 people will be diagnosed with prostate cancer and over 12,000 will die of the disease. Prostate cancer often doesn't cause any symptoms until it has started to grow and spread outside the prostate. We do not currently have a national screening programme for prostate cancer which enables us to detect the disease at its earliest, most treatable stage.

A screening programme could save thousands of lives each year in the UK; however, we do not have definitive evidence to demonstrate that screening can not only help find the most life-threatening prostate cancers early, before they have spread, but also avoids unacceptable levels of harm. Harms of screening include performing biopsy tests on men who turn out not to have cancer. Harms can also occur from detecting and treating low-risk prostate cancer unnecessarily as these men are unlikely to benefit from treatment. We also need to provide information to the NHS that screening represents a good use of limited NHS resources.

We have several highly promising tests that look like they might overcome many of the potential harms from earlier PSA-screening studies. For instance, small-scale studies have suggested that using a short MRI scan in the community (Prostagram™ MRI), or using genetic risk profiling based on polygenic risk scores, might find important prostate cancers better than PSA. In addition, these approaches may lead to fewer biopsies and fewer unnecessary treatments.

TRANSFORM is a national randomised controlled trial designed to provide definitive data. The findings from TRANSFORM should allow policymakers to decide whether screening for prostate cancer should be recommended. The study will provide data on the potential reductions in prostate cancer related mortality and couple this with the potential reductions in harm through fewer biopsies and treatment delivered to those who would benefit from it. TRANSFORM will also assess value for money to the NHS and deliverability within the UK healthcare system.

1.2. TRANSFORM STAGE 1 AND STAGE 2

Stage 1 (pilot and feasibility) will (a) test a number of different screening approaches to decide which is the optimal screening strategy for Stage 2; (b) evaluate how best to run the trial in the next stage, including how best to engage men in the community to take part; (c) the optimal form of randomisation to carry out; and (d) develop a national prostate cancer repository of biological specimens and associated digital data a powerful platform for the discovery and rapid development of new tests and treatments (TRANSFORM Discovery).

Stage 2 (trial) will take forward the most robust design and screening test(s) based on Stage 1 data, in order to assess whether the new screening strategy is beneficial and value for money. During Stage 2 there will also be an in-depth analysis of the costs and cost savings of screening, resource and capacity requirements within the NHS to deliver an effective screening programme, as well as an evaluation of the potential challenges and barriers to the uptake of screening. This will mean that if screening is eventually recommended, we will have learnt how we might improve participation at a population level. Alongside the trial, this programme will also build TRANSFORM Discovery with clinical data and imaging files as well as blood, urine and tissue samples from consenting trial participants, creating a valuable resource for the future development and testing of novel approaches to diagnosing prostate cancer or predicting outcomes from treatment.

Stage 2 has been designed with a view to incorporating new promising interventions over time. Any new intervention would be judged in the same way as described above. It would undergo

a staged assessment, as per the principles set out in Stage 1, so that early outcomes (acceptability, feasibility, biopsy rates, cancer detection, patient reported outcomes, cost-effectiveness modelling) would determine whether the intervention continues to recruit large numbers of participants for an assessment of cancer control.

We will monitor the trial participants through linkage to national databases to determine the long-term impact of screening on rates of cancer progression and prostate cancer specific mortality and to provide updated information on value for money to the NHS.

1.3. TRANSFORM DISCOVERY

Alongside the trial, we will establish TRANSFORM Discovery. This will be a large vault of tissue, images and biomarker data. The TRANSFORM Discovery data will be linked to the main trial database using the same pseudo-anonymised patient identifiers. TRANSFORM Discovery will help researchers make new scientific discoveries into the causes and consequences of prostate cancer, and retrospectively evaluate other biomarkers than those included so far in the TRANSFORM platform trial. We will securely store information on consenting participants and their scans in digital files, as well as tissue samples that include blood, urine, saliva, stool and prostate tissue. The aim is to use all the data from the tissue collection to enable researchers to create a “Bio-Digital Twin” for each participant. These data will enable researchers to use modelling techniques for scientific discovery and retrospective evaluation of new tests. The aim is that this resource will provide an opportunity for research to change how we understand and treat prostate cancer.

1.4. SCIENTIFIC ABSTRACT

1.4.1 Background

Each year in the UK, over 50,000 people are diagnosed with prostate cancer and over 12,000 die of the disease. The European Randomised Study of Screening for Prostate Cancer (ERSPC) showed that PSA testing every 2-3 years is likely to reduce the relative risk of men dying from prostate cancer, by 7-45%[1]. However, screening in this trial also led to false positives and over-detection of clinically insignificant cancer with resultant harms of biopsy, diagnosis and treatment (and hence waste of health care resources). PSA screening can also miss some clinically significant prostate cancers. As a result of all these issues, prostate cancer screening using PSA tests has not been recommended by the UK National Screening Committee because the associated harms from the earlier screening processes that were trialled were likely to outweigh the benefits. There have since been several pivotal changes in secondary care diagnostic and therapeutic pathways which have been shown to reduce harms. Whilst this means the overall balance of harms and benefits are likely to have shifted in favour of screening for prostate cancer, it is also clear that new ways to use strategies to screen for prostate cancer may provide further advantages. The TRANSFORM study will deliver a randomised controlled trial evaluating these new screening strategies in primary care coupled with harm reduction strategies that have occurred in secondary care.

1.4.2 Aims

- Deliver a multi-arm multi-stage platform RCT of prostate cancer screening strategies
- Demonstrate acceptability and clinical and cost-effectiveness of screening strategies
- Determine barriers and facilitators to ensure equitable engagement of participants from different backgrounds

- Create TRANSFORM Discovery, a tissue collection, comprising of linked multi-modal digital data (clinical, imaging, histological and molecular) and biospecimens (urine, blood, saliva, stool and prostate) for rapid biomarker testing and translational research

1.4.3 Potential Impact

In the general population of men that are invited to and attend screening, prostate cancer screening strategies, compared to current UK standard of care, will increase the early detection of clinically significant prostate cancer, reduce long-term rates of metastatic cancer and improve prostate cancer specific survival.

The benefits from earlier detection of prostate cancer will outweigh the potential physical and psychological harms of biopsy, over-detection of clinically insignificant disease, over-treatment and associated costs.

A cost-effective scalable screening strategy for prostate cancer that will change guidelines and healthcare policy.

A platform trial to enable robust evaluation of new screening and diagnostic strategies in future with intervention arms being added or removed.

TRANSFORM Discovery will accelerate biomarker development and validation for improvements in screening for, diagnosing, and modelling the impact of therapeutic changes to management of prostate cancer.

1.5. PLAN

1.5.1 Stage 1: Pilot and Feasibility

Stage 1 will assess feasibility of trial processes and recruitment strategies to measure rates of acceptance to an invitation to a screening study as well as rates of non-compliance and contamination (PSA and MRI testing) in standard of care. We will test whether a pre-consent RCT could form the basis of a pivotal Stage 2 trial or whether a post-consent RCT is preferred. We will recruit a diverse study population including adequate representation of lower socio-economic, ethnic minority and vulnerable participants such as those with learning disability. This stage will pilot four new screening strategies termed Prostate Health Checks.

A mixed methods approach will be used to determine facilitators and barriers to participation in TRANSFORM using patient reported outcomes that measure cancer anxiety, reinforced with focus groups and interviews with men and their families who accept or decline participation, as well as selected healthcare professionals.

We will collect data on diagnostic outcomes including rates of biopsy and cancer detection by different grade and risk groups, as well as reporting on rates of localised, locally advanced and regional and distant metastases. Patient reported outcome measures will be collected using validated questionnaires evaluating functional and overall health related quality of life. Costs and resources will be collated at a participant and health care system level. These data will be used to evaluate the potential benefits, harms, costs- and modelled cost-effectiveness, of the Prostate Health Checks in Stage 1. This will help guide decisions on which Prostate Health Check moves forward to Stage 2.

Stage 1 will operationalise TRANSFORM Discovery, capturing prospective multi-omics data from biospecimens matched with multi-modal clinico-radio-pathological datasets. A focus will be academic and commercial partners to undertake rapid clinical validation exercises of commercially available and late-stage development biomarkers with established signals of efficacy. Successful candidates will also be considered for further evaluation embedded into Stage 2 of TRANSFORM as new intervention arms.

1.5.2 Stage 2: Main Trial

Stage 2 will recruit the main participant groups to an RCT that is designed to have sufficient power to evaluate long-term outcomes. This will include invitation to at least two screening rounds using one of the Prostate Health Checks assessed in Stage 1 (deemed as PHC-Optimal in Stage 2). We will continue to collect data on the same diagnostic outcomes as Stage 1, patient reported outcome measures, healthcare resources and cost use at a participant and healthcare system level to estimate cost-effectiveness. We will conduct an NHS care pathway analysis, linked to the health economics analyses to refine costs within the model, and budget impact analysis to determine the healthcare resources and manpower impact if a screening recommendation was made based on the intervention being evaluated. If new screening interventions are added, then as in Stage 1, these will undergo a pilot evaluation first before proceeding to an evaluation of long-term outcomes.

The long-term follow up of trial participants will occur through national database linkage to report on outcomes including cancer specific and all-cause mortality, and use of further tests and treatments for prostate cancer, and the treatment of side-effects and complications from those tests and treatments. These data will be used to provide updates estimates of cost-effectiveness.

During this stage TRANSFORM Discovery will continue to collect, process and store tissue samples and participant-linked multi-modal data. Rapid biomarker testing will be undertaken across the spectrum of prostate cancer management decisions, and programmes of externally-funded discovery science and translational research will be supported. TRANSFORM Discovery will complement the evaluation of TRANSFORM screening strategies by independently testing a portfolio of validated markers for better diagnosis and participant care that could be subsequently introduced into the trial or tested independently. We will also establish a sustainable long-term model for discovery science and translational research, including linkage of biomarker and multi-modal dataset testing.

2. BACKGROUND

2.1. SCREENING FOR PROSTATE CANCER

Each year in the UK, over 50,000 people are diagnosed with prostate cancer and over 12,000 die of the disease. Invitation to regular screening with serum prostate specific antigen (PSA) testing reduced the risk of dying from prostate cancer by about 20% in the European Randomised Study of Prostate Cancer (ERSPC), but with false positives and false negatives, and over-detection with resultant harms1. PSA screening has not been recommended by almost all healthcare systems, including the UK, because analysis based on the randomised trial and other data suggests the harms outweigh the benefits. Several studies summarised in a Cochrane review[2], the US Preventative Services Taskforce[3] and the UK National Screening Committee[4] (NSC) have evaluated the role of PSA testing as a screening strategy. The data in these assessments included the UK Cluster Randomised Trial of PSA Testing for Prostate Cancer (CAP)[5]; Prostate Lung Colorectal and Ovarian Screening trial in the USA[6], European Randomised Study of Screening for Prostate Cancer; Norrköping, Sweden; Quebec, Canada;

Stockholm, Sweden)1. In addition, the Goteborg trial (part of the ERSPC trial) was recently updated with 22 years follow-up[7].

2.1.1 Changes in UK Secondary Care

A UK NSC report published in February 2021 did not incorporate recent changes in the diagnostic secondary care pathway that have occurred in the UK (i.e., multi-parametric MRI, triage to biopsy, targeted biopsy, transperineal biopsy), and the therapeutic pathway (i.e., tissue preserving active surveillance and focal therapy, lower early morbidity from robotic prostatectomy, reductions in healthcare burden from radiotherapy, improvements in survival for metastatic prostate cancer). Despite these changes leading to an improvement in the therapeutic ratio in men diagnosed with prostate cancer in secondary care, the changes have not been formally evaluated in a research study that could usefully inform a screening intervention pathway. Such secondary care changes need to be evaluated in the context of a screening programme to determine whether these changes impacted on the clinical and cost-effectiveness modelling. Furthermore, early reports suggest that incorporation of genetic risk profiling may enrich for clinically significant disease.

2.1.2 Type of Screening Study Design - Pre-Consent or Post-Consent Randomisation

A key decision to make is whether to consent each participant prior to randomisation to an invitation to a screening intervention (also known as an efficacy design and is standard for most RCTs), or to randomise and then obtain consent from those randomised to an invitation to a screening intervention who respond to the invitation (Zelen RCT)[8]. The latter would mean that men who were identified as eligible and assigned to the control group, would not know they were in a control. This is a common design used in screening trials and reduces percentage contamination in the control group, which unarguably affected the eventual outcomes of the negative PLCO RCT in the USA[9]. If the trial design involves consent before randomisation, we expect a higher than usual request for PSA testing by participants in the control group leading to contamination. In other words, the control arm will then not reflect standard UK care at all but is an intervention in which PSA testing is carried out in a higher proportion of men than usual. This undermines our ability to test the effect of the screening intervention against current standard care.

The disadvantage of a Zelen design is a potentially much lower response rate and healthy volunteer bias (where those responding benefit less from the intervention) leading to an underpowered trial. For instance, only 36% accepted the invite and then turned up for the screening test (PSA and biopsy if necessary) in the UK CAP study which used the Zelen design. Accounting for participation at this low level would require a sample size of several million men[10,11]. However, other studies using the Zelen design have demonstrated higher uptake of cancer screening (60-68%), most notably within ERSPC which used repeat screens. One other disadvantage of using a Zelen design would mean that data such as patient reported outcome measures and rates of metastases may be more problematic to collect, certainly from cancer registry data where the outcome of metastases is not systematically and routinely collated at present. This could lead to ascertainment bias and greater missing data on metastases in the control group.

We can learn from screening studies in other disease areas. Particularly pertinent to our consideration is the Flexi-Sig RCT which led to a practice-changing recommendation for screening using flexible sigmoidoscopy for colorectal cancer[12]. In this study eligible participants were sent a questionnaire to assess their interest in having a single flexible sigmoidoscopy screen and those who said they were interested were then randomised using a Zelen design such that only those randomised to the screening invitation from those who responded were later asked for consent at the point of the screening clinic visit. People in the

community were approached with a short letter addressed from their GP asking whether they would be interested, in future, in having the flexible sigmoidoscopy test. The question was phrased as “If you were invited to have the bowel-cancer screening test, would you take up the offer?”. Of 368,142 people approached, 194,726 (53%) responded ‘yes’. From these, 170,432 were randomised (1:2) with 57,237 allocated to intervention. A high proportion of these people (40,674 [71%]) attended their screening visit.

Given the importance in having a trial sample that is representative of the UK population, to robustly evaluate clinical and cost-effectiveness of any screening intervention, we will evaluate whether a similar approach might lead to a high enough acceptance rate for a feasible and adequately powered trial. In the current era there is greater awareness for early diagnosis of cancer and numerous learnings from a body of evidence about how to phrase and construct such an approach (e.g., Prostate Health Check and stepped approach to information giving). In addition, we will further improve and inform the design of a large screening trial for prostate cancer with our proposed qualitative work to evaluate facilitators and barriers to participation and constructing recruitment strategies.

2.1.3 Comparator

Current UK national guidance for the use of PSA testing in the community is determined by the Prostate Cancer Risk Management Programme (PCRMP)[13]. This involves men who are concerned about prostate cancer reading the Prostate Cancer Risk Management Guidance leaflet and speaking to their GP about the advantages and disadvantages of having a PSA test. PSA levels for referral into secondary care are ≥2.5ng/mL for men aged 45-49 years or those with a family history or ethnic risk, ≥3.0ng/mL for men aged 50-69 years and ≥5.0ng/mL for men aged 70-75 years. Although the recent NICE guidance has reverted back to age-specific ranges for men with urinary symptoms (NICE NG12[14]); the PCRMP still recommends a fixed threshold of PSA ≥3ng/mL regardless of age for asymptomatic men.

There is no guidance as to repeat testing in those men who have a baseline PSA under these thresholds. Upon referral to secondary care, men normally undergo a multi-parametric MRI (mpMRI) and those with a negative mpMRI usually avoid a biopsy. An mpMRI takes 30-40 minutes and requires gadolinium contrast injection.

TRANSFORM will therefore evaluate the feasibility of a pre-consent randomisation design in order to ensure standard of care is not contaminated as a result of the actual invitation to join the trial. Our approach is detailed below in the design section and flow charts where we propose to monitor rates of PSA testing and potential contamination (see flowcharts in Section 3.1), by measuring rates of PSA testing in control groups using routinely collected data.

2.1.4. Evaluating the Clinical Utility of Multiple Screening Strategies

Each participant will receive one screening intervention to test the feasibility of each separate screening strategy and its future clinical utility. We would want the interventions to closely reflect their application in real practice. We have considered that there are several highly promising screening strategies that address the issues of over-testing with biopsy and overdiagnosis with radical treatment. There are a number of trial designs that allow for evaluation of multiple screening strategies. Our team has experience in the multi-arm multi-stage (MAMS)[15,16] designs and we have also evaluated and shown the acceptability/feasibility of the cohort multiple RCT (commonly known as Trial WithIn a Cohort [TWIC])[17,18]. During Stage 1 we will evaluate a number of promising screening strategies that use combinations of PSA, Prostagram™ and a polygenic risk score. The overall approach we have proposed enables dropping (following robust independent advice) as well as adding new screening arms (pending appropriate approvals and additional funding).

2.2. RATIONALE FOR SCREENING INTERVENTIONS TO TEST IN TRANSFORM

2.2.1 Prostagram™

The IP1-PROSTAGRAM[19] and ReIMAGINE Screening[20] studies show that MRI might be more accurate for detecting clinically significant prostate cancer than PSA. A Prostagram™ is a simple, non-invasive MRI scan which lasts around 10-15 minutes.

In the IP1-PROSTAGRAM study, 411 volunteers aged 50-69 years were screened using both a PSA test and a Prostagram™. GP practice lists were used to identify men who could be invited to take part and following a GP review of these lists, a short letter with a visual summary of the study was sent to men inviting them to a 'Prostate Health Check'. The study completed recruitment 19 months ahead of schedule. Consenting men had PSA, Prostagram™ and ultrasound test. The Prostagram™ scans were reported by radiologists without knowledge of the PSA test. If either of these tests were suspicious for prostate cancer the participants underwent a prostate biopsy, blinded to which test(s) was positive. Results suggest that Prostagram™ outperformed PSA at detecting aggressive prostate cancer. In total, 4% of men had clinically significant prostate cancer, with 65-82% detected by a Prostagram™ and 41% by PSA ≥3ng/mL. Crucially, if PSA and Prostagram™ were used together, more clinically significant cancers were detected with fewer men needing a biopsy, all without increasing detection of clinically insignificant cancers than PSA testing alone.

One of the potential problems of MRI as used in the current prostate detection pathway with an MRI Score ≥3 is low specificity. PROMIS reported a specificity of 41% for MRI Score ≥3 in men suspected of prostate cancer. In the IP1-PROSTAGRAM screened population, correction methods showed higher sensitivity and specificity for MRI Score ≥4 at 85.1% and 91.9% respectively[21]. It is important for MRI to have a high specificity for significant prostate cancer as even highly specific tests will lead to a high number of false-positive results when applied across a large asymptomatic population with a low disease prevalence, particularly over many screening cycles.

Participants completed validated questionnaires before and after each screening test. The Perceived Burden Questionnaire (PBQ) has been developed for use in studies investigating the acceptability of bowel cancer screening tests and was adapted for the screening tests in this study. We found that the overall level of burden for MRI and PSA was minimal. Few men reported high levels of anxiety, burden, embarrassment or pain following either test. Participants indicated an overall preference for MRI after completing all screening tests[22].

Thirteen hypothetical screening pathways were evaluated including a single test, or PSA and MRI in combination. The pathways can be considered in 3 groups starting from a single test screening strategy (Pathways 1 to 5) to a sequential pathway with PSA ≥1ng/mL as a first-line triage test (Pathways 6-9) and finally a group with PSA ≥3ng/mL as the first line test (Pathways 9-13). A comparison between each combined pathway with the standard pathway found that Pathway 8 which combines an initial low PSA threshold and MRI Score ≥4 would accurately identify most men with prostate cancer while recommending fewer participants for biopsy and reducing false positive rates. This pathway provides an attractive trade-off between maximising detection of significant prostate cancer (2.5%, 95% CI 1.3-4.6) and minimising biopsy rate (7.1%, 95% CI 4.9-10.2). An evaluation of the optimal PSA threshold suggested that 1ng/mL would be an appropriate triage option to provide maximal sensitivity for significant cancer in combination with MRI[23].

The ReIMAGINE Screening study identified men aged 50 to 75, who were identified from participating GP practices and randomly selected for invitation to a screening MRI and PSA[20.] The screening MRI scan consisted of T2-weighted, diffusion-weighted and research-specific

sequences. Men with a positive MRI or a raised PSA density (≥0.12 ng/mL) were recommended to have further standard NHS assessment, with a secondary care mpMRI. Biopsy decisions were based on findings of the mpMRI, in combination with PSA density. Recruitment was paused due to COVID, and then restarted in July 2020. Extensive work with the patient and public panel led to several COVID-modifications to increase the safety of a hospital visit for MRI at that time, leading to completion ahead of the original schedule. Eight GP practices sent invitations to 2,096 men. 457 men (22%) responded, and 303 completed both screening tests. Older white men were most likely to respond to the invitation, with Black men having 20% of the acceptance rate of white men. One in six men (48/303, 16%) had a positive screening MRI, and an additional 1 in 20 men (16/303, 5%) had a raised PSA density. Over half with a positive screening MRI had clinically significant cancer, and 1 in 4 men with a negative MRI but a raised PSA density had clinically significant prostate cancer. After NHS assessment, 29 (9.6%) were diagnosed with GG ≥2 cancer, and 3 (1%) with GG 1. Two in 3 with a positive MRI, and more than half with clinically significant disease, had a PSA <3ng/mL, suggesting MRI and PSA density may be more effective at finding higher grade cancers. The use of an NHS MRI allowed a very low rate of unnecessary and negative biopsies (5 in 303 screened men, 1.6%), and of low-risk prostate cancer diagnosis (3/303, <1%).

As a result of these findings, we believe further evidence on the use different forms MRI in the community are required to gain a better understanding of effectiveness with a larger number of participants as set out in Stage 1.

2.2.2. Polygenic Risk Scores

With the advent of the genome-wide association study (GWAS) and the increasing numbers of cases and controls included in such studies, prostate cancer GWAS and meta-analyses have identified approximately 269 loci associated with prostate cancer development[24–26]. These loci explain an estimated 43% of the familial relative risk of prostate cancer.

Most of these variants are commonly occurring single nucleotide polymorphisms (SNPs, i.e., minor allele frequency [MAF] ≥5%) and although each locus is associated with a low to moderate per allele odds ratio, the genetic risk increases with increasing number of risk alleles in a person's germline DNA as the interaction between risk alleles both within and between loci is log-additive. Then a combination of multiple risk alleles, each with a weak effect, results in a distribution of risk in the population that is sufficiently wide to be useful for risk stratification. The top 1% have an odds ratio of 11.6-fold. With this risk distribution, 50% of the population at highest risk account for 81% of the prostate cancer cases. In 2023 we published an updated multi-ethnic SNP profile which will be applicable to men of both European and African descent of 451 SNPs which will be used in TRANSFORM[27].

The use of a genetic test utilising the known prostate cancer risk SNPs could allow prostate cancer screening to be targeted to men at high risk of prostate cancer development. Germline DNA for genotyping requires a one-off collection, usually in the form of a blood draw or saliva sample. By genotyping the known prostate cancer risk SNPs, a polygenic risk score (PRS) can be calculated for an individual, and combined with age, the absolute risk of having prostate cancer can be estimated for each individual. Individuals would be stratified into different risk groups and the screening strategy (varying by age of start, of stop, and frequency of screening) could be tailored to each risk group. Absolute risk based on polygenic risk score and age would be used to decide to whom and when to offer the screening test, such as MRI and/or PSA.

If prostate cancer screening were to be offered from age 55, then instead of offering screening, for example with MRI, to all men of age 55, screening could be offered to men when they have a 10-year absolute risk equivalent to the 10-year absolute risk at age 55. The use of PRS stratification within a prostate cancer screening programme has been shown through

modelling studies to reduce the level of over-diagnosis and improve the benefit-harm balance of screening, at an incremental cost per quality adjusted life year of between $30,000-40,000[28–30]. With increasing risk threshold compared to age-based screening, risk-stratified screening would be associated with 10% to 73% fewer overdiagnoses and 2% to 15% fewer prostate cancer deaths averted.

The BARCODE1 study (NCT03857477) is the first study to assess the utility of a population prostate cancer screening programme using polygenic risk score stratification. It enrolled men of European ancestry in the UK aged 55-69 from the community via their GP to undergo a germline genetic profile test utilising 130 prostate cancer risk SNPs extracted from saliva. Men in the top 10% of the study population's genetic risk distribution were offered screening with mpMRI of the prostate followed by systematic and targeted transperineal biopsy regardless of PSA level. Uptake was 22%; 6,142 participants had PRS calculated: 745 (12.1%) had a PRS >90th centile and were invited for screening. 468/745 participants underwent both MRI and prostate biopsy detecting 187 (40.0%) prostate cancers. Median age at diagnosis was 64yrs (range 57-73yrs). Using NCCN criteria (2023) 103/187 (55.1%) of cancers were Intermediate or High-Risk; of these 40/187 (21.4%) were 'Intermediate Unfavourable'/'High'/'Very High-Risk'. Only 30 cancers would have been detected, missing 74 of the clinically significant cancers, following the UK prostate cancer diagnostic pathway having both PSA ≥3.0ng/mL and MRI lesions. As the PRS used in BARCODE1 is based on SNPs discovered in European populations, it cannot be applied to men of other ethnicities. Although multi-ethnic GWAS have demonstrated that many prostate cancer risk SNPs are shared between populations, the risk associated with a variant may vary according to ethnicity. Additionally, some prostate cancer risk SNPs will be population specific. Further studies are underway to investigate the use of genetic profiling in prostate screening in other ethnic groups[31].

2.2.3 Clinically Significant Prostate Cancer on Biopsy

We know that some prostate cancers are clinically significant, and that other prostate cancers are clinically insignificant. Whilst there is still some uncertainty about exactly what entails clinical significance, particularly with respect to whether men diagnosed with low volume Gleason 3+3 or Gleason 3+4 cancer should be on active surveillance, most physicians, researchers and guideline panels agree detection of Gleason 3+4=7 (or World Health Organisation [WHO] / International Society of Uropathology [ISUP] Grade Group 2) or greater is the key target condition for any diagnostic pathway. As a result, this is the primary histological threshold we will measure for stage 1. There is also acknowledgement that a low amount of cancer or low percent pattern 4 is perhaps not as aggressive. So, whilst we define 'clinically significant prostate cancer' to be the detection of any Gleason 3+4 or greater, there are important secondary definitions of clinical significance that we will measure as well. These definitions will incorporate the wide and divergent views on clinical significance as well as evidence on the relevance of amount of pattern 4 and maximum cancer core length. Therefore, our other definitions will be:

- any amount of Gleason 4+3=7 or more,
- any amount of Gleason ≥4+3 OR Gleason 3+3=6 of ≥6mm (PROMIS definition 1)
- any amount of Gleason ≥3+4 OR Gleason 3+3=6 of ≥4mm (PROMIS definition 2)
- any amount of Gleason ≥3+4 OR Gleason 3+3=6 of ≥6mm[32]

3. OBJECTIVES

Objectives are listed below and outcomes are listed in the Statistical Analysis section (Section 10).

3.1. STAGE 1: PILOT AND FEASIBILITY

3.1.1. Trial Design Optimisation

Assess feasibility of pre- and post-randomisation consent designs in terms of screening uptake (overall and in specific sub-groups) and rates of contamination in the control groups.

Investigate which recruitment approaches are most effective in terms of rate of recruitment, number of men recruited in specific sub-groups and uptake of screening.

Investigate barriers and facilitators to participation in, and compliance to, screening interventions at each screening round within different socio-economic, ethnic and vulnerable groups in the community and if necessary, create strategies to improve participation and compliance.

3.1.2. Pilot Prostate Health Checks

Evaluate biopsy rates, early-stage high, intermediate and low risk prostate cancer detection rates and model cost-effectiveness of the different intervention arms.

Management of prostate cancer, testing and treatment relative adverse events and side effects.

3.1.3. TRANSFORM Discovery

Operationalise TRANSFORM Discovery through optimisation and establishment of a bio-digital twin comprising a trial related tissue collection, multi-omic tissue processing, digital pathology and imaging data matched with clinical data from the main TRANSFORM database.

3.2. STAGE 2: MAIN TRIAL

3.2.1. Long Term Cancer Outcomes

Evaluate prostate cancer mortality and prostate cancer metastases.

Evaluate prostate cancer incidence.

Biopsy rates, early stage high, intermediate and low risk prostate cancer detection, management of prostate cancer, testing- and treatment-related adverse events and side effects.

3.2.2. Costs and Cost-Effectiveness

Estimate the cost-effectiveness of strategies based on the screening intervention, compared with the current UK standard of care and update these estimates as the trial progresses.

Carry out a care pathway analysis and budget impact analysis to determine resource and manpower implications of a screening recommendation within the UK healthcare system.

3.3 TRANSFORM Discovery

TRANSFORM Discovery will deliver digital data and biospecimen collection from the trial and undertake (i) biomarker testing at scale and pace, (ii) accelerate translational & discovery science, and (iii) establish a sustainable long-term Bio-Digital Twin model.

Biomarker testing will be undertaken, with embedded health economic evaluations, to deliver rapid real-time testing of biomarkers in collaboration with academic and commercial partners. TRANSFORM Discovery will facilitate exploratory simulations of novel strategies of healthcare delivery though data modelling to inform development of new hypotheses for prostate cancer management.

4. STUDY DESIGN

Our screening study includes 2 stages.

Stage 1 will pilot multiple interventions to determine the optimal screening strategy to take forward into Stage 2, assess the feasibility of two trial designs (of which the optimal design will be taken forward to Stage 2), and determine feasibility and resource implications of setting up TRANSFORM Discovery.

Stage 2 will recruit to a large RCT with at least 2 screening rounds with long term follow-up for cancer control outcomes.

TRANSFORM is intended as a platform trial that allows additional screening tests to be evaluated in future, using the same trial infrastructure.

4.1. FLOWCHARTS

4.1.1. Stage 1

We will evaluate the feasibility of two trial designs, evaluating a post-consent and pre-consent randomisation approach.

We will initially randomise, prior to consent, eligible participants in the community between the Design 1 Research Cohort and the Design 2 study arms (Pre-consent Control group, and one of four arms evaluating different screening strategies (Prostate Health Checks [PHCs]).

4.1.2. Stage 1: Design 1

Eligible men in the community who have been randomised to the Design 1 Research Cohort will be invited to consent to join the TRANSFORM study as a member of the TRANSFORM Research Cohort. More specifically, we will ask eligible men to consider taking part in a study to assess the value of Prostate Health Checks.

Those ultimately randomised to be invited to join the study will undergo a two-step consent process. In the first step (prior to randomisation to a PHC), they have the option to consent to long-term, related health data collection, and future contact for participation in research opportunities arising in TRANSFORM (the Research Cohort). In the second step, those eligible and selected from the Research Cohort will be randomly allocated to either a control group (post-consent randomised control, Control 1) or one of four PHCs. Those randomised to a PHC will then be invited to consent to receive it. Men will only be aware of the details of the PHC they are randomly allocated to, and this will be explained in the Participant Information Sheet.

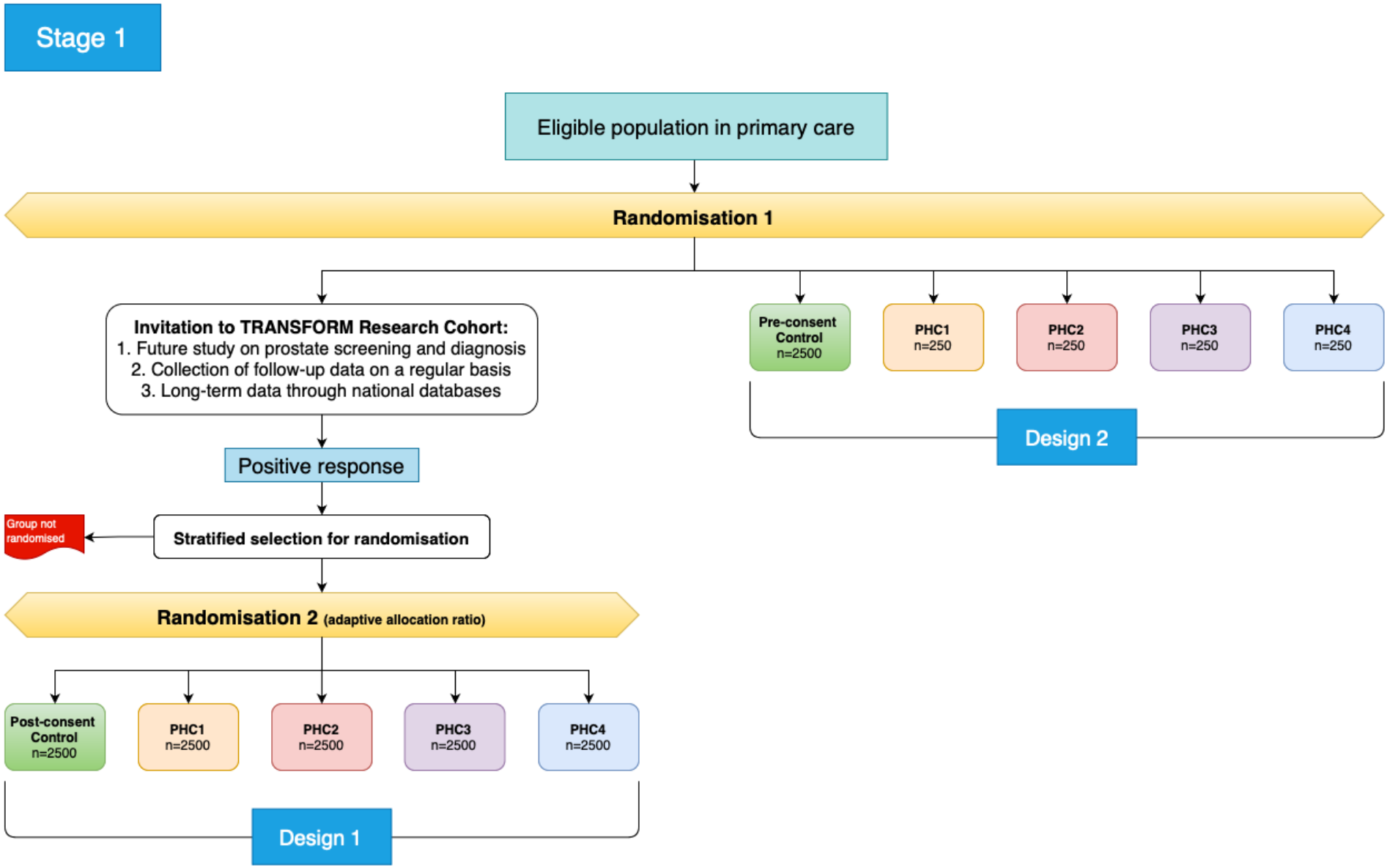
4.1.3. Stage 1: Design 2

We will evaluate a pre-consent randomisation design (a Zelen design) where eligible men will be allocated at random to receive a direct invitation to a specific Prostate Health Check (either of PHC1, PHC2, PHC3 or PHC4).

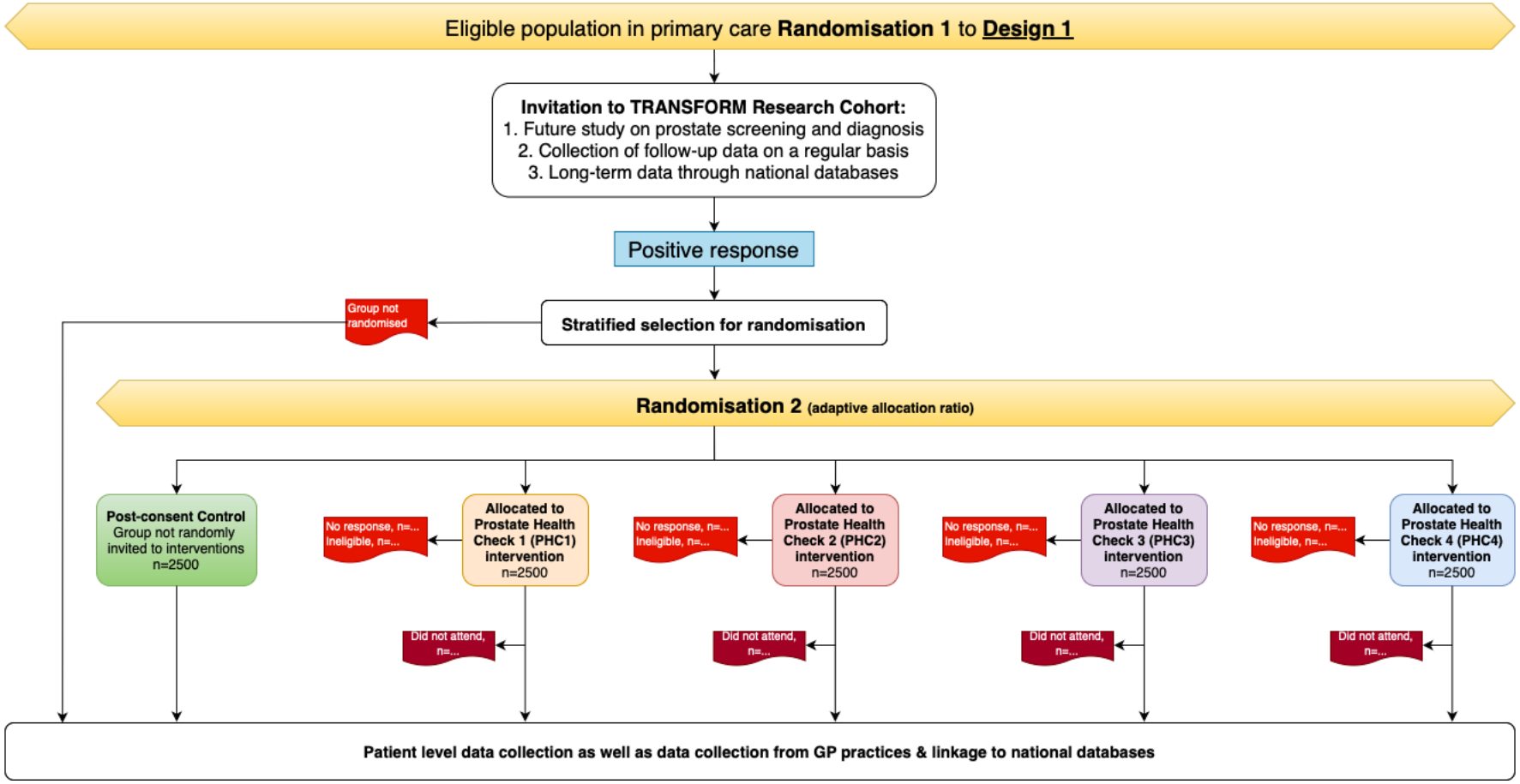
Those not randomised to a PHC will be randomised to the pre-consent control arm (Control 2). Given that randomisation will occur pre-consent, participants in Control 2 will not be aware they are in the trial, nor that they are in a control group. Participants in this control group will continue in the standard of care with their GP.

4.1.4. Stage 2

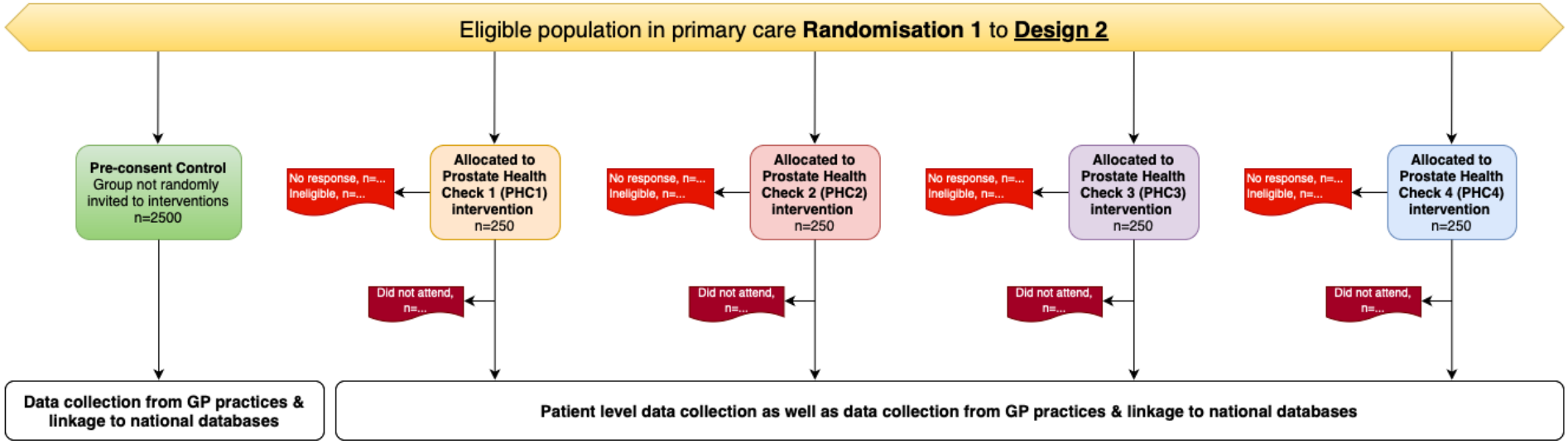
The trial design for the main trial will be determined following review of outcomes from Stage 1. A substantial amendment will be submitted for this purpose.


Stage 1
Eligible population in primary care
Randomisation 1
Invitation to TRANSFORM Research Cohort:
1. Future study on prostate screening and diagnosis
2. Collection of follow-up data on a regular basis
3. Long-term data through national databases
Pre-consent Control n=2500
PHC1 n=250
PHC2 n=250
PHC3 n=250
PHC4 n=250
Design 2
Positive response
Group not randomised
Stratified selection for randomisation
Randomisation 2 (adaptive allocation ratio)
Post-consent Control n=2500
PHC1 n=2500
PHC2 n=2500
PHC3 n=2500
PHC4 n=2500
Design 1

Design 1


Eligible population in primary care **Randomisation 1** to **Design 1**
Invitation to TRANSFORM Research Cohort:
1. Future study on prostate screening and diagnosis
2. Collection of follow-up data on a regular basis
3. Long-term data through national databases
Positive response
Group not randomised
Stratified selection for randomisation
Randomisation 2 (adaptive allocation ratio)
Post-consent Control Group not randomly invited to interventions n=2500
No response, n=... Ineligible, n=...
Allocated to Prostate Health Check 1 (PHC1) intervention n=2500
Did not attend, n=...
No response, n=... Ineligible, n=...
Allocated to Prostate Health Check 2 (PHC2) intervention n=2500
Did not attend, n=...
No response, n=... Ineligible, n=...
Allocated to Prostate Health Check 3 (PHC3) intervention n=2500
Did not attend, n=...
No response, n=... Ineligible, n=...
Allocated to Prostate Health Check 4 (PHC4) intervention n=2500
Did not attend, n=...
Patient level data collection as well as data collection from GP practices & linkage to national databases

Design 2


Eligible population in primary care **Randomisation 1** to **Design 2**
Pre-consent Control
Group not randomly invited to interventions
n=2500
No response, n=...
Ineligible, n=...
Allocated to Prostate Health Check 1 (PHC1) intervention
n=250
Did not attend, n=...
No response, n=...
Ineligible, n=...
Allocated to Prostate Health Check 2 (PHC2) intervention
n=250
Did not attend, n=...
No response, n=...
Ineligible, n=...
Allocated to Prostate Health Check 3 (PHC3) intervention
n=250
Did not attend, n=...
No response, n=...
Ineligible, n=...
Allocated to Prostate Health Check 4 (PHC4) intervention
n=250
Did not attend, n=...
Data collection from GP practices & linkage to national databases
Patient level data collection as well as data collection from GP practices & linkage to national databases

5. STAGE 1: PARTICIPANT ENTRY

5.1. STUDY SETTING AND POPULATION

5.1.1. GP practice search criteria

These will be defined in a Recruitment SOP.

5.1.2. Age Group for Recruitment

Higher age ranges will confer higher rates of cancer likely to impact on life expectancy, so a screening effect is more likely to be seen with a more cost-efficient trial if older men are included. An upper threshold of age to 74 years is included to reflect PPI feedback and the increasing life expectancy in the UK. We will endeavour to ensure that men with significant other co-morbidities highly likely to impact 10-year life-expectancy are excluded.

We will monitor recruitment to ensure appropriate representation of all age groups in those who receive a PHC, and will use a stratified approach to recruitment where needed.

5.1.3. Diversity of Recruitment and Specific Targets for Recruiting Black Men

We aim to ensure that both those invited and those who take part in the active arms of the trial are representative of the male population of England and Wales aged 50-74 years. TRANSFORM aims to ensure adequate representation of all major ethnic groups and men from all levels of deprivation are included in reasonable numbers. This does not mean that the proportion from each group should exactly mirror that of the population. For example, the study will aim to over-recruit Black men as current evidence shows that this ethnic group are at increased risk of prostate cancer. We would also like to over-recruit participants from more deprived areas and other minority ethnic groups as such groups have generally poorer health outcomes arising from the social determinants of health. Additionally, these groups are usually substantially under-represented in clinical trials. The recruitment strategy will therefore aim for equity rather than equality.

Specifically, in Stage 1, we aim that Black men will be over-represented in the invited population by a factor of at least three, and that at least twice as many people in the lowest quintile of the index of multiple deprivation will be invited compared with the highest quintile. 10% of the invited population will be Black. We will achieve this by recruiting to the trial from areas in England with higher ethnic diversity than overall (particularly London), and by recruiting Black men from a younger age (45 years and above) than other ethnicities. We will also prioritise high deprivation areas around the country. This will be done both at an area level (e.g., London), as well as a local level (e.g., inviting from GPs that serve more deprived and ethnically diverse populations).

Our diversity target is based on data from the 2021 census in England and Wales where approximately 3.1% of males aged 45-75 years in England and Wales were Black (325,610/10,642,215). If uptake is at least one third for Black vs other ethnicities, then at least the population frequency of Black men will be represented in the active trial arms. There is mixed data on this: in IP1-PROSTAGRAM it was approximately 8:9; whereas in ReIMAGINE screening it was approximately 1:5 probably reflecting the latter recruiting during Covid. Therefore, whilst the worst-case scenario is achieving a percentage of Black men that reflects the general population, given optimal circumstances and optimised recruitment strategies using our qualitative and PPIE work, we anticipate surpassing this baseline percentage. We will use data from Stage 1 on uptake to inform recruitment strategies in Stage 2 to ensure our

targets are met for the main trial, as well as determining whether a Zelen design is feasible with such a targeted recruitment approach, as well as variation in rates of contamination.

Our recruitment strategy will identify eligible participants from GP practices across the UK, and then invite a proportion of men to participate in TRANSFORM. Electronic GP records will be searched to identify potentially eligible participants. They will be sent information about our study from their named GP as endorsement.

Community champions and organisations will help raise awareness and facilitate recruitment, This approach was piloted IP1-PROSTAGRAM which, of its 411 participants, recruited 32% Black men and 23% Asian.

Information sheets and recruitment materials will be available in easy read/simple English formats and recruitment strategies will be developed in conjunction with PPIE groups. During Stage 1, the TRANSFORM Behavioural Sciences Subgroup will assess the linguistic needs of participants in the regions targeted for recruitment. This assessment will explore the languages most commonly spoken and determine whether translated study materials are required to support participant comprehension and inclusivity. In addition, the team will evaluate the appropriate formats and delivery methods for these materials to ensure accessibility. Extensive engagement with patients and the public (PPI) will be undertaken to inform these decisions. Insights gathered through this engagement will guide the development and provision of translated materials, where appropriate, for use in Stage 2 of the study. Recruitment strategies will additionally be developed in conjunction with PPIE groups.

Accessible, easy read participant information sheets will be provided to facilitate understanding. For those who lack capacity (e.g. those with severe learning disability), a personal consultee (e.g. relative or a friend) will be approached and provided with a consultee information form. Their views about the individual's participation in the study, in particular, the participant's wishes and feelings about taking part, will be sought, and if they agree, they will be asked to sign a declaration form. In the absence of a personal consultee, a nominated consultee (e.g. a clinician involved in the individual's care but not directly with the study) will be approached and provided with a nominated consultee form. Participants will only be enrolled into the study if the consultee has agreed to their participation.

5.2. ELIGIBILITY CRITERIA

5.2.1. Eligibility Check 1

The following criteria will first be applied prior to randomisation through assessment of primary care records.

- **Inclusion Criteria**
  - Men in the general population aged 50-74 years.
  - Additionally, men aged 45-49 years who self-identify in GP practice lists as of Black ethnicity.
  - Additionally, men aged 45-49 years who are on the GP learning disability Quality Outcome Framework (QOF) register.

- **Exclusion criteria**
  - History of prostate cancer (clinical diagnosis or histological).
  - Known history of one or more PSA tests, prostate MRI scans, prostate biomarker tests or prostate biopsies in the preceding 5 years.
  - Known use of androgen deprivation therapy, androgen receptor (AR) targeting agents, and oestrogens (N.B. 5-alphareductase inhibitors and testosterone supplementation are both permitted).

- Culture proven urinary tract infection in the 3 months prior to screening even if subsequent culture shows no urinary infection prior to screening.
- Significant co-morbidities or other cancers likely to impact on their life-expectancy in the next 10 years.

5.2.2. Eligibility Check 2: Pre-Consent

Prior to consent, all participants invited to join the TRANSFORM study will be asked to self-report the above inclusion and exclusion criteria (excluding GP registered learning disability, and significant comorbidity which will both be assessed solely through GP search criteria using clinical coding) to confirm their eligibility. Self-report In Design 1 will be assessed prior to randomisation to PHC at the time of invitation to the TRANSFORM Research Cohort. In Design 2 the self-report will be completed after randomisation to PHC.

6. PROCEDURES AND MEASUREMENTS

6.1. SCREENING INTERVENTIONS

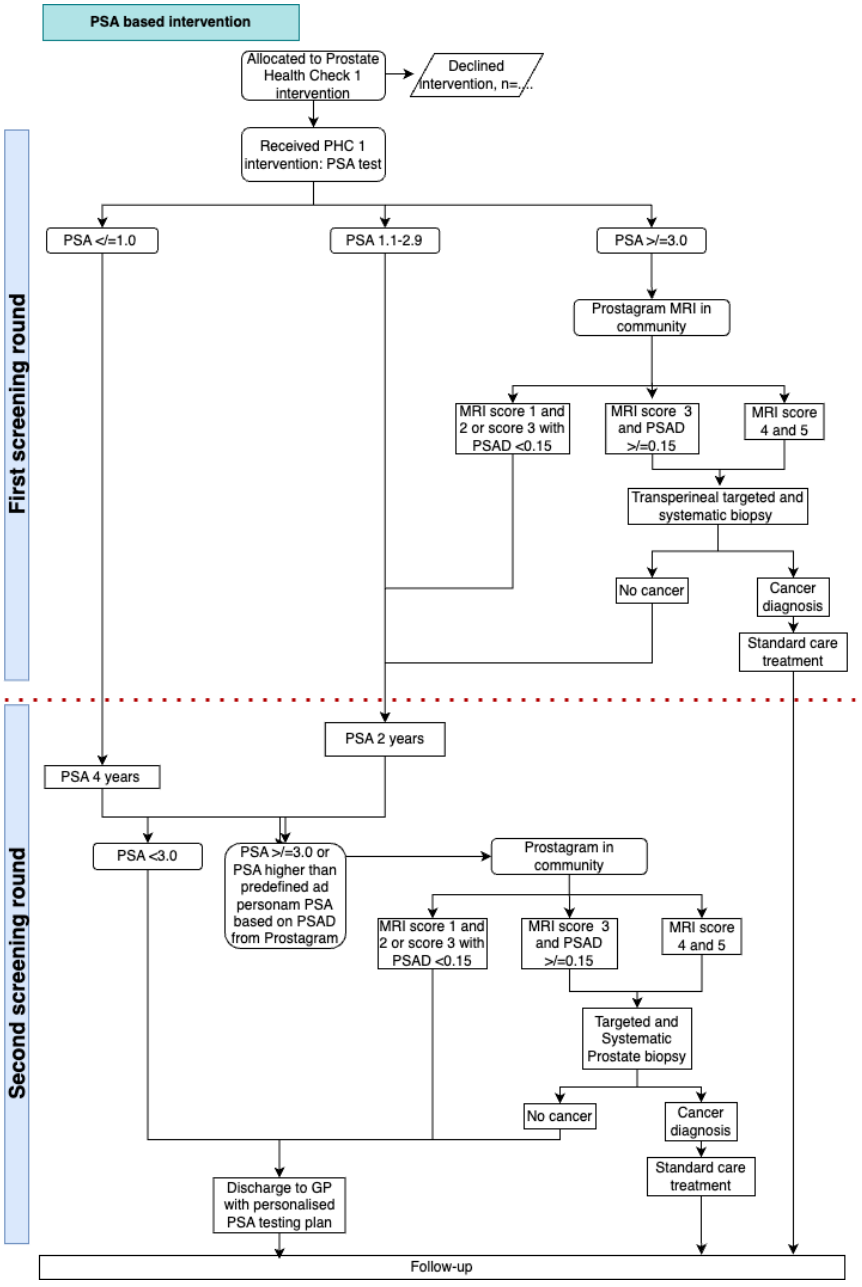
There are a number of screening strategies that the NSC and the Prostate Cancer UK (PCUK) health economics reports identified to be ready for a randomised trial. We discussed these strategies in the joint National Cancer Research Institute (NCRI)/PCUK Screening Study Proposal Development Group (May 2022). We have detailed the evidence behind these and the current uncertainties upon which we have determined the make-up of each arm. This will minimise any cross-over risk as we will not be emphasising a particular test such as germline genetics or MRI. The four strategies, known as Prostate Health Checks (PHC), will be:

- **PHC1:** Prostagram™ MRI in men who have a PSA ≥3ng/mL. For men aged 45 to 49 years who self-identify as Black, or those men who have a first-degree relative (father, brother, son) with a history of prostate cancer, the PSA threshold for a Prostagram™ MRI will be ≥2.5ng/mL
- **PHC2:** Prostagram™ MRI in men who have a PSA of ≥1ng/mL
- **PHC3:** Prostagram™ MRI in all
- **PHC4:** Polygenic risk score (PRS) stratification followed by Prostagram™ MRI in those with an absolute risk of developing significant prostate cancer in the following 10 years of ≥3.5%.

6.2. PROSTATE HEALTH CHECK 1

PSA test followed by Prostagram™ MRI if PSA ≥3ng/mL. The ERSPC PSA screening trial conducted in 7 European countries found that using a PSA threshold of 3ng/mL or above to recall men for further diagnostic tests reduces prostate-cancer mortality in the long-term. However, the strategy also led to significant over-detection and over treatment, which outweighed the benefits. PSA screening with this threshold with new (secondary care) standards based on pre-biopsy MRI and triage to targeted and systematic transperineal biopsy, as well as use of active surveillance and minimally invasive treatments, may reduce the harms reported with this strategy and tip the balance in favour of PSA screening. A PSA threshold of ≥3ng/mL will therefore be adopted for PHC1. For men who self-identify as Black or who have a first-degree relative with a family history of prostate cancer, the PSA threshold for community-based Prostagram™ MRI will be ≥2.5ng/mL.

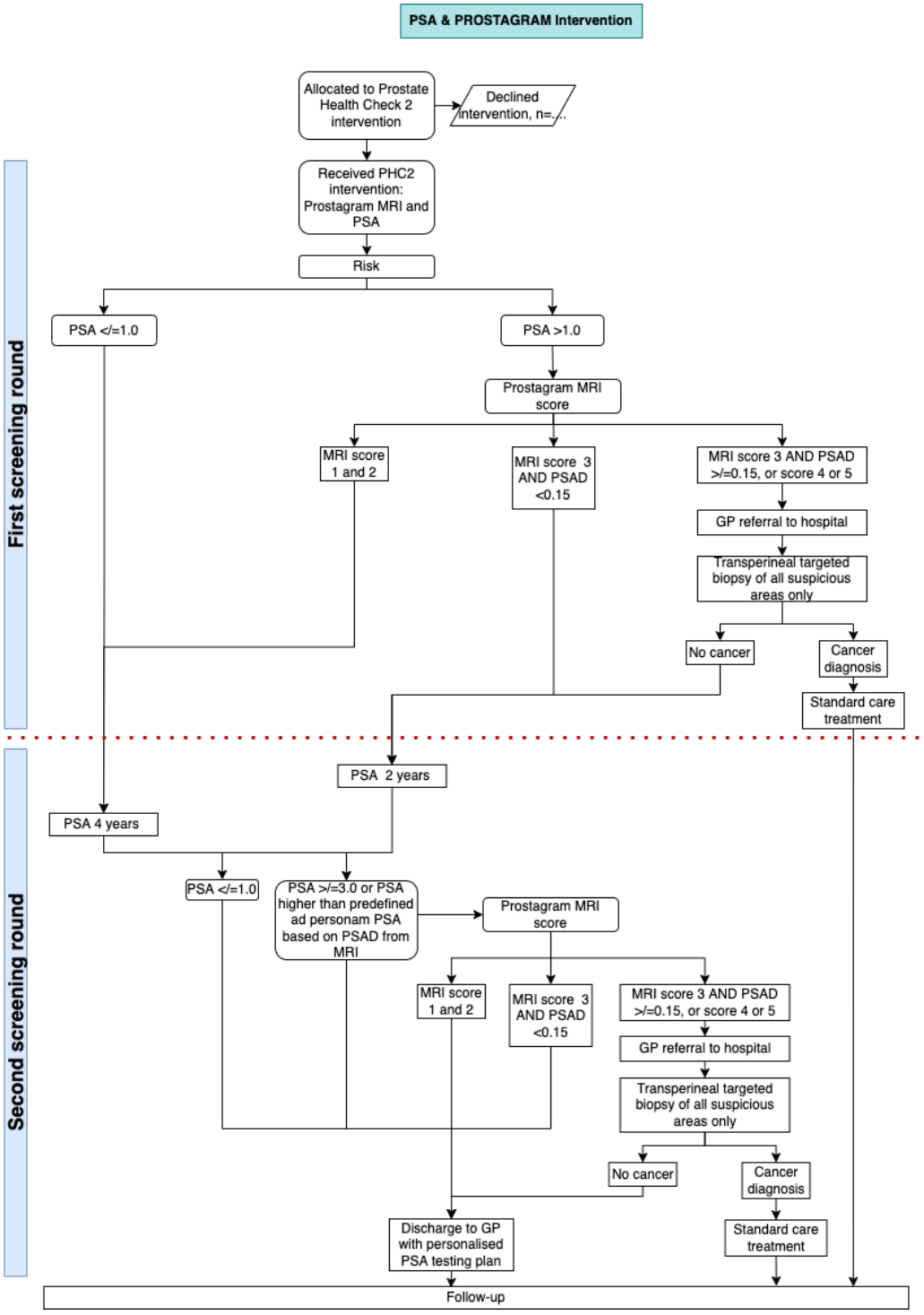
N.B. Only one round of screening will be completed in Stage 1, pilot phase.



6.3. PROSTATE HEALTH CHECK 2

PSA test followed by Prostagram™ MRI in the community if PSA ≥1ng/mL. Evaluation of optimal strategies from the findings of the IP1-PROSTAGRAM and ReIMAGINE Screening studies suggest that using this lower PSA threshold to trigger MRI can optimise cancer detection rates compared to the traditional cut-off of 3ng/mL or greater whilst ensuring biopsy rates remain appropriate. Further, Swedish and US population data demonstrates the ability of a PSA threshold of approximately 1ng/mL to rule-out life-threatening prostate cancer[37-38].

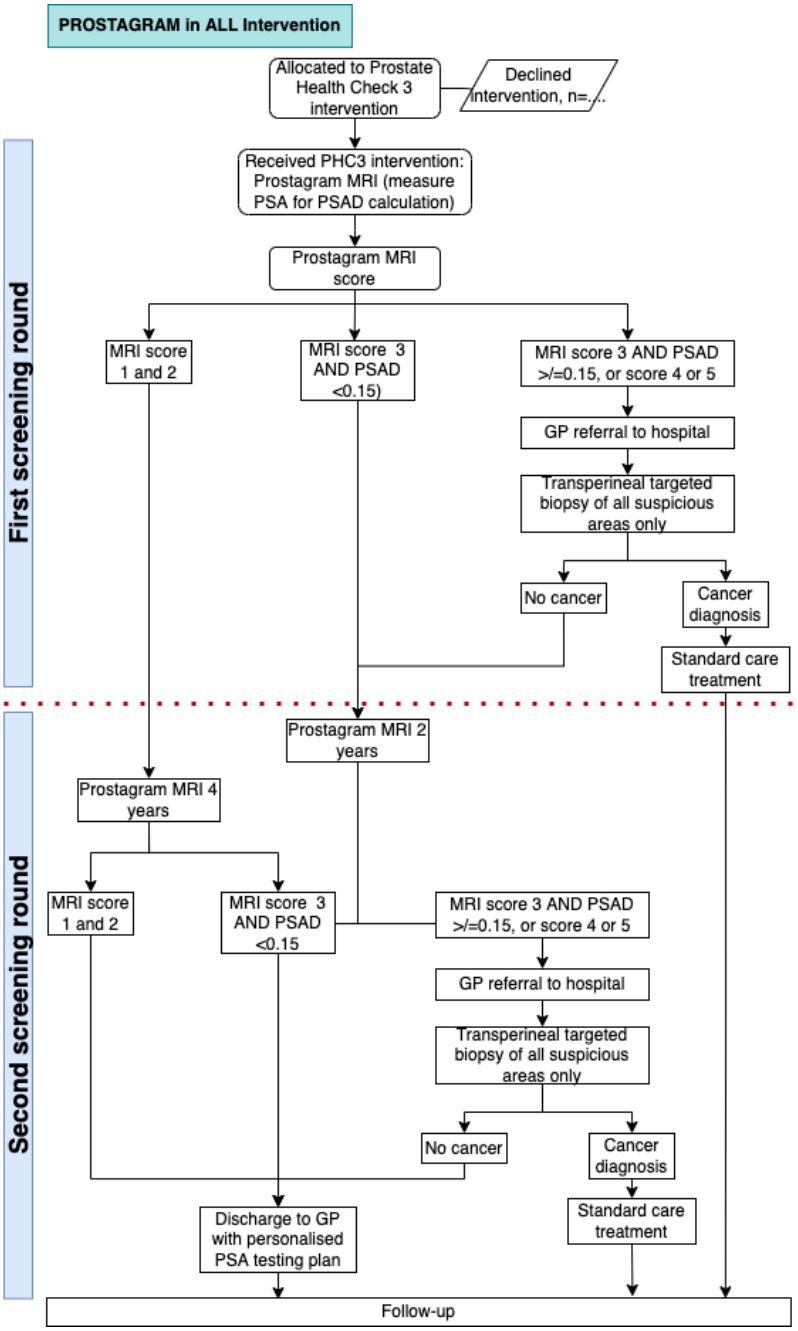
N.B. Only one round of screening will be completed in Stage 1, pilot phase.



6.4. PROSTATE HEALTH CHECK 3

Prostagram™ MRI in all men in the community, with PSA level taken for derivation of PSA density only. Both the IP1-PROSTAGRAM and ReIMAGINE screening studies employed upfront MRI and did show that some cancers of a significant nature were missed in men when the threshold PSA of 1ng/mL was applied but detected by a Prostagram™ MRI. The number of missed cancers varied between the two studies, likely reflecting different populations, different recruitment strategies and different approaches to what constituted a positive screening MRI, as well as the downstream tests offered. As a result of this uncertainty, there is a requirement to formally evaluate this arm in a larger cohort of men.

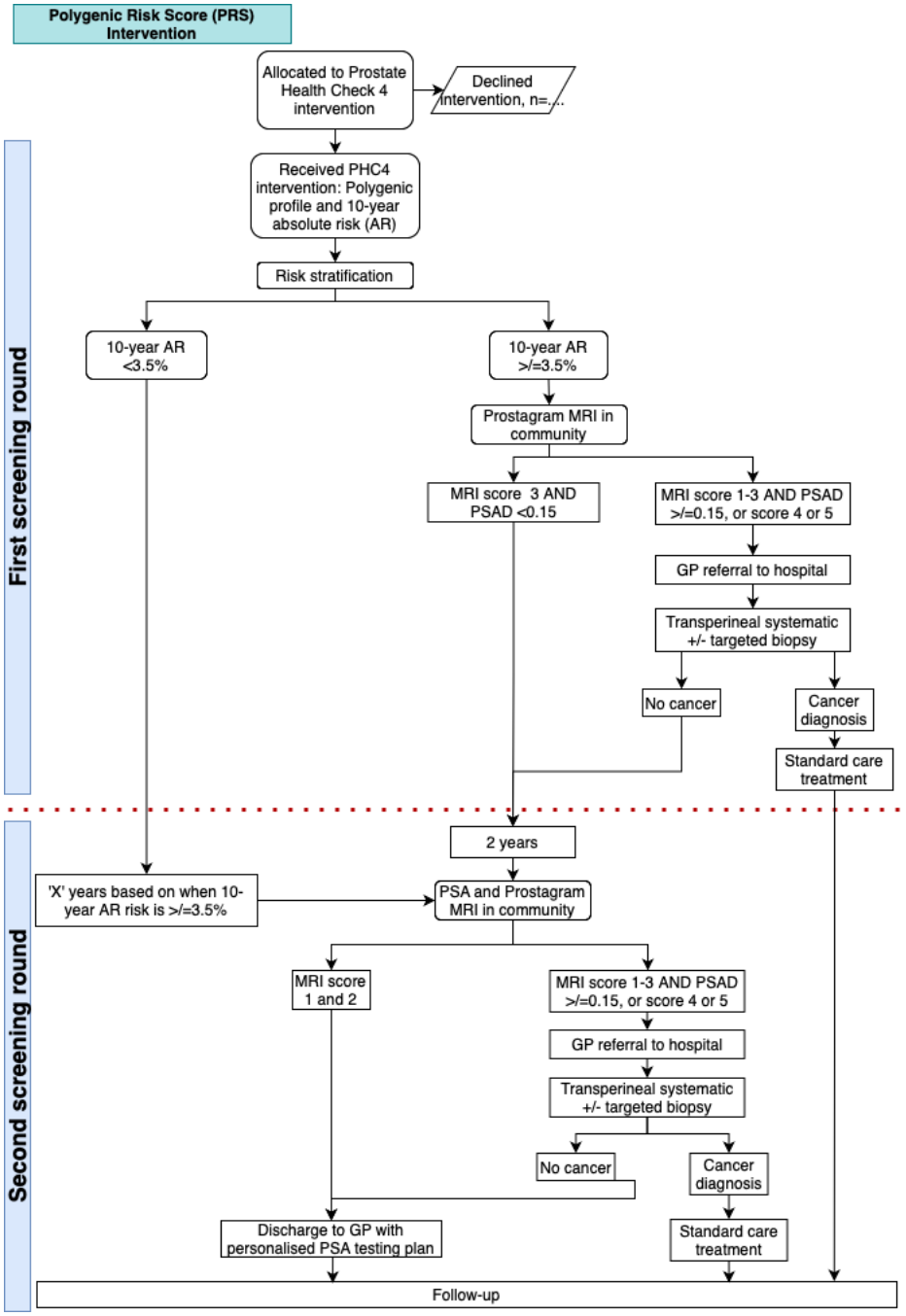
N.B. Only one round of screening will be completed in Stage 1, pilot phase.



6.5. PROSTATE HEALTH CHECK 4

Polygenic Risk Score to determine which men get an upfront Prostagram™ MRI and determine the interval for subsequent screening rounds. This will involve a saliva-based germline genetic test followed by MRI in those with the highest age-stratified genetic risk. The BARCODE 1 study showed that offering MRI and biopsy to those at highest genetic risk of significant prostate cancer detects substantially more prostate cancers that require treatment than PSA testing.

N.B. Only one round of screening will be completed in Stage 1, pilot phase.



6.6. PROSTAGRAM™ MAGNETIC RESONANCE IMAGING

6.6.1 Prostagram™ MRI Conduct

The Prostagram™ MRI will be a short non-contrast MRI using T2-weighted images and diffusion images. The exact parameters used for the conduct of the scan are detailed in a separate Prostagram™ MRI Conduct SOP.

6.6.2. Quality Assurance and Quality Control of Prostagram™ MRI

A separate MRI QA/QC SOP will be drafted building on our experience in the PROMIS, PICTURE, PRECISION, PRIME, IP7-PACIFIC, ReIMAGINE Screening and IP1-PROSTAGRAM studies. Scanners will be either 1.5T or 3.0T in order to reflect current UK practice at each recruiting centre and would need to meet the required standards set out for the UK as stipulated in the recent NICE guidance (2019) and reflecting recent expert radiology consensus39. Our lead radiology co-applicants alongside the National Cancer Imaging Translational Accelerator (NCITA) imaging QA/QC process will conduct a quality review of MRI scans of all scanners prior to recruitment and optimise where necessary.

NCITA will quality control MRI scans. Standardisation meetings will be held prior to recruitment to ensure all radiologists work to the same reporting standards and biopsy operators carry these out following the standard operating protocol. The study will use the NCITA MR Core Lab's basic level of service. This involves the evaluation, qualification and periodic re-qualification of all MR scanners involved in the study, access to study template documents, and assistance in the harmonisation of a locked-down imaging protocol. This will ensure all scanners are capable of acquiring quality data throughout the study duration. Stage 1 will use the NCITA MR Core Lab's advanced level of service. In addition to scanner qualification, this also includes fully-auditable repository-integrated data quality control (imaging protocol checking and visual assessment) and locked-down data analysis via XNAT of all MR imaging data and quality management reporting via Q-pulse.

6.6.3. Radiology Expertise

Prostagram™ MRI reporting will involve training and standardisation meetings. Reporters will be those with a significant experience of reporting secondary care prostate MRI scans.

6.6.4. Prostagram™ MRI Reporting Scheme

A standardised reporting proforma will be used.

6.7. TARGETED ONLY TRANSPERINEAL BIOPSY

Centres will use local anaesthetic transperineal targeted biopsy only. Sedation or general anaesthetic will be reserved for those participants unable to tolerate a local anaesthetic procedure. Visual-registration or image-fusion targeting will be permitted. The exact anaesthesia type (local only, sedation, general anaesthetic) and biopsy type (image fusion vs visual-registration) will be recorded. Six cores per target and unlimited number of targets will be sampled, dependent on the Prostagram™ MRI findings[40-42]. Full biopsy procedure information is set out in the Biopsy Conduct SOP.

6.7.1 Histology

The histological report will evaluate the following aspects for each targeted biopsy carried out according to Royal College of Pathology (UK) guidance: number of biopsies, number positive

for cancer, core length in mm, cancer presence, maximum cancer core length in mm (where continuous and discontinuous numbers are given, for the purpose of analysis, the continuous number will be used), primary, secondary and highest Gleason grade, percentage of Gleason pattern 4 and presence of cribriform pattern when Gleason 3+4, perineural invasion/lymphovascular invasion/intraductal components/neuroendocrine differentiation; and other features (high grade prostatic intraepithelial neoplasia/atypical acini/inflammation/atrophy)[43]. Full details are set out in the Biopsy Reporting SOP.

6.8. VALIDATED PATIENT REPORTED OUTCOME MEASURES

Questionnaires can be completed on paper and uploaded to the eCRF or completed electronically. We will ask for consent from participants to be contacted by the central study team in order to issue and collate these directly from the central trials team. Completeness of data and questionnaire response rates is an important outcome as it informs our analysis of side-effects and adverse events. We will prompt participants to complete the questionnaires sent to them by text or email with up to two reminders; this will be coordinated by the central trials team. The researchers at the participating centres may also co-ordinate with the departmental clinic appointments in order to hand the questionnaires to the participant personally.

N.B. Participants in Control 2 (Zelen/Design 2) **will not** receive **any** questionnaires throughout the study.

All PHC participants: All PHC participants will complete the **EQ-5D-5L** validated Patient-Reported Outcome Measures (PROMs) as a generic measure of health-related quality-of-life which can be linked to public preferences.

The EQ-5D-5L (or equivalent, modified EQ-5D-3L (Learning Disability) or EQ-5D-5L Proxy version 2) will be administered at baseline and annually for up to 15 years following consent.

Participants randomised to Control 1 will receive the EQ-5D-5L or equivalent.

PHC and Control 1 participants will additionally complete an annual **Health Service Use questionnaire** for comparative health economics analysis, to capture information on the utilisation of health and social care services. This questionnaire will be implemented following Patient and Public Involvement (PPI) review and subsequent approval via a study amendment.

Participants undergoing a Prostagram™ MRI: A questionnaire on Prostagram™ MRI related side-effects will be given to all participants to be completed after the MRI scan but before the biopsy (if they have a biopsy).

Participants undergoing biopsy: Adapted versions of the **PROBE** questionnaire will be used. Participants perceptions of the biopsy will initially be assessed within 24 hours of biopsy by self-report of pain and discomfort (referred to as pain hereafter) and reassessed at 35 to 90 days post biopsy. Specific related complications such as fever, flu-like shivers, pain, haematuria, haematochezia, and haemoejaculate will additionally be self-reported at 7 days and 35 to 90 days after prostate biopsy as absent or present following biopsy on a purpose designed questionnaire. For each symptom, participants will be asked to score the degree of “problem” as not a problem, minor, moderate, or major. This will be used to derive a binary outcome for each symptom (present/moderate/severe problem vs. absent /minor problem).

For participants undergoing biopsy, functional status will be assessed using the **EPIC-26 Short Form** instrument and where appropriate the **SMACS** tool, initially within 24 hours of biopsy and annually thereafter.

Timelines for all Health Economic and main trial questionnaires are outlined below.

6.9. HEALTH ECONOMICS AND MAIN TRIAL QUESTIONNAIRES (WITH TIMEPOINTS)

Baseline

- EQ-5D-5L, modified EQ-5D-3L (Learning Disability) or EQ-5D-5L Proxy version 2 (all trial arms and Control 1 - subgroup only)

After MRI but before biopsy

- Prostagram questionnaires (All participants who received an MRI)

Day of biopsy (after biopsy completion)

- PROBE – Biopsy details and perceptions
- SMACS/IPSI
- EPIC-26 Short Form

7 days after biopsy

- PROBE - General symptoms

35 - 90 days after biopsy

- PROBE – Perceptions and general symptoms
- SMACS/IPSI

Annually (for up to 15 years post consent)

- EQ-5D-5L, modified EQ-5D-3L (Learning Disability) or EQ-5D-5L Proxy version 2 (all trial arms and Control 1 - subgroup only)
- SMACS/IPSI (to be completed by participants who received a biopsy).
- EPIC-26 Short Form (to be completed by participants who received a biopsy).
- Health Service use questionnaire (all PHC arms and Control 1) - N.B. Following PPI review and subsequent study amendment.

There will be a 14-day data collection window for all timepoints. An email reminder will be sent to individual participants after 7 days if the data has not been submitted.

6.10. PROCESS EVALUATION ON STUDY AND SCREENING PARTICIPATION FOR OVERALL STUDY POPULATION AND ETHNIC GROUP

Participant Acceptability Measures

All participants will be either sent an email or text message with a link to online questionnaires (or mailed questionnaires if they have expressed a preference for this).

These questionnaires will consist of:

6.11. BEHAVIOURAL QUESTIONNAIRES (WITH TIMEPOINTS)

Baseline

- **Demographics questionnaire**, adapted from the DISTINCT questionnaire (all participants except control 2).
- **EPIC-26 Short Form** (Items 1 – 5) - Urinary symptoms, (all participants except control 2).
- **GAD-7**, a screening tool and severity measure for generalised anxiety disorder (GAD-7). This 7-item, highly sensitive scale has been widely used to measure generalised anxiety in various participant populations, including cancer studies[44] (all participants except control 2).
- **Cancer Worry Scale (CWS)** adapted to prostate cancer, to assess concerns about developing cancer and the impact of such concerns on daily functioning. Taken together these two measures will give a composite score that measures both state anxiety and cancer-specific worry[45] (all participants except control 2).
- **Health behaviour and family history questionnaire** (all participants except control 2 and those who are diagnosed with cancer).
- **Risk perceptions of developing prostate cancer** will be measured via 4 adapted items. The first two items will assess perceptions of absolute risk and comparative risk by comparing a person of the same age and sex[46]. These two items have been widely used for other cancer risk assessments. A further two items will assess affective risk which is associated with screening behaviour[47] (all participants except control 2 and those who are diagnosed with cancer).
- **Single-Item Literacy Screener Questionnaire (SILS)**[48] is a single question assessing subjective assessment of one's own health literacy. It is low burden yet has high correlation with much longer health literacy questionnaires in primary care settings (all participants except control 2)
- **Theoretical Framework of Acceptability (TFA)** Questionnaire - prospective wording. Adapted items from this scale will be used to prospectively understand the acceptability of the intervention(s) to the participants. Items include those measuring perceived effectiveness, burden, and opportunity costs and will be used to understand demographic and cultural differences in terms of acceptability (all trial arms except control groups (i.e., PHC1, PHC2, PHC3, PHC4)).

Next Day Assessment (following PHC) – Follow-up 1

- GAD-7 (Participants as listed above).
- CWS (Participants as listed above)
- Risk perceptions
- Patient Satisfaction Measure (All trial arms except Control Group 1 & Control Group 2)

8 Weeks Post PHC Test – Follow-up 2

- GAD- 7 (all participants).
  TFA – retrospective wording (all trial arms except control groups (i.e., PHC1, PHC2, PHC3, PHC4))

6 Months Post PHC Test – Follow-up 3

- GAD-7 (all participants)
- CWS * for those who have not received a diagnosis of cancer
- Health behaviour and family history questionnaire (all participants except control 2 and those who are diagnosed with cancer).
- Risk Perceptions of Developing Cancer Measure (all participants)
- Patient Satisfaction Measure (all trial arms except control groups (i.e., PHC1, PHC2, PHC3, PHC4))

6.12. INTERVIEWS WITH PARTICIPANTS AND GPS

6.12.1 Invited Participants

Semi-structured interviews will be conducted with a subset of men (from Design 1, excluding those allocated to the control arm) about their views and experiences of the different Prostate Health Checks, including Black British ethnicities; people from rural and coastal areas in the UK; people from lower socio-economic backgrounds (based on Index of Multiple Deprivation quintile); people with learning disabilities & neurodevelopmental disorders (e.g. autism); older men (aged 65+) and people from other minoritised ethnic groups. A full, theoretically-informed sampling framework will be developed to track and manage recruitment and ensure variation in contributions across the listed criteria, and to ensure there is even representation across the four intervention arms.

All trial participants from Design 1 will have their baseline demographic data screened and any individuals who fall into one or more of the groups of interest, and who consent to being approached for a further interview, will be added to a 'longlist'. Participants will have indicated their consent to be approached for this part of the study at the point of entry into the TRANSFORM Research Cohort. Individuals who fall into two or more of the categories will be prioritised for invitation.

Our aim is to gain in-depth insight regarding the differences in attitudes and barriers towards different PHCs to inform potential solutions to enable their effective and equitable implementation. Up to 60 men will be interviewed within 6-9 months of receiving their initial test results. At least 9 men of Black ethnicity (15% of the interview sample) will be interviewed to ensure adequate representation of this population. Participants will provide consent verbally prior to interviews after having already given written informed consent for invitation to this aspect of the study at baseline.

Verbal consent will be taken and audio-recorded using the interview consent form and an encrypted audio-recording device. To achieve this, each participant will be asked to state their name and the date of the interview. The researcher will read aloud each of the statements on the consent form and ask the participant to state whether they agree with each statement. Verbal consent is being used for three reasons: 1) interviews are being carried out remotely, 2) to reduce unnecessary participant burden of correspondence (i.e. written consent), and 3) to ensure interviews are carried out in a timely fashion (additional time may reduce participant recall of their experience and reduce the quality of the data collected). The consent form will clarify that no medical care nor legal rights of participants will be affected by participating in, or not participating in, nor withdrawing participation from the interview.

The verbal consent process will be audio-recorded as a separate audio file from the interview itself, to avoid identification, using an encrypted digital audio-recording. Following the interview, the audio-recordings will be uploaded immediately to a secure folder within QMUL's Data Safe Haven and deleted from the recording device. The consent and interview audio-recordings will be saved and stored as separate files. The audio-recordings will be transferred

securely to a professional transcription service using a secure file transfer mechanism via the Data Safe Haven and governed by a data sharing or processing agreement. Transcripts will be de-identified using a pseudonym and stored on a password-protected network drive for five years. Audio-recordings of the interview itself will be deleted after the transcriptions have been checked for accuracy by the researcher.

Interviews will remain confidential and will not be shared with the participant's GP. Data will be analysed using Thematic Analysis 50 supported by NVivo. The qualitative analysis will be an inductive and iterative process, meaning themes will be generated from the data.

Interviews are intended to be one-to-one, but where men require support from family members or carers (particularly where there is an intellectual disability or neurodevelopmental disorder) then a joint interview will take place and the carer's responses will be taken into account as part of the analysis. Carers who agree to participate will give recorded verbal consent before the interview, as outlined above.

6.12.2. General Practitioners, Urologists, Commissioners of Care

Semi-structured interviews with up to 30 healthcare practitioners/commissioners will be undertaken to identify and gain an understanding of the facilitators and constraints influencing use of the PHCs in current primary care practice. Healthcare practitioners/commissioners will be identified through existing professional networks (e.g. Deep End) and primary care surgeries linked with the TRANSFORM pilot trial (e.g. as recruitment sites). Any individual meeting the eligibility criteria can be invited to participate in an interview.

GPs will be recruited purposively to sample as widely as possible (by region, gender, age, GP trainer status, and rural / urban location).

Professionals will be eligible for inclusion if:

- They are over 18 years old

And they have prior experience of:

- referring patients for prostate cancer investigation

or

- commissioning prostate cancer services

Recorded verbal informed consent will be obtained before the interview, following the same process as that of trial participants. Data collection, transcription and analysis will be undertaken in a similar way to the participant interviews, although data from healthcare practitioners/ commissioners will be analysed separately.

6.12.3. Mixed Methods Analysis

Descriptive analyses of the questionnaire data and themes from the qualitative analysis will be combined in a multi-methods analysis to look for overarching commonalities from the two datasets. Quantitative and qualitative data will be integrated in a rigorous way following the Pillar Integration Process.[50]

6.13. HEALTH ECONOMICS

The health economic component will include a within study analysis of use of services, costs and health state utilities derived from response to the EQ-5D-5L, or a modified version of the EQ-5D-3L (for people with mild/moderate learning disability) and proxy version 2 of EQ-5D-5L. It will also include a model-based cost-utility analysis with results presented as an incremental cost per quality adjusted life year (QALYs) gained over the estimated lifetime of participants for current practice and the screening strategies outlined above for Stage 1 and with comparators revised for Stage 2. The perspective of the analysis will be NHS and personal social services but widened to also include men and their families. Use of other health and care services and participant costs will be based on data collected from annual questionnaires and data from the trial. Combined with unit cost data from routine sources51. The model development, design and analysis will follow best practice methods. This will include comprehensive sensitivity analyses to explore key uncertainties e.g., in disease and screening process; values for model parameters.

The within-study analysis will derive and statistically analyse costs and utilities data. No within-study economic evaluation will be conducted but rather these data will be used to parameterise an economic evaluation model (see below). An appropriate regression model (e.g., general linear model) will be fitted to estimate marginal costs and utilities between strategies over the follow up period whilst controlling for baseline covariates (e.g., age).

The cost of the invitation and testing approaches used will be based upon participant and clinical expert opinion and data from centres. Use of other health and care services will be based on data collected from the health service use questionnaires (administered annually). Costs will be derived by combining all the resource utilisation with the unit costs of each resource item estimated from study specific estimated and routine sources (e.g., Unit Costs of Health and Social Care[51]; NHS reference costs[52]. Unit costs will be combined with information on the use of services to estimate a cost for each participant. Responses to the EQ-5D will be converted in utility values using recommended scoring algorithms[53].

6.13.1. Economic Model

A discrete event simulation model will be developed using best practice methods[54-55] to compare screening strategies, estimating life-time costs and outcomes. Costs and outcomes will be discounted at 3.5% per the National Institutes of Health and Care Excellence (NICE) reference case[55]. The results will also be presented as shorter time horizons (as informed by recommendations of stakeholders). The model will also be configured to produce other outputs deemed relevant by stakeholders where possible.

6.13.2. Model Structure

In the model, events will be explicitly mapped through care pathways describing the process of care and disease incidence and progression and will be linked by logical and mathematical relationships. The care pathways followed will be based upon a scoping review of previous prostate cancer screening modelling studies in this area[28,29,56,57], clinical guidelines[58], and expert advice from stakeholders. Opportunistic diagnosis and current care will also be included.

6.13.3. Assembly of Data

The model parameters will come from the within study analysis (described above), existing economic evaluations, specialist databases, guidelines. The model will simulate individual men who are eligible for screening to estimate costs and outcomes over their lifetime. The progression of participants through time will depend upon their characteristics (age, comorbidities, etc.). A set of parameters [transition probabilities and state rewards (cost and

health utility scores)] will be assigned for each participant in each follow up pathway modelled based on their characteristics.

As noted above, a cost-utility analysis (CUA) will be conducted with the results presented as incremental costs, incremental QALYs, incremental cost per QALY. Uncertainties in the model will be explored in deterministic and probabilistic sensitivity analyses (PSA). Deterministic sensitivity analysis (DSA) will consider the impact of different discount rates, different time horizons and different parameter sets. Further sensitivity analyses will be presented in the form of tornado diagrams (for DSA) to illustrate the impact of changes in model parameters on the estimated incremental cost per QALY. In the PSA, suitable distributions will be assigned to each model parameter (the choice of these distributions will be guided by parameter type and standard statistical methods of their estimation but for example, gamma or log normal distributions for cost parameters, beta distribution for utility and transition probability parameters are commonly used) and Monte-Carlo simulation (which samples the parameters at random) will be performed to generate the estimates of costs and outcomes accounting for any parameter uncertainties. The results of this will be presented as cost-effectiveness acceptability curves (CEAC), cost-effectiveness (CE) plane (scatter plot) and tornado diagram (for DSA) will be used to illustrate these uncertainties in the cost-effectiveness. Value of information Analysis, which is an extension PSA approach of the will be used during Stage 1 to help identify which screening strategies should be taken forward to Stage 2.

In Stage 2, the model developed in Stage 1 will be refined. This may include changes to the model comparators, changes to data and model structure as practice, methods and data all develop.

7. TRANSFORM DISCOVERY

7.1. AIMS

TRANSFORM Discovery will establish a bio-digital twin for modelling studies of clinical care and deliver translational research. TRANSFORM Discovery will aim to help:

- Improve ways to detect prostate cancer early
- Gain a better understanding of how prostate cancer develops and grows
- Develop new medicines, surgery, minimally invasive treatments and radiotherapy to treat prostate cancer
- Improve the management and monitoring of prostate cancer

TRANSFORM Discovery will involve:

Next-generation bio-digital collection: Create a contemporary biorepository linked with high resolution multi-modal data comprising of digital radiology and digital histology. Link to clinical data from the TRANSFORM database will be through a unique trial identifier.

Digital Twin methodology: Generate a “living” avatar with the high-resolution biological data to mirror real-life as closely as possible, creating a “virtual twin” on an individual participant level.

“Real time” biomarker discovery: Undertake real-time processing of biospecimens for rapid biomarker development and testing. Provide rapid and efficient biomarker testing potentially informing the addition of further screening strategy arms to the trial.

Agile design: Facilitate a fit-for-purpose Bio-Digital Twin by establishing bespoke biospecimen collections and processing designed for specific individual biomarker tests.

Long term utility: In addition to real-time testing, there will be long term tissue and data storage within existing or future research tissue banks with appropriate regulatory permissions.

7.2. OVERVIEW

TRANSFORM Discovery will align with the main TRANSFORM study, capturing prospective multi-omics data from biospecimens matched with multi-modal clinico-radio-pathological datasets. Biospecimens and data will be processed and stored centrally at Imperial College London. Collecting additional samples and accessing pseudo-anonymised clinical data from the main TRANSFORM study will allow for TRANSFORM Discovery to accelerate its translational research aims. We plan upfront processing of tissue and other biospecimens (blood, urine, saliva, stool) to secure greater long-term utility. Consequently, we will generate (i) stable biospecimen derivatives (DNA, RNA etc.) and (ii) digitised storage of omics, histology and radiology metadata. The concealed allocation of the trial arms will remain blinded to TRANSFORM Discovery until the clinical study has completed.

7.2.1. Tissue and Multi-omic Digital Data Collection

Collected tissue from all consenting participants, using dedicated collection and transportation kits, will include: (i) blood (whole/plasma/buffy coat), (ii) urine (spun sediment and supernatant) and (iv) faecal swabs; and from those men undergoing prostate biopsy, v) prostate tissue (fresh and formalin-fixed paraffin-embedded (FFPE)). For those randomised to the polygenic risk score (PRS) arm, we will also collect saliva, using bespoke kits. For all other TRANSFORM Discovery participants, blood samples will be used for PRS testing.

Subject to local resources, additional fresh tissue will be taken once a prostate is removed during surgery in those men who are subsequently diagnosed with prostate cancer and choose prostatectomy as their treatment option. Tissue sampling, in excess of diagnostic needs for participants undergoing surgery or biopsy as part of routine care, will also include lymph nodes and periprostatic fat.

Digital data from all consenting participants will comprise (i) digitised scans of the prostate histology (ii) digital files of imaging scans. TRANSFORM Discovery will be linked to the main trial database for specific approved projects, whilst concealing allocation throughout the duration of the main study. Statistical analysis plans will be developed for these defined projects in collaboration with partner organisations. Recontact consent will be sought for linkage to new relevant studies in time. Such recontacts will only be conducted with oversight and approval from the Trial Management Group and on the advice of the independent Trial Steering Committee, and patient contact for such purposes will only be done by the main TRANSFORM study team.

7.3. BIO-DIGITAL TWIN

A “living” Bio-Digital Twin framework will allow us to accurately mirror the clinical care pathway, comprising of complex multi-modal, high dimensionality data, that provides unparallelled opportunities for testing clinical hypotheses. Advances in computing power and machine learning technologies will allow approaches such as Artificial Intelligence (AI) to handle the complexity of the digital twin data and harness the full power of integrative analyses. Researchers will have the ability to simulate virtual experiments (trial emulation) on individual

participants, diagnostics, treatments, and scale to population perspective for service design/policy. Given the range of characteristics at diagnosis, and the natural spread of different treatment approaches and treatment outcomes, the scale of the Twin will be able to entertain multiple hypotheses using established methodological approaches for trial emulation. Additional emerging methodology for AI-based prediction will also be utilised.

7.3.1 Prospective Tissue, Data Collections and Biomarker Testing

The prospective Bio-Digital Twin design will use material provided by consenting participants from the main TRANSFORM study with bespoke tissue processing fit for specific biomarker testing.

7.4. SCIENTIFIC REACH

By creating a Bio-Digital Twin platform, TRANSFORM Discovery will support basic discovery science projects and multi-dimensional data modelling through to biomarker discovery and validation, which has the potential to positively impact outcomes for men with and at risk of prostate cancer. For example, (1) fundamental basic research by using a discovery cohort of human biospecimens or other multi-modal data (opposed to animals or cell lines) will accelerate clinical translation; (2) putative molecular pathway targets or signals in multi-modal datasets from the discovery cohort can be scaled in the full trial to allow testing in humans through associated biomarkers studies; (3) correlating biomarker expressions with real-world clinical outcomes will provide insights into clinical utility; (4) ultimately, cost-effectiveness of potential biomarkers can be modelled to inform clinical practice, based on costs taken from the clinical trial health economic analyses, and (5) a “living” digital avatar will offer an unprecedented opportunity for “real time” data simulations based on AI-driven algorithms for disease prediction and prognostication.

TRANSFORM Discovery has the potential to provide scientific scope for a range of prostate cancer studies that have not been possible in a UK prospective cohort before, examples include:

- Basic science discovery, e.g. on the molecular basis for early/premalignant pathway for carcinogenesis
- Epidemiological and aetiological research, e.g. linking multiple sociocultural and ethnicity risk factors to the molecular basis of prostate cancer
- Characterising biomarkers for the detection of clinically significant disease e.g. AI-based radiomic markers on MRI
- Describing new approaches for the detection of missed clinically significant disease, e.g. AI digital imaging processing of “negative” biopsies for field change
- Identifying sensitivities to certain treatment approaches to help personalise care, e.g. fluidic biomarker for radiosensitivity
- Providing insights for commercial partners on the positioning of biomarkers in the clinical pathway, e.g. estimate competitive price points for specific biomarkers with specific diagnostic accuracies to provide value-for-money for policy-makers
- Providing a flexible research platform that can be linked to other new projects through prospective consent for re-contact (including commercial work and international studies), e.g. linking to longitudinal cohort studies capturing epidemiolocal data on lifestyle behaviours, such as wearable data metrics (pending additional funding and regulatory approvals)
- Modelling changes to the service pathway, e.g. consider the cost and safety of novel strategies to follow-up after treatment for prostate cancer to informal policy, such as stratified frequency of PSA testing or PSA replacement with a novel biomarker

7.5. ADAPTIVE BIOMARKER TESTING IN REAL-TIME

TRANSFORM Discovery will be constructed from two complementary strategies for data and biospecimen collection in parallel. First, a conventional clinical trials biospecimen collection which will incorporate long-term archiving and which will link, through unique trial identifiers, to the main TRANSFORM study clinical database for healthcare outcomes obtained through the main TRANSFORM study and its linkage to national databases. Second, a novel innovative “living” Bio-Digital Twin employing a multi-arm adaptive design for real time prospective biomarker testing (short term outcomes).

An adaptive rapid biomarker testing SOP will describe delivery (which will include a pilot and main phase of testing), analysis and reporting. The TMG, TRANSFORM Discovery oversight committee and the main TRANSFORM TSC will advise on a per project basis as outlined in the adaptive biomarker testing SOP.

Commercial and academic partners with biomarkers with a proven signal of efficacy will undergo review by the TRANSFORM Discovery oversight committees to prioritise those tests that are ready for testing with the highest likelihood of successful validation and ability to change clinical practice. Cost recovery, potential clinical impact for participants and the NHS, and a contractual commitment of companies to open reporting of the outcomes in peer-reviewed validation will help determine candidates to be tested. A detailed SOP will be used to determine how biomarker testing and performance characteristics will be carried out and reported.

7.6. THE TRANSFORM DISCOVERY LABORATORY

The laboratory will oversee the translational sample collection, working to defined quality standards that incorporate the regulatory requirements of Good Clinical Practice (GCP) and Good Laboratory Practice (GLP). These include the logistics of acquiring, storing and analysing high quality human biological samples linked via a unique trial identifier to clinical data held in the main TRANSFORM study database. The laboratory infrastructure will reside within the Department of Surgery and Cancer at Imperial College, also aligning with local protocols.

7.6.1. Robust Approaches to Generate High Quality Measures from the Tissue

The laboratory will produce standard in house operating protocols, aligned with GCP and GLP, that will provide transparent, reliable, reproducible results whilst also giving traceability, auditability and accountability. The laboratory will develop, test, compare and optimise protocols for tissue processing, archiving and retrieval from storage. There will be a “soft launch” pilot phase to ensure the logistics are secure, before upscaling tissue collections across Stage 1 sites. Large scale tissue collections will be carried out in Stage 2. There will be regular auditing and quality assurance of the tissue processing and of the quality of the tissue archived.

7.6.2. Laboratory Standards

To minimise processing variation, we will undertake centralised storage and standardised tissue processing. Processing will include automation with robots and micro-aliquoting to avoid artefactual degradation from repetitive retrieval from deep storage. Furthermore, we will employ industry standards - GCL, ISO/TC 212, Royal College of Pathology’s Clinical Pathology Accreditation (CPA) for Clinical Pathology Services. These quality assurance processes will provide the desirable utility for commercial partners looking to test biomarkers for CLIA/FDA validation.

7.6.3. Processing for Tissue Archiving

Storing whole tissue allows greater accessibility to specific processing in time to suit specific research questions. However, archived tissue undergoes degradation. To offset this risk, tissue will be serially fractionated into (1) tissue archiving during the trial duration and (2) real-time processing for bespoke biomarker testing projects. Thereafter, tissue archiving will be fractionated into (1) whole tissue and (2) processed tissue. The latter involves processing into specific measures for end-users, such as (a) DNA, (b) RNA, and (c) protein extractions that can be stored in freezers and liquid nitrogen with less degradation over time. There will be further fractionating of these tissues to avoid the degradation effects of repeated freeze/thawing cycling from bulk storage.

7.6.4. Secure Storage

Samples in the TRANSFORM Discovery Laboratory will be split and stored at several separate and secure sites across Imperial College London. This will guard against catastrophic events, such as fire. There will be alarm systems to detect critical failures in storage (such as a temperature drop in freezers) and emergency recovery plans. There will be controlled access for the TRANSFORM Discovery research team only.

During Stage 1, the TRANSFORM Discovery team will develop the necessary protocols and documentation required to establish a stand-alone HTA approved Biobank. Surplus tissue from the phase one biomarker analyses will be transferred to this biobank pending further approvals from trial committees, sponsor, REC and HRA.

In the event that the TRANSFORM Discovery Bio-digital Twin has not been established by the end of the study, and once ethical approval for the study has expired, any surplus blood, urine, and tissue samples will either be transferred to a licensed tissue bank or disposed of in accordance with the Human Tissue Act 2004 and any subsequent amendments.

Data Laboratory

The laboratory will also house the computing and data-base infrastructure for the Bio-Digital Twin. There will be cloud based, secure solutions for data-storage, aligned with Imperial College London and GDPR regulations.

7.7. TISSUE SPECIFICATIONS

- **Blood**
  - Whole blood
  - Plasma and serum compartments

- **Urine**
  - Whole urine
  - Fractionated urine – cell pellets and supernatant

- **Saliva**
  - For polygenic risk score assessment

- **Faecal swabs**
  - For interstitial microbiome

- **Prostate tissue (surplus to diagnostic needs) (pending local resources) in those participants undergoing routine management (e.g. prostatectomy or biopsy)**
  - Prostate biopsy (additional 3 index target biopsies will be specially consented for)
  - Prostatectomy tissue

- **Lymph node and peri-prostatic fat tissue from prostatectomy cases**

These tissue collections will include processing to capture (a) circulating tumour cells (CTCs) from blood, (b) cfRNA, cfDNA and miRNA from blood and urine, (c) tissue-derived DNA and RNA and (d) feacal swabs for microbiome analyses. Additionally, specific collection kits will be determined for collecting dedicated biospecimens (blood, urine, saliva, stool, tissue) for specific biomarker technologies undergoing testing as required (see “Adaptive biomarker testing in real-time”).

7.8. DATA MANAGEMENT

Clinical Meta-Data

The concealment of trial allocation will remain blinded while the TRANSFORM study is running. Pseudo-anonymised linkage with case report form data that is held in the main trial database, will capture essential demographic data, key diagnostic measures and staging details/digital data as well as longer term outcomes. Data held in the main trial database will be released for link to TRANSFORM Discovery with concealed allocation of study arms from the main TRANSFORM study following evaluation by the TRANSFORM TMG to address specific research questions sperate to clinical trial outcomes. Relevant TRANSFORM Discovery data will be linked to data held in the main trial database for analysis by the trial statisticians in order to maintain independence and scientific integrity of the main trial. NHSE registry data linkage for details of healthcare utilisation will all be captured in the main TRANSFORM study database (e.g. management of complications of treatment and for longer term follow-up data) and linkage with other databases will be sought for added value, such as Our Future Health (https://ourfuturehealth.org.uk/) (for epidemiological study) for specific research questions reviewed by the TRANSFORM Discovery oversight group and approved by the TRANSFORM TMG.

Digital Imaging

Raw imaging files from diagnostic and staging imaging. We will use Digital Imaging and Communications in Medicine (DICOM), the technical standard for the digital storage and transmission of medical images and related meta-data. A DICOM file, will be stripped of participant identifier and linked to participant identifier study number (pseudonymised). The DICOM file will include meta-data on acquisition parameters, image dimensions, matrix sizes, colour spaces and image pixel intensity data. DICOM is used together with Health Level 7 (HL 7) standard to exchange textual data among Hospital Information System (HIS), Radiology Information System (RIS), and Picture Archiving and Communication System (PACS).

Digital Pathology

Raw image data scanned pathology will be archived. The appropriate digital format will be used with participant number linkage. To create DICOM files, we will (1) extract pixel data and pixel-related metadata from proprietary file formats from whole slide imaging (at sites where digital capabilities are established or at the TRANSFORM Discovery Laboratory); (2) capture

descriptive meta-data from scan capture; and (3) populate and encode attributes as DICOM data elements. Appropriate codes will be written for automation.

7.9. DATA LABORATORY

7.9.1. State of the Art Computing Facilities

Housed within Imperial College London, the TRANSFORM Discovery Laboratory will contain state of the art computing suite to help generate models. The model architecture is described below. There will be access to the Data Observatory at the Imperial College Data Science Institute (DSI), to assist with analytic and big data visualisation making complex data more accessible. Large language models and natural language processing will capture covariates at the points of diagnosis, treatment and follow up and be asked questions such as, “Is geography, age, or ethnicity a factor in prostate outcomes?” The accessible nature of big data visualisations will make this ideal to present outcomes to participants and other lay stakeholders.

7.9.2. Secure Digital Data

- **Secure Cloud Storage**
  Data will be stored in the cloud using secure methods with established storage providers.

- **General Data Protection Regulation**
  The data will adhere to the General Data Protection Regulation (GDPR) framework. Imperial College London has produced the Data Asset Registration Tool (DART) Platform. Completion of DART Registrations will appease two legal requirements as defined under GDPR: create Data Protection Impact Assessments (DPIA), as defined under Article 35 of the UK GDPR, and populate the College’s Records of Processing Activity (RoPA) and ensure personal data is being recorded and managed in an effective manner. A Data Protection Impact Assessment (DPIA) at Imperial College London will assess and minimise the data protection risks and will inform the CAG application through IRAS for the HRA reviews.

7.10. AI PREDICTIVE MODELS OF HEALTH AND DISEASE STATUS

Using the longitudinal data collected from TRANSFORM, capturing research biomarker metrics at baseline, TRANSFORM Discovery will allow the development and validation of predictive models of health and disease status. There will be a study focus on the impact of biomarkers.

7.10.1. Model Design

A mapping exercise from the clinical pathway for each case will cover diagnosis, treatment and the possible health states the participant might pass through over time and thus describe potential outcomes to create a disease model. The disease models will be reviewed by stakeholders together to ensure face validity, and a design brief centred on participant experience. Probabilities for transition between states will be inputted, including second-order uncertainty, based on clinical data from the main TRANSFORM study. Cost-effectiveness will be assessed as incremental cost per quality-adjusted life year (QALY) over a lifetime horizon from the perspective of the NHS and Personal Social Services. These will be informed from the health economic model from the main TRANSFORM study.

7.10.2. AI Prediction Model

Healthcare data involve high-dimensionality, integrated multimodal and complex non-linear effects that can be a challenge for established statistical analyses and appear to be suited to deep learning approaches. A supervised approach to machine learning will be undertaken to ensure clinical relevance. Accordingly, we will map nodes (based on the disease model) for Network Analysis and graph-based AI predictive analysis. This will inform a Digital Twin machine learning model, simulating clinical histories, in the form of a forward model. Inputs/interventions will determine transition states and effects will be observed on the clinical and cost outputs.

7.10.3. Modelling Biomarker Performance

We will adjust model inputs to simulate the assumed impact of new, as yet unidentified biomarkers, to deliver high throughput assessments and accelerate biomarker validation. Biomarker types explored in the design will include companion diagnostics to guide precision medicine, risk stratification markers, early detection biomarkers to aid recurrence detection (e.g., ctDNA, polygenic risk scores and imaging). We will explore trade-offs in their cost and test performance and so identify a cost-effective envelope. This will help researchers and the UK life sciences to prioritise new biomarker technologies, set benchmarks for performance and price and inform the design of clinical trials. The development of these technologies to prioritise biomarker testing in clinical trials.

7.10.4. Integrative Analyses

With the development of increasingly sophisticated machine learning approaches, previously challenging analyses, involving the combination of different types of data (such as imaging, text and gene sequencing) are plausible. We will explore new AI methodologies such as symbolic systems and approaches for dimensionality reduction for integrative analyses to maximise the value of TRANSFORM Discovery in terms of relevant contributions towards research involving prediction diagnosis and modelling personalised therapeutic approaches which can provide hypotheses for testing in future comparative studies. TRANSFORM Discovery, similar to the prospective rapid biomarker testing approach, will allow testing of new AI-based technologies for (i) each type of data or (ii) integrative data analyses to identify data-patterns as new biomarkers.

7.11. CONSENT

7.11.1. Parallel Consent for Clinical and Translational Study

If a participant is randomised to a Prostate Health Check, they will be offered the opportunity to consent to TRANSFORM Discovery.

7.11.2. Detailing Tissue Studies

Specific tissue types for collections will be detailed and options for consent will include:

- Use of molecular omics data (DNA, RNA, protein, metabolites etc)
- Use of biospecimens by commercial and academic partners
  Use of biospecimens for non-UK collaborations

7.11.3. Withdrawal Options for TRANSFORM Discovery after Consent has been Provided

- Participants will be informed on the process to withdraw part or all of their data and or tissue from the collection.
- Accordingly, and depending on the level of withdrawal requested by a participant, tissue may be destroyed and data securely erased according to local protocol.

7.11.4. Re-contacting for Additional Studies or Linkage Across Other Studies

- Consent will be sought for re-contact to invitations to new future research and additional research tissue sampling or questionnaires, on the advisement of the TRANSFORM oversight committees. This includes the re-contact of participants into third-party studies. Studies are only for related health technologies and data, and tissue and data will not be sold for profit. The main TRANSFORM study team will be the point for any re-contact of participants for this purpose.
- Participants will be consented using the principles of the already-approved UK Biobank "on the understanding that no results would be fed back to them" and so "care is taken to ensure that re-contact does not represent implicit feedback of which participants are not aware". and "recruitment based on genotype or on phenotype that is not explicitly self-reported by the participant is highly restricted"

7.12. STAKEHOLDER ENGAGEMENT

7.12.1. Commercial and Academic Partnerships for Biomarker Development and Testing

- **Biomarkers Consideration**
  There is a limit to the amount of tissue available and the funding envelope to deliver the TRANSFORM Discovery programme. Accordingly, priority will be given to those commercial or academic partners that have a test with an established signal of clinical efficacy. Cost recovery will be sought, with commercial rates for industry projects and for research partners reliant on grant funding. Each partner and their experimental and testing needs will be reviewed case by case (see Governance section).
- **Open Reporting**
  Contracted partners will be generally required to sign up to open reporting of their biomarker's performance if undergoing prospective validation testing, unless there is specific strategic benefit for confidential work, reviewed by the TRANSFORM Discovery oversight committees and ultimately the TMG, with advisement by the TSC.

7.12.2. Patient and Public Involvement and Engagement (PPIE)

Strategy and Oversight committees for TRANSFORM Discovery

These committees will include patients with lived experience. They will maintain an involvement throughout the delivery of study. PPIE from within the parent trial will also inform TRANSFORM Discovery

- PPIE to help co-design of consent and recruitment
- PPIE will help design recruitment pathways for TRANSFORM Discovery that are feasible, relevant, accessible, and inclusive for the UK public. We will co-design the approach to informed consent for participants, including participant information leaflets to improve the experience of participation
- PPIE will include the voice of people and communities that have traditionally been excluded or omitted from health research, with a specific focus on Black men

PPIE will play an essential role in the dissemination of research findings to participants, the public and stakeholders.

7.13. GOVERNANCE

7.13.1. Governance Structure

The TRANSFORM Discovery governance structure will comprise of (i) a strategy and steering board and (ii) a research operations board. Both committees with be informed by (iii) an advisory board. These boards will comprise of experts in the field of biomarker discovery and validation, and include PPIE. The TRANSFORM TMG will have oversight and make final decisions on all analyses carried out in relation to TRANSFORM Discovery.

7.13.2. Strategy and Steering Board

The Strategy and Steering board will provide high level oversight to the operations board. The purpose of this committee will be to provide steer on the program priorities and general course of the TRANSFORM Discovery operations.

7.13.3. Research Operations Board

The Research Operations board, reporting to the strategy and steering board, will cover (i) day to day management, (ii) review and recommendations of partners for tissue access, (iii) oversee research governance. This group will also oversee promotion and visibility of TRANSFORM Discovery, including newsletters, website pages, and targeted outreach to potential researchers (academic and commercial). These activities of both the above boards will be reported to the trial management group.

7.13.4. Advisory Board

The Advisory board will provide advice to the two boards above, and will comprise of PPI representatives, research partners undergoing testing in the translational program, experts to advise on (i) ethics and legal compliance, (ii) digital data security and (iii) research governance.

7.13.5. Contractual Basis of Collaborations

Collaboration agreements will be secured with research partners, and where appropriate their employing institutions, to access TRANSFORM Discovery. Cost recovery will be employed, and a statement of cost will be included in the agreed program of work. The agreement will be organised through the contacting teams at Imperial College London. Open reporting by the research team will be mandated in contracts for biomarker validation testing. Participants can choose to withdraw from the programme at any time. The contract will reflect this obligation.

7.13.6. Intellectual Property

Intellectual property (IP) agreements will map out background and foreground IP between collaborating partners and, where appropriate, their institutions. Tripartite agreements between partners, sponsor (Imperial College) and funders will be established prior to contracting. These will be underpinned by the main contract between the TRANSFORM funder, Prostate Cancer UK, and TRANSFORM Sponsor, Imperial College London.

7.13.7. Data and Tissue Access

Access will be underpinned by the principles of the “Five Safes”: safe data, safe projects, safe people, safe settings, safe outputs. Researchers will apply to the research operations board to access anonymised digital information and samples for projects aligned with TRANSFORM Discovery aims. All requests will be reviewed by the TMG prior to approval with advice from the TRANSFORM Discovery oversight committee. Commercial partners looking to validate established biomarker products will be expected to fund the TRANSFORM Discovery laboratory to independently run and validate their biomarker. Approved primary discovery, methodological development or early biomarker translation research projects will be required to return their results to the TRANSFORM Discovery and to publish their findings so that other researchers can use and build on this knowledge to further benefit the public interest (public health benefit). In order for a basic or early-stage translational research project to be approved, the researchers will need to demonstrate that their research will provide knowledge, further scientific understanding and that it meets our definition of public health benefit.

Data to be shared for research will be pseudonymised to protect the privacy of participants while maintaining its scientific and research value. Comprehensive data dictionaries and meta-data will be made available for researchers to use. Wherever possible data will be structured and coded using commonly used standards to allow for the broadest use of the data, in the public interest. Research data will be accessible within accredited trusted research environments. A trusted research environment is a secure online environment that allows researchers to access data and perform analysis or computation. No participant-level data can be exported from a trusted research environment.

8. IDENTIFICATION AND RECRUITMENT OF PARTICIPANTS

Eligible GP practices who wish to participate will be identified by the central team, and portfolio recruitment will be attributed to secondary care (research) site associated with those GP practices.

GP practices will act as Participant Identification Centres (PIC) sites to identify eligible participants from their database, as per the Recruitment SOP. GPs will be asked to give formal permission to use their names as sign offs on letters sent to participants listed on their practice through the recruitment invitation sent out via Docmail.

8.1. PRE-RANDOMISATION EVALUATIONS

8.1.1. Stage 1

Patients who have opted out (National Opt-out) will not be invited. Of the remaining eligible participants, study inclusion and exclusion criteria will be evaluated using primary care records prior to the first randomisation to Design 1 or Design 2. In addition, for Design 1, information provided in the first-stage consent will be used to inform stratified sampling for randomisation between Control 1 and the four PHCs.

8.1.2. Stage 2

To be confirmed

8.2. RANDOMISATION AND BLINDING

8.2.1. Stage 1

Identified eligible participant listings will be provided for randomisation to Design 1 or Design 2, which will be undertaken following a randomisation working instruction and in accordance with TRANSFORM Randomisation SOP.

There will be two randomisation steps.

The first randomisation step will randomise between the Design 1 Research Cohort, and the Design 2 pre-consent control and the four PHCs in Design 2.

A second randomisation will be applied to those participants who consent to be part of the Design 1 Research Cohort and will randomise participants between the Design 1 Post-consent control, and the four PHCs in Design 1.

The randomisation allocations may be adapted during the trial. To begin, the suggested starting allocations are:

- **Randomisation 1**
  Design 1 Research Cohort: Pre-consent control : PHC1 (design 2) : PHC2 (design 2) : PHC3 (design 2): PHC4 (design 2)
  70: 10 : 1 : 1 : 1 : 1
- **Randomisation 2**
  Post-consent Control : PHC1 : PHC2 : PHC3 : PHC4
  7: 10 : 10 : 10 : 10

8.2.2. Stage 1: Design 1

The list of men randomised to the Design 1 Research Cohort will be sent a letter of invitation and a short information sheet. A subset of those invited will express an interest and consent to further contact. It is possible that some of the men who express an interest will not be randomised to invitation to a PHC or control, in accordance with their earlier consent, as we will use a stratified approach to ensure balanced representation in each group. Individual randomisation will be undertaken following a randomisation working instruction and in accordance with the TRANSFORM Randomisation SOP. The randomisation ratio will be adapted as needed to achieve the target numbers consented with a suggested starting ratio of 7:10:10:10:10. Participants in the post-consent randomised control (Control 1) will not be informed they have been randomised to a control group, in accordance with their earlier consent and information given in the participant information sheet. Participants randomised to each Prostate Health Check will not be informed about the interventions in other arms.

8.2.3. State 1: Design 2

Participants randomised to Design 2 will be directly randomised to the pre-consent randomised control arm (Control 2) or one of four PHCs in a ratio of 10: 1: 1: 1: 1. Participants in Control 2 will not be consented to take part in the study or be aware that they are in a control arm of the study; their care will continue as standard in the community with their GP. Participants randomised to each Prostate Health Check will not be informed about the interventions in the other arms or about Design 1.

8.3. SCHEDULE

Pre-consent Randomised Control (Control 1)

- Continue as normal in standard care. No research study visits.

Post-consent Randomised Control (Control 2)

- Continue as normal in standard care. No research study visits.
- Optional consent to qualitative mixed methods interview

Intervention Groups (PHC1, PHC2, PHC3, PHC4)

Screening Round 1

Community Based

i. Consent. Remote (letter/electronic), telephone or in person.
ii. PSA blood test (PHC1, 2, 3), or Polygenic Risk Score saliva test (PHC4), with optional tissue collection of urine, blood, saliva and stool for TRANSFORM Discovery.
iii. Prostagram™ in those identified from initial PSA and PRS testing as outlined in each PHC flowchart and SOP. Prostagram™ for all participants in PHC3.

Secondary Care

iv. Transperineal targeted prostate biopsy in those testing positive on Prostagram™
v. If no cancer, then bespoke advice about ongoing prostate care will be given in Stage 1. Stage 2 will incorporate at least one further screening round which will be detailed upon a substantial amendment.

If cancer, then management of cancer in secondary care.

8.4. SCHEDULE OF EVENTS

Study Period	Screening Round 1							
Visit	**Pre-screening**	**Screening/ Baseline**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Follow-up**	**Long Term Follow-up (up to 30 years)**
GP Search	✓							
Inc/Exc	✓	✓ (self-report)						
Randomisation 1 (Design 1 / Design 2 arms)	✓							
Invite letter (Design 1 Cohort / Design 2 PHCs)	✓							
Informed Consent (Design 1 Cohort / Design 2 PHCs)		✓						
Demographics	✓	✓						
Targeted Medical History	✓	✓						
Randomisation 2 (Design 1 only)		✓						
2nd Informed Consent (Design 1 only)		✓						

PSA [1]			✓	✓ (PHC4 only)				
PRS [2]			✓					
Prostagram™ [3]				✓				
Transform Discovery samples			✓	✓ (PHC4 only)				
Biopsy (in selected patients) [4]					✓			
Questionnaires	See tables below							
AEs			✓	✓				
Harms (Biopsy and treatment related)					✓	✓	✓	✓
Staging scans [5]							✓	✓
Treatment options [5]							✓	✓
Interviews (60 men only)							✓	
Long term data linkeage (all participants)								✓

[1] PHC1, 2 and 3. PHC4 if PRS is >3.5% risk

[2] PHC4 only. PRS sample kits will be posted

[3] PHC 3, and if PHC1 ≥3ng/mL, PHC2 ≥1 ng/mL or if PHC4 PRS is >3.5% risk

[4] If Prostagram™ returns positive results

[5] In those diagnosed with cancer

8.5. BEHAVIOURAL QUESTIONNAIRES

Behavioural Questionnaires	Construct it is Measuring/Assessing	Who Completes & How Identified?	Baseline	Next Day Assessment (Follow up 1)	8 Weeks Post-PHC Test Date (Follow up 2)	6 Months Post-PHC Test Date (Follow up 3)
Demographic questionnaire (adapted from DISTINCT)	General demographics	All (Design 1 & Design 2) participants, except Control Group 2	✓			
GAD-7	General anxiety	All (Design 1 & Design 2) participants, except Control Group 2	✓	✓	✓	✓
Cancer Worry Scale (CWS)	Concerns about developing cancer	All (Design 1 & Design 2) participants, except Control Group 2	✓	✓		✓ *Only for those who have not received a diagnosis of cancer

Lifestyle and family history questionnaire	Current health behaviours & family history	All (Design 1 & Design 2) participants, except Control Group 2 AND participants who are diagnosed with cancer)	✓			✓
Risk Perceptions of Developing Cancer Measure	Risk perceptions of developing cancer	All (Design 1 & Design 2) participants, except Control Group 2 AND participants who are diagnosed with cancer	✓	✓		✓ *Only for those who have not received a diagnosis of cancer
Single item Literacy Screener Questionnaire (SILS)	Health literacy	A All (Design 1 & Design 2) participants, except Control Group 2	✓			
Theoretical Framework of Acceptability (TFA) Questionnaire [adapted]	Acceptability of PHC	All trial arms except Control Group 1 & Control Group 2	✓ (prospective wording)		✓ (retrospective wording)	
Patient Satisfaction Measure	Satisfaction with specific PHC received	All trial arms except Control Group 1 & Control Group 2		✓		✓

N.B. Participants in Control 2 (Zelen/Design 2) will not receive any questionnaires throughout the trial.

8.6. HEALTH ECONOMICS AND MAIN TRIAL QUESTIONNAIRES

Health Economics and Main Trial Questionnaires	Screening/Baseline	Completed: After MRI but Before Biopsy	Biopsy Day	7 Days Post Biopsy	35-90 Days Post Biopsy	Annually (for up to 15 years post consent)
Prostagram Questionnaire[6]		✓				
PROBE[7]			✓ 10	✓ 11	✓12	
SMACS[7]			✓		✓	✓
EPIC-26 Short Form (1-5 only)[7]	✓		✓			✓
EQ-5D[8]	✓					✓
Health Service Use Questionnaire 9						✓

[6] To completed by all PHC participants who receive an MRI

[7] To be completed by all PHC participants who receive a biopsy

[8] EQ-5D-5L, modified EQ-5D-3L (Learning Disability), EQ-5D-5L Proxy V2 (all PHC arms and all participants in Control 1)

[9] To be completed by all PHC arms and all participants in Control 1. N.B. to be implemented following PPI review and study amendment.

[10] Adapted PROBE – Biopsy Specification and Biopsy Perceptions

[11] Adapted PROBE – General Symptoms

[12] Adapted PROBE – Biopsy Perceptions and General Symptoms

8.7. PARTICIPANT PATHWAY

Eligible participants for **Stage 1 (Design 1)** will be sent an individualised letter from their named GP practice via Docmail, inviting them to take part in TRANSFORM Research Cohort. It will include a link to an online system which will include a participant information sheet and consent form. Participants who consent to join the TRANSFORM Research Cohort will then be randomly allocated to any one of the four PHCs or to the post-consent control group. Those who have been allocated to a PHC will be sent a further invitation letter with access to a further participant information sheet and consent form.

Eligible participants for **Stage 1 (Design 2)** will be sent an individualised letter from their named GP practice via Docmail, inviting them to take part in one of the PHCs. It will include a link to an online system which will include a participant information sheet and consent form. Those who are allocated to the pre-consent randomised control will not be contacted.

Consent via post, phone (with documents later signed electronically or in paper form) as well as face to face will also be available. Reminders will be sent via SMS, email, and post where appropriate. For participants with learning disabilities easy read, and consultee (nominated/personal) versions will be made available upon request.

Following consent to PHC1, PHC2 and PHC3, a PSA test appointment slot will be sent to the participant. A saliva collection kit will be sent to participants in PHC4 to obtain a PRS. A PSA test appointment slot will be sent to participants in PHC4 who return a PRS which conveys a 10-year prostate cancer risk of 3.5% or higher.

Participants will attend a recruitment hub to have blood for their PSA test taken. In consenting participants, additional samples for TRANSFORM Discovery will also be taken during this visit or another visit, according to the preference of the participant.

Participants in PHC1 and PHC2 will be informed of their PSA result via letter or email with instructions about next steps. If the PSA is above the designated threshold (PHC1 ≥3ng/mL or PHC2 ≥1ng/mL), they will be sent a Prostagram™ appointment slot. Participants in PHC3 who have completed their PSA test will be sent a Prostagram™ appointment slot regardless of the PSA level. Participants in PHC4 who have been advised to have a PSA test will also be sent a Prostagram™ appointment regardless of the PSA level.

Prostagram™ scans will take place at an imaging hub which might be at a local imaging facility or a mobile MRI scanner. Once the Prostagram™ has been reported by a central pool of radiologists, the outcome will be conveyed to the participant by letter. A positive Prostagram™ result will be first conveyed by a recruitment officer via telephone to explain the result, offer support, and explain next steps. This will be followed by an email/letter. A negative test result will be communicated by email/letter to the participant with advice about further prostate care via their GP in Stage 1. In Stage 2, the trial will incorporate at least one further screening round.

For those with a positive Prostagram™, the results letter will also be sent to the named GP. Referral to a designated secondary care centre within the study for a targeted transperineal biopsy will then be made.

Once the participant is referred into secondary care, clinical recruitment staff will check when biopsies occur and obtain results directly from the secondary care centre. The trial research team will hold an honorary contract or Letter of Access/Research Passport for all participating secondary care centres.

8.8. FOLLOW-UP

8.8.1. Stage 1 (Control Arms)

These reflect standard care and there will be no additional follow-up visits required for the study other than an optional consent for qualitative interviews for the post-consent randomised control group.

8.8.2. Intervention Arms

We will collect information about what staging scans were carried out if a cancer diagnosis was made. Treatment options that were suitable for patients with prostate cancer and what treatment they chose through multidisciplinary team (MDT) processes will be recorded in the eCRF from the clinical records.

Patients will be able to choose from a number of options that range from active surveillance, focal therapy, radical surgery or radiotherapy or systemic drug therapy, depending on cancer risk and cancer stage. All participating secondary care centres must have expertise to deliver counselling and treatment for all types of treatment in their local MDT network. Patterns of type of treatment will be assessed by each centre and outliers will be identified for a discussion with the TMG and if necessary, participation paused for any remedial action to be taken.

We will determine whether patients had further diagnostic tests, prostate cancer diagnosis and its risk (stage, grade, PSA level), as well as any subsequent treatments and cancer-related outcomes (progression, metastases, cancer-related mortality).

We will ask participants to give permission to be contacted by a member of the central/local study research team within 15 years of signing their consent form to complete questionnaires about their health status (including details of any other tests and treatment they have had since the study) and quality of life. If the participant decides to take part, a member of the study research team may send this request to their home address or email. Participants can opt-out of the questionnaires at any time and do not need to answer every question to remain in the study.

Following appropriate approvals (CAG, HRA) a data access request will be submitted to obtain curated NHS data (e.g. HES) for linkage in order to investigate relevant prostate cancer related treatments and procedures across all arms of the trial including both Design 1 and Design 2.

8.8.3. Health Status

Long-term healthcare information will be collected from national records (i.e., Office for National Statistics, NHS Digital, Office for Health Improvement and Disparities, and/or other applicable NHS information systems, or national databases) at any timepoint within 30 years of consent.

This applies to all participants: those who undergo a direct, individual consent process (Participants in Design 1, and Design 2 (excluding the pre-consent Control), and those who do not have the opportunity to provide direct consent (Design 2, pre-consent Control). For all groups, a section 251 exemption under the NHS Act 2006 will be sought from the Confidentiality Advisory Group (CAG). This will permit the collection of confidential patient information from national data sources for the purpose of long-term follow-up.

This approach will ensure more equitable long-term follow-up particularly for participants in the non-consented control group and only for those not registered with the National Data Opt-

Out. To enable accurate data linkage, a limited set of identifiable fields (NHS number, date of birth, full name, post code, gender) will be used. These identifiers will be securely transferred to organisations holding national records.

We will therefore not seek individual consent from any participants for long-term follow up of their health status. This will be conducted solely under the section 251 exemption by linking identifiable participant data with their health records held by NHS bodies, including the NHS Information Centre, the NHS Central Register, and any applicable NHS information system. This linkage will enable the study team to observe what happens after the study finishes, including whether participants undergo further tests, investigations or treatment related to prostate health.

As prostate cancer is often a slow-growing disease which may take many years to develop or progress, we will retain and access personal data for an additional 30 years on the NHSCR (National Health Service Care Register) so that data from national registries can be evaluated. For instance, long-term survival information to be flagged through national registries, for example NHS Digital (previously the Health and Social Care Information Centre); Office of National Statistics (ONS) in England/Wales; General Register Office in Scotland; Hospital Episode Statistics (HES) or Office for Health Improvement & Disparities. This data will be accessed under the section 251 exemption.

Non-responders (i.e. those that do not respond within 31 days of the second reminder) will receive no further study communications, though their data will still be used for long-term follow-up of outcomes through linkage to national databases. This will be completed under the section 251 exemption.

Participants can opt-out of long-term data collection under the section 251 exemption at any time by contacting the study team. Alternatively, they can choose not to have their health data used for any research by completing the **NHS National Data Opt-Out** at: https://www.nhs.uk/your-nhs-data-matters.

The **Participant Opt-Out and Withdrawal SOP** outlines how members of the public and participants in the TRANSFORM study can opt-out of their data being accessed or collected for research purposes.

8.9. LABORATORY EVALUATIONS

- **Haematology**
  Not applicable

- **Biochemistry**
  Prostate Specific Antigen (PSA) testing will be carried out as per local standards using standard methods and protocols by a United Kingdom Accreditation Service (UKAS) ISO 15189 medical laboratory(ies) accreditation.

- **Polygenic Risk Score**
  Saliva samples will be collected and stored at room temperature until DNA extraction, which will be performed at UCL Genomics using standard methodologies.
  Genotyping will then be conducted at the same facility using the Illumina OncoArray platform.

- **Urinalysis**
  Not applicable

- **Exploratory/Research Samples**
  Evaluations of specific biomarkers using samples collected through TRANSFORM Discovery will be provided in an amendment for each biomarker. Details of laboratory processes planned for each biomarker will be detailed in a TRANSFORM Discovery Biomarker Testing SOP.

- **Sample Storage and Analysis**
  As above for Polygenic Risk Score

- **Incidental Findings**
  Incidental findings on Prostagram™ will be stated on the clinical report and the GP informed in the letter for advice on ongoing action to be taken commensurate with the specific finding(s).

8.10. INTERVENTION

8.10.1. Permanent Discontinuation of Study Intervention and Withdrawal from Study

- **Permanent discontinuation of study intervention**
  Participants may discontinue study intervention for the following reasons:
  - At the request of the participant
  - Adverse Event/Serious Adverse Event
  - If the investigator considers that a participant's health will be compromised due to adverse events or concomitant illness that develop after entering the study

- **Withdrawal from study and loss to follow-up**
  Withdrawal from the study refers to discontinuation of study intervention and study procedures and can occur for the following:
  - Participant or clinical decision

Loss to follow-up alone will also be noted but will not constitute a withdrawal unless accompanied by explicit patient, clinician or study investigator withdrawal.

- **Procedures for withdrawal from study or loss to follow-up**
  Participants may decide to withdraw from the study at any time. In such cases, the withdrawal will be reported to the Research Team Office to ensure no further data are entered onto the database and no further contact occurs, in line with the participants wishes, and as outlined in the participant information sheet. Data and samples collected before withdrawal of consent will continue to be used in the study. A patient may request for their samples to be destroyed, and the study team will ensure these wishes are carried out. If the participant provides a reason for withdrawal, it will be recorded in the electronic Case Report Form (eCRF) and in their medical records.

  Unless the participant specifically requests otherwise, long-term health follow-up from national records will continue under the Section 251 exemption of the NHS Act 2006, as described in the participant information sheet.

  A **Patient Opt-out and Withdrawal SOP** provides detailed guidance on how participants can withdraw from the study at any time.

9. SAFETY REPORTING

9.1. OVERVIEW

This study involves screening interventions referred to as PHCs, which for each arm will include a defined screening intervention, followed by a Prostagram™ MRI in those with a positive result from the first element of their PHC, unless a Prostagram™ MRI was already part of the initial screening. It is essential to distinguish between adverse events (AEs/SAEs) related to the PHC (i.e. the study intervention) and subsequent events (termed Harms) related to investigations and treatments undertaken as part of standard of care following a positive screening result.

9.2. ADVERSE EVENTS (AE)

The Common Terminology Criteria for Adverse Events (CTCAEv5.0) domain will be used to report adverse events. Please refer to the below hyperlink for further details:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

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

AEs and SAEs will be recorded for all participants during the PHC period, from the point of consent to the point of completion of the Prostate Health Check. Completion of the PHC is defined as either:

- Receipt of a negative result for the first screening intervention (where no further procedures are indicated), or
  Completion of the Prostagram™ MRI, where this is required as part of the screening pathway.

Adverse Event Recording

AE/SAE Reporting Window:

- Start: from the date of consent to participate in the PHC
- End: to completion of the PHC

All AEs and SAEs occurring during this defined intervention window will be documented in the electronic Case Report Form (eCRF) using standard clinical trial safety reporting protocols.

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

Severity of adverse events will be stratified as:

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

Causality of Adverse Events

- **Unrelated**
  No evidence of any causal relationship with the intervention or trial conduct
- **Unlikely**
  - There is little evidence to suggest there is a causal relationship with the intervention or trial conduct
  - There is another reasonable explanation for the event (e.g. The participant's clinical condition, other concomitant treatment).
- **Possible**
  There is some evidence to suggest a causal relationship with the intervention or trial conduct. However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
- **Probable**
  There is evidence to suggest a causal relationship with the intervention or trial conduct and the influence of other factors is unlikely.
- **Definite**
  There is clear evidence to suggest a causal relationship with the intervention or trial conduct and other possible contributing factors can be ruled out.

9.3. SERIOUS ADVERSE EVENTS (SAE)

Definition of SAE

A SAE is defined as any untoward medical occurrence that takes place whilst a participant is undergoing any part of a Prostate Health Check procedure which:

- Results in death;
- Is life-threatening*;
- Requires hospitalisation or prolongation of existing inpatient's hospitalisation**;
- Results in persistent or significant disability or incapacity;
- Is a congenital abnormality or birth defect;

* "Life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

** "Hospitalisation" means any unexpected admission to a hospital department. It does not usually apply to scheduled admissions that were planned before study inclusion or visits to casualty (without admission).

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

Reporting of SAEs

Reporting of all SAEs (for exceptions see below), occurring during the PHC period must be performed as detailed in SAE reporting instructions. If the investigator becomes aware of safety information that appears to be related to the trial, involving a subject who participated

in the study, even after an individual subject has completed the study, this should be reported to the Sponsor.

All SAEs will be reviewed by the CI or a designated medically qualified representative to confirm expectedness and causality within 24 hours. Reporting of SAEs and review by the CI will be via the trial data collection system (eCRF).

List of Expected Adverse Events

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

- Claustrophobia leading to abandoning of Prostagram™ MRI scan
- Vasovagal fainting episode before, during or after venous blood sampling or Prostagram™ MRI, and any admission required for this.

Reporting of SAEs that are Related and Unexpected

Related SAEs are defined as any SAE that results from administration of any of the research procedures. Unexpected SAEs are any type of event that is not listed in the protocol as an expected occurrence.

All SAEs should be reported to the approving REC where in the opinion of the CI, the event was:

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

Reports of related and unexpected SAEs should be submitted within 15 days of the CI becoming aware of the event, using the NRES SAE form for non-IMP studies. The CI must also notify the Sponsor of all SAEs where in the opinion of the CI, the event is 'related' and 'unexpected'. Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details of the Sponsor for reporting SAEs are as follows:

The Research Governance and Integrity Team
Imperial College London and Imperial College Healthcare NHS Trust
Email: rgit@imperial.ac.uk

Chief Investigator
Professor Hashim U. Ahmed
Imperial College London, Hammersmith Hospital Campus
E-mail: transform@imperial.ac.uk

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

Reporting urgent safety measures

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

9.4. HARMS (POST-PHC FOLLOW-UP)

Participants referred to secondary care based on PHC findings (e.g., abnormal Prostagram™ MRI) will undergo further investigations and potentially treatment as part of routine clinical care. While these are outside the scope of the study intervention, the study will capture Harms resulting from these downstream procedures to assess the full impact of screening.

Harms

Medical events or complications occurring after the PHC that are attributable to diagnostic or therapeutic procedures undertaken in standard care as a result of screening. These may include:

- Biopsy-related complications (e.g., urinary tract infection, bleeding, haematuria, dysuria, urinary retention)
- Treatment-related effects (e.g., deep vein thrombosis or pulmonary embolus, incontinence, erectile dysfunction)

Harms Reporting Window

- **Start**
  Referral into secondary care for further assessment
- **Applies to**
  Participants referred for further assessment and/or treatment within standard care following a positive PHC

Harms will be recorded in the eCRF under a dedicated "Harms" section, distinct from AE/SAE reporting.

Justification for the Distinction Between AEs/SAEs and Harms

This delineation reflects the participant’s transition from receiving a study intervention (PHC) to undergoing standard of care. It ensures:

- AEs/SAEs capture safety signals directly related to the PHC
- Harms reflect the broader impact of screening, including consequences of overdiagnosis, overtreatment, or downstream medical complications

This distinction supports a comprehensive evaluation of the screening programme's risk-benefit profile, in line with ethical and regulatory guidance for screening studies.

10. STATISTICAL ANALYSES

Outcome measures

Evaluation in Stage 1 is based on one round of screening.

10.1. STAGE 1: FEASIBILITY

Outcomes will be reported for both Design 1 ("approach first design") and Design 2 ("Zelen design"). The aim is to evaluate which method is most feasible in terms of screening uptake to power the main trial, taking into account potential contamination where possible.

10.1.1. Primary Outcomes

- Proportion who receive the PHC in each screening intervention arm (Design 1 and Design 2, separately)
    - Numerator: number who receive PHC
    - Denominator: number offered PHC
- Proportion with PSA test in each of the control groups (Design 1 and Design 2, separately
    - Numerator: number in control known to have had a PSA test after randomisation
    - Denominator: number randomised to control

10.1.2. Secondary Outcomes

- Proportion who provide Stage 1 consent (Design 1)
    - Numerator: number who provide Stage 1 consent
    - Denominator: number randomised and invited to Design 1
- Proportion with Black ethnicity invited (Designs 1 and 2 combined)
    - Numerator: number invited with Black ethnicity (to Stage 1 consent in Design 1, to prostate health checks in Design 2)

  Denominator: number invited (Designs 1 and 2 combined)
- Cost per successful consent (Design 1 and Design 2 separately)
    - Numerator: Total cost of invitations
    - Denominator: Number of successful individual consents
    - Cost includes postage and staff time (permissions/setup needed per location recruiting)
- Proportion who provide Stage 1 consent (Design 1) by age group, ethnicity, IMD quintile
    - Numerator: number who provide Stage 1 consent by subgroup
    - Denominator: total number who provide Stage 1 consent
- Proportion of men with learning disability or severe mental illness who provide Stage 1 consent (Design 1)
    - Numerator: number who provide Stage 1 with learning disability or severe mental illness
    - Denominator: total number who provide Stage 1 consent
- Proportion undergoing PHCs in each screening intervention arm by age, ethnicity, IMD quintile (Design 1)
    - Numerator: number who receive PHC 1-4 by subgroup
    - Denominator: number offered PHC 1-4
- Performance indicators, including compliance with further assessment and compliance with treatment

10.2. STAGE 1: PROSTATE HEALTH CHECKS INTERVENTION PILOT OUTCOMES

Outcomes which are proportions will be expressed as percentages with the denominator being the number who received a PHC in each randomised PHC screening arm, unless otherwise stated.

10.2.1. Primary Outcomes

In each PHC group:

- Proportion diagnosed with intermediate-risk prostate cancers (NCCN*) [also collected in control groups]
- Proportion diagnosed with low-risk prostate cancers (NCCN*) [also collected in control groups]
- Proportion having a prostate biopsy [also collected in control groups]
- Costs and cost-effectiveness modelling of each PHC intervention (from first visit to diagnosis/treatment)

10.2.2. Secondary Outcomes

In each randomised PHC group:

Timelines

- Time (days) from randomisation to a) undergoing the first part of each PHC to b) receiving the result of the first test to c) undergoing Prostagram™ to d) receiving the result of the Prostagram™ to e) having a prostate biopsy in those advised to undergo a prostate biopsy

10.2.3. Detection

- Proportion diagnosed with high-risk prostate cancers (NCCN*)
- Proportion diagnosed with low/intermediate/high-risk prostate cancer according to NICE risk groups* (* based on Cambridge Prognostic Group, low-risk = CPG1, intermediate-risk = CPG2-3, high-risk = CPG4-5, ref: ww.nice.org.uk/guidance/ng131)
- Proportion diagnosed by ISUP Grade Group: GG1, GG2, GG3, GG4, GG5 prostate cancer
- Proportion diagnosed by T stage
- Proportion diagnosed with any amount of Gleason 4+3=7 or more
- Proportion diagnosed with ≥ Gleason 4+3 OR Gleason 3+3=6 of ≥6mm (PROMIS definition 1)
- Proportion diagnosed with ≥ Gleason 3+4 OR Gleason 3+3=6 of ≥4mm (PROMIS definition 2)
- Proportion of GG2 cancers in each of the following categories of percentage pattern 4 involvement: ≤10%, 11-20%, 21-30%, 31-40%, 41-50%
- In those diagnosed with prostate cancer:
- Maximum cancer length on biopsy in millimetres
- Gleason Score Ratio of GS6 to GS7+
- Proportion with lymph node cancer involvement of the pelvis (N1) only
- Proportion with distant / metastatic disease by individual stage categories: distant lymph nodes (M1a), bones (M1b) and organs such as the liver, brain or lungs (M1c) stratified by N0 or N1 status

**NCCN Guidelines Version 4 (2024)59 will be used to define prostate cancer risk groups where indicated.*

10.2.4. Biopsy-Related Harms

- Biopsy-related harms measured by ProBE questionnaire score[60]
- Proportion with infection related to biopsy/within 90 days after biopsy

- Proportion with sepsis related to biopsy/within 90 days after biopsy
- Proportion with retention of urine related to biopsy/within 90 days after biopsy
- Rate of hospital admissions within 90 days after biopsy

10.2.5. Treatment

- Proportion receiving active surveillance, focal therapy, prostatectomy, and radiotherapy (with and without ADT and planned duration of ADT) as first option by low, intermediate and high-risk disease subgroups (NCCN*). Proportion having ADT and type of ADT as monotherapy to be reported.
- Proportion receiving active surveillance, focal therapy, prostatectomy and radiotherapy (with and without ADT and planned duration of ADT) as first option by low, intermediate and high-risk disease subgroups (NICE risk groups). Proportion having ADT and type of ADT as monotherapy to be reported.
- Proportion receiving active surveillance, focal therapy, prostatectomy and radiotherapy (with and without ADT and planned duration of ADT) as first option by ISUP Grade Groups (GG1, GG2, GG3, GG4, GG5). Proportion having ADT and type of ADT as monotherapy to be reported.
- Proportion receiving active surveillance, focal therapy, prostatectomy and radiotherapy (with and without ADT and planned duration of ADT) as first option by T stage. Proportion having ADT and type of ADT as monotherapy to be reported.
- In those diagnosed with ISUP GG2 prostate cancer, proportion receiving active surveillance, focal therapy, prostatectomy and radiotherapy (with and without ADT and planned duration of ADT) as first option by pattern 4 percentage categories (≤10%, 11-20%, 21-30%, 31-40%, 41-50%). Proportion having ADT and type of ADT as monotherapy to be reported.
- In men undergoing active surveillance, proportion who progress on biopsy or on imaging
- In men undergoing active surveillance, proportion who go on to receive focal therapy, prostatectomy and radiotherapy. Proportion having ADT and type of ADT as monotherapy to be reported.
- In each of the following categories of stage of disease, proportions of type of local prostate treatment by focal therapy, surgery, radiotherapy and type of systemic treatment: ADT, chemotherapy, androgen receptor inhibitors (ARIs), other drugs for prostate cancer treatment and type of treatment directed at distant disease.

NB: Breakdown of type of modality used for focal therapy to be collated.

NB: Radiotherapy will be divided into numbers undergoing external beam radiotherapy, external beam radiotherapy with neoadjuvant ADT (and duration), external beam radiotherapy with adjuvant ADT (and duration), low dose rate brachytherapy and combination radiotherapy (high dose rate or low dose rate brachytherapy combined with external beam radiotherapy and ADT). Numbers undergoing proton therapy and stereotactic ablative radiotherapy (SABR) will also be collected.

10.2.6. Treatment-Related Harms

- Rate of hospital admissions within 90 days after treatment
- Focal therapy-related harms graded by Clavien-Dindo severity category
- Surgery-related harms graded by Clavien-Dindo severity category
- Radiotherapy-related harms graded by Clavien-Dindo severity category
- Other treatment-related harms graded by Clavien-Dindo severity category
- Investigations/ tests for treatment related symptoms, interventions for complications, death

10.2.7. Patient Reported Measures

- PROMS on urinary, sexual and bowel function measured by EPIC-26 Short Form Prostagram Questionnaire – all participants who received an MRI
- PROBE – adapted for Specification, Perceptions and General questionnaires
- In participants from sexual minority group, Sexual Minorities and Prostate Cancer Scale (SMACS)[61]
- Health Service Use (in draft)
- Health related quality of life measured by EQ-5D-5L
- For participants with mild or moderate learning disability, the modified version of EQ-5D-3L[62] Learning Difficulty and for those with severe learning disability, the proxy (informant) version 2 of the EQ-5D-5L
- Demographics Questionnaire
- Health Behaviour and Family History Questionnaire
- Anxiety measured by the GAD-7 and Cancer Worry Scale (CWS) adapted to prostate cancer
- Health Literacy measured by the SILS
- Risk perception of developing prostate cancer measured on 4 items
- Acceptability of the received prostate health check measured (prospectively and retrospectively) on the TFA Questionnaire
- Participant Satisfaction Measure Questionnaire

10.2.8. Health Economics

- Proportion using health services
- Costs falling on men and their families

10.2.9. TRANSFORM Discovery

- Define and initiate first wave biomarker validations
- Define consent rates to TRANSFORM Discovery and metrics of tissue (including quality assurance of biological measures), digital pathology, imaging collection and integration with clinical data.

10.3. STAGE 2: MAIN TRIAL

10.3.1. Primary Outcomes

To be decided per intervention evaluation after Stage 1.

Outcomes of interest include prostate cancer mortality at 10 and/or 15 years, metastases/prostate cancer mortality at 10 years and advanced disease/metastases/prostate cancer mortality at 10 years.

10.3.2. Secondary Outcomes

10.3.3. Cancer Control Outcomes

- Time to distant metastases in each randomised group
- Rates of high-risk and advanced prostate cancer (ISUP GG ≥3, stage ≥T3 or N≥1 or M≥1), cancer-specific mortality to end of follow-up through linkage to health status through national databases

10.3.4. Demographics and Recruitment

- Number who join the trial divided by number who are invited, overall and by age, deprivation

10.3.5. Screening Interventions

- Uptake / compliance (number who are randomised to the intervention who receive at least part of the intervention, overall and by age, deprivation, invitation method)
- Contamination in control (number and proportion who receive PSA test outside trial overall and by age group, deprivation, and invitation method)
- Proportion of invitations and consented participants by key demographics status (ethnicity, socioeconomic background, learning disability status)
- Proportion of bottom 20% IMD recruited by invitation method (number in bottom quantile divided by number men)
- Biopsy rates (proportion of men randomised to the intervention who have a prostate biopsy)
- Biopsies avoided compared to a strategy of PSA>3
- Biopsy related harms using validated questionnaire and to measure rates of infection, sepsis, retention of urine, and admissions for biopsy-related complications

10.3.6. Cancer Detection and Management

In each randomised PHC group:

- Proportion diagnosed with high-risk prostate cancers (NCCN*)
- Proportion diagnosed with low/intermediate/high-risk prostate cancer according to NICE risk groups* (* based on Cambridge Prognostic Group, low-risk = CPG1, intermediate-risk = CPG2-3, high-risk = CPG4-5, ref: ww.nice.org.uk/guidance/ng131)
- Proportion diagnosed by ISUP Grade Group: GG1, GG2, GG3, GG4, GG5 prostate cancer
- Proportion diagnosed by T stage
- Proportion diagnosed with any amount of Gleason 4+3=7 or more
- Proportion diagnosed with ≥ Gleason 4+3 OR Gleason 3+3=6 of ≥6mm (PROMIS definition 1)
- Proportion diagnosed with ≥ Gleason 3+4 OR Gleason 3+3=6 of ≥4mm (PROMIS definition 2)
- Proportion of GG2 cancers in each of the following categories of percentage pattern 4 involvement: ≤10%, 11-20%, 21-30%, 31-40%, 41-50%
- In those diagnosed with prostate cancer:
- Maximum cancer length on biopsy in millimetres
- Gleason Score Ratio of GS6 to GS7+
- Proportion with lymph node cancer involvement of the pelvis (N1) only
- Proportion with distant / metastatic disease by individual stage categories: distant lymph nodes (M1a), bones (M1b) and organs such as the liver, brain or lungs (M1c) stratified by N0 or N1 status

**NCCN Guidelines Version 4 (2024)59 will be used to define prostate cancer risk groups where indicated.*

10.3.7. Biopsy-Related Harms

- Biopsy-related harms measured by ProBE questionnaire score60

- Proportion with infection related to biopsy/within 90 days after biopsy
- Proportion with sepsis related to biopsy/within 90 days after biopsy
- Proportion with retention of urine related to biopsy/within 90 days after biopsy
- Rate of hospital admissions within 90 days after biopsy

10.3.8. Treatment

- Proportion receiving active surveillance, focal therapy, prostatectomy, and radiotherapy (with and without ADT and planned duration of ADT) as first option by low, intermediate and high-risk disease subgroups (NCCN*). Proportion having ADT and type of ADT as monotherapy to be reported.
- Proportion receiving active surveillance, focal therapy, prostatectomy and radiotherapy (with and without ADT and planned duration of ADT) as first option by low, intermediate and high-risk disease subgroups (NICE risk groups). Proportion having ADT and type of ADT as monotherapy to be reported.
- Proportion receiving active surveillance, focal therapy, prostatectomy and radiotherapy (with and without ADT and planned duration of ADT) as first option by ISUP Grade Groups (GG1, GG2, GG3, GG4, GG5). Proportion having ADT and type of ADT as monotherapy to be reported.
- Proportion receiving active surveillance, focal therapy, prostatectomy and radiotherapy (with and without ADT and planned duration of ADT) as first option by T stage. Proportion having ADT and type of ADT as monotherapy to be reported.
- In those diagnosed with ISUP GG2 prostate cancer, proportion receiving active surveillance, focal therapy, prostatectomy and radiotherapy (with and without ADT and planned duration of ADT) as first option by pattern 4 percentage categories (≤10%, 11-20%, 21-30%, 31-40%, 41-50%). Proportion having ADT and type of ADT as monotherapy to be reported.
- In men undergoing active surveillance, proportion who progress on biopsy or on imaging
- In men undergoing active surveillance, proportion who go on to receive focal therapy, prostatectomy and radiotherapy. Proportion having ADT and type of ADT as monotherapy to be reported.
- In each of the following categories of stage of disease, proportions of type of local prostate treatment by focal therapy, surgery, radiotherapy and type of systemic treatment ADT, chemotherapy and androgen receptor inhibitors (ARIs) and type of treatment directed at distant disease.

NB: Breakdown of type of modality used for focal therapy to be collated.

NB: Radiotherapy will be divided into numbers of external beam radiotherapy, external beam radiotherapy with neoadjuvant ADT (and duration), external beam radiotherapy with adjuvant ADT (and duration), low dose rate brachytherapy and combination radiotherapy (high dose rate or low dose rate brachytherapy combined with external beam radiotherapy and ADT). Numbers undergoing proton therapy and stereotactic ablative radiotherapy (SABR) will also be collected.

10.3.9. Treatment-Related Harms

- Rate of hospital admissions within 90 days after treatment
- Focal therapy-related harms graded by Clavien-Dindo severity category
- Surgery-related harms graded by Clavien-Dindo severity category
- Radiotherapy-related harms graded by Clavien-Dindo severity category
- Other treatment-related harms graded by Clavien-Dindo severity category

- Investigations/ tests for treatment related symptoms, interventions for complications, death

10.3.10. Participant Reported Measures

- PROMS on urinary, sexual and bowel function measured by EPIC-26 Short Form
- Sexual dysfunction measured by ICHOMS core dataset medication use questions
- In participants from sexual minority group, Sexual Minorities and Prostate Cancer Scale (SMACS)61
- Health related quality of life measured by EQ-5D-5L
- For participants with mild or moderate learning disability, the modified version of EQ-5D-3L62 and for those with severe learning disability, the proxy (informant) version 2 of the EQ-5D-5L
- Anxiety measured by the GAD-7 and Cancer Worry Scale (CWS) adapted to prostate cancer
- Health Literacy measured by the SILS
- Risk perception of developing prostate cancer measured on 4 items
- Acceptability of the received prostate health check measured (prospectively and retrospectively) on the TFA questionnaire
- Participant satisfaction

10.3.11. Health Economics

- Use of health services and costs falling on men and their families
- Modelled cost-effectiveness

10.3.12. NHS Dissemination and Healthcare Resource Impact

- Use of health services and costs falling on men and their families
- Cost-effectiveness
- NHS dissemination care pathway evaluation and budget impact assessment
- Net cost and resource impact to the NHS of adopting screening at scale

10.3.13. TRANSFORM Discovery

Generate a portfolio of TRANSFORM Discovery validated biomarkers for diagnosis, prognosis and stratification for personalised cancer care with embedded health economic modelling.

Establish programmes of translational research to inform the next generation of biomarkers, through new biological discovery and/or multi-omic methodology (such as AI-informed integrated processing of high-dimensionality data from multiple sources, including pathology slide high resolution scans as well as paraffin embedded tissue, imaging [nuclear medicine, MRI, ultrasound, CT]).

Through validation exercises, present candidate biomarkers for potential clinical utility assessment within TRANSFORM as novel Stage 2 study arms, studies within trials (SWAT) or trial emulation within the Twin cohort.

10.4. SAMPLE SIZE AND POWER CONSIDERATIONS

10.4.1. Stage 1: Pilot and Feasibility

We have planned the sample size to provide sufficient precision around estimation of key parameters for the design and interventions for Stage 2.

In Design 1, participants will be randomised equally between all PHC analysis groups to maximise precision on comparisons between arms. For example, if we anticipate 70% uptake, independent of PHC, approximately 17,000 would be randomised for Design 1. In parallel, we will randomise approximately n=2,500 to control and n=1,000 invitations directly to each PHC1-4 for Design 2. The rate of these invitations will be determined based on uptake, so as far as possible these occur over the same calendar time period. We next justify why this sample size provides sufficient precision for stage 1 objectives.

To decide between the different design options, we require precision on uptake following each randomisation. For the two-stage consent process (Design 1), assuming a 70% uptake we expect precision (one standard error) on uptake following the second randomisation is to be approximately 0.8% (sqrt(0.7*0.3/3600)) per arm, which is more precise than needed for this objective, but the sample size is needed for analysis of intervention outcomes (see below). We do not have direct data for the 70% assumption, and it will be a key finding from Stage 1. However, it approximately matches an earlier study with this approach (Flexi-Sig trial)[12]. For Design 2, we wish to evaluate whether uptake is sufficiently high (>40%) to consider this design. If uptake is 50% then with n=1000 participants randomised directly to PHC1-4 precision (1SE) will be 2.2%, which we deem sufficient to inform decision making.

The above sample size is also sufficient to inform which strategy to carry forward. It is informative for cancer detection, for which there is very little comparative data. For instance, the IP1-PROSTAGRAM (n=408) and ReIMAGINE (n=303) studies were not designed to evaluate differences in detection rates; there were 7 clinically significant prostate cancers in the PSA-testing group compared with 11 within the Prostagram™ group. If detection rate is 1% then 2500 who receive the test per PHC will provide precision (1SE) for each arm is approximately 0.2%; equivalently, there would be approximately 80% power at the 5% level to show a difference between two arms, if the detection rate is 1% vs 2%. The study will also provide data on the potential differences in biopsy rates, which are also not known with precision on a comparative basis. We anticipate biopsy rates of no more than 10%, so that n=2500 would provide precision measured by standard error of approximately 0.85% between pairs of strategies, which we consider sufficiently precise to evaluate differences between the strategies for decision making.

10.4.2. Stage 2: Main Trial

The sample size for Stage 2 will be determined once the Stage 1 pilot and feasibility findings are known.

10.5. INTERIM ANALYSES

At the end of Stage 1, we will seek guidance from the Independent Scientific Advisory Group and the Independent Trial Steering Committee regarding which design to use in Stage 2, including confirmation of control groups, method of randomisation and the optimal Prostate Health Check to use in the intervention arm.

Pre-defined criteria will be developed to support the decision-making process, informed by red-amber-green (RAG) descriptions. The decision will be guided by uptake, risk of contamination (PSA testing in each of the control groups), expense of collecting data via national databases and success in developing algorithms to obtain outcome data via linkage to national databases,.

It will also be informed by choice of comparator group (e.g., pre-consent randomised control requires high uptake for the trial to be adequately powered), number of minority men and more deprived men recruited, rate of recruitment, and cost-effectiveness. One method might be recommended, or a combination of different strategies, depending on the comparator recommended and strengths and weaknesses of the different strategies potentially in different areas. The decision on which interventions to carry forward/drop will consider uptake of the interventions, projected cost and cost-effectiveness, detection rates of clinically significant prostate cancer, biopsy rates and participant acceptability.

The decision to drop arms will be made if there is strong evidence suggesting likely harms with higher biopsy rates together with inferior early detection of clinically significant disease or implausibility that an arm could be cost-effective. The choice of arm to take forward will be based on a preliminary evaluation of the potential benefits, harms, and costs of each intervention. The best strategy will maximise detection of clinically significant prostate cancer at prevalent screen, with few unnecessary biopsies or detection of low-grade prostate cancer (GG </=6), and for reasonable cost. Strategies that are highly unlikely to be cost-effective based on modelling using data from Stage 1 are doubtful for consideration for Stage 2; albeit that such modelling may have considerable uncertainty and therefore the independent committees will provide valuable input.

Modelling of cost-effectiveness will be informed by using multistate survival modelling to study the natural history parameters[63] and then construct micro-simulation algorithms based on these parameters. The algorithms will simulate the life trajectories of individuals undergoing different interventions, allowing us to compare long term outcomes, such as interval cancers, false findings, biopsy and MRI use, overdiagnosis, and cancer-specific mortality reduction.

A sample size will be estimated for Stage 2 taking into account preferred design, preferred outcome, rates in a non-screened population, previous trial evidence, magnitude of effect and uptake.

10.6. PLANNED RECRUITMENT RATE

We would propose the following RAG criteria to be evaluated in Design 1 at the end of the Stage 1.

Pilot Trial Targets	Red	Amber	Green
% Recruitment threshold	<60%	60 – 99%	≥100%
Total number of participants consenting to the TRANSFORM Research Cohort	<7,500	7,501-12,499	≥12,500
Number of secondary sites opened (accounting for sequential site opening) It is expected that in some regions, one site will take on the equivalent of 2-3 sites' worth of recruitment. For the purpose of this table, such sites will count as a multiple of centres.	<6	6-9	≥10

10.7. STATISTICAL ANALYSIS

Separate statistical analysis plans (SAP) will be written for Stage 1 and Stage 2. The main analysis planned is summarised below.

10.7.1 Stage 1: Trial Design Optimisation

There are three potential comparator groups for Stage 2, to be evaluated in Stage 1:

- Those who are randomised not to be invited to receive a Prostate Health Check (pre-consent randomised control)
- Those who consent to join the TRANSFORM Research Cohort, are eligible, and are randomised to no intervention (post-consent randomised control)
- Those who consent to join TRANSFORM and are randomised to Prostate Health Check 1

The main analysis to evaluate feasibility of each potential comparator group will consider (1) feasibility of recruitment, (2) uptake after randomisation of interventions (proportion of those randomised who are included in the comparator), and (3) potential contamination (proportion of those randomised who receive a prostate screening intervention outside study protocol). These parameters will inform the sample size needed to use each as a comparator in order to achieve high statistical power for a given effect size. Statistical analysis will evaluate sample size requirements for a design using these control groups, based on data from Stage 1 to inform these requirements.

10.7.2 Stage 1: Pilot Prostate Health Checks

Primary and secondary outcomes will be estimated for each arm using per-protocol and intention to treat populations, with appropriate 95% confidence intervals as described in the outcomes section. These will be presented in a table to summarise data (by row) on the important potential benefits (intermediate- and high-risk prostate cancer detection rates) and harms (including biopsy rates, low-risk cancer detection rates, management of low-risk cancer, testing-related AEs and treatment-related harms) for each PHC (column).

The size of potential differences between arms in primary and secondary outcomes will be estimated using a 95% confidence interval for each comparison using statistical analysis that is (1) unadjusted for differences between arms in baseline variables, or (2) adjusted based on a PSA-stratified analysis. Stratification based on PSA level will increase precision on comparisons across arms, including the ability to evaluate the potential benefit on cancer detection of different PSA thresholds other than 1ng/mL or 3ng/mL.

A further analysis will also be undertaken for PRS evaluation, where information on the PRS in all cancers diagnosed across arms (and retrospectively tested for PRS in participants who consent to TRANSFORM Discovery). This will help evaluate characteristics of cancers detected by other PHCs that are not detected with the PRS pathway.

10.7.3 Stage 2

The primary analysis in the statistical analysis plan for Stage 2 will follow the design and sample size calculations used to plan the study.

11. REGULATORY, ETHICAL AND LEGAL ISSUES

11.1. Declaration of Helsinki

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

11.2. Good Clinical Practice

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

11.3. Research Ethics Committee (REC) Approval

Initial Approval

Prior to the enrolment of participants, the REC must provide written approval of the conduct of the study at named sites, the protocol and any amendments. There will be specific invitation letters and Participant Information Sheets and Consent Forms, as well as video/audio material for participants for each of the stages and designs. REC and HRA approval will be sought before commencing Stage 1, then again for Stage 2.

A blinded pre-final report will be prepared by the statistician at 2 years such that analyses can be updated in an efficient manner with the final Stage 1 data after data lock. The TMG will monitor progress towards these timelines at regular intervals. Enrolled participants would, of course, be given the opportunity to have outstanding/delayed interventions even if data collected were not to be included in the final data lock, and clinics/community locations where interventions are ongoing will stay open and in place to allow for smooth roll out of the next stage, should Stage 2 be approved.

Approval of Amendments

Amendments will be reviewed and approved by the TMG. Amendments will be version controlled and updated study documents will have an updated version number and date. Proposed amendments to the protocol and aforementioned documents must be submitted to the REC for approval as instructed by the Sponsor. Amendments requiring REC approval may be implemented only after a copy of the REC's approval letter has been obtained. Amendments that are intended to eliminate an apparent immediate hazard to participants may be implemented prior to receiving Sponsor or REC approval. However, in this case, approval must be obtained as soon as possible after implementation. Approved amendments will be circulated to all sites and any online trial registry materials will be updated.

End of Trial Notification

The REC will be informed about the end of the trial, within the required timelines. The end of trial notification will be submitted within 90 days of the end of trial definition being met.

11.4. HRA Approval

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

11.5. Other Required Approvals

The study design will require approval from the HRA's Confidentiality Advisory Group (CAG).

11.6. Non-Compliance and Serious Breaches

All protocol deviations and protocol violations will be reported via the eCRF/CRF and reviewed by the CI and reported to the ICTU QA manager on a monthly basis. Protocol violations will be reported to the Sponsor. An assessment of whether the protocol deviation/violation constitutes a serious breach will be made. A serious breach is defined as:

- A breach of the conditions and principles of GCP in connection with a trial or the trial protocol, which is likely to affect to a significant degree:
- The safety or physical or mental integrity of the UK trial participants; or
- The overall scientific value of the trial

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

11.7. Insurance and Indemnity, Sponsor and Funding

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study. Imperial College London will act as the main Sponsor for this trial. Delegated responsibilities will be assigned to the NHS Trusts taking part in the trial. The study is funded by Prostate Cancer UK and the National Institute of Health Research – Health Technology Assessment. There is no payment to participants for taking part in this study. The researchers will not receive any personal payment over and above normal salary, nor any other benefits or incentives. All researchers will declare any and all potential conflicts of interest.

11.8. Trial Registration

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

11.9. Informed Consent

All subjects in the intervention arm must sign and personally date the REC-approved Informed Consent Form after having received written, and where applicable, verbal information about the reason, nature and possible risks associated with the research study. The right of the participant to refuse to participate without giving reasons must be respected. In these cases of deviation from protocol, the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time without giving reasons and without prejudicing further treatment.

The ICF can be issued and signed electronically, remotely by postage of consent form or in person. Subjects should be provided with a copy of the Participant Information Sheet and signed Informed Consent Form. The original Informed Consent Form should be retained with the source documents.

Due to the nature of the study, in which screening requires minimisation of contamination, we will not be seeking consent from those in the pre-consent randomised control but will be collecting routine data from linkage to national databases with approval from the HRA's CAG.

11.10. Contact with General Practitioner

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

11.11. Participant Confidentiality

The investigator must ensure that the subject's confidentiality is maintained. On the CRF subjects will be identified by a subject ID number only. Documents that are not submitted to the Sponsor (e.g., signed informed consent form) should be kept in a strictly confidential file by the investigator. The investigator shall permit direct access to subjects' records and source document for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor, NHS, Regulatory Authorities and REC.

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

Queen Mary – University of London (QMUL) will be sent participants' identifiable details for the purposes of randomisation and for performing linkage to the NHS Information Centre and the NHS Central Register or any applicable NHS information system. QMUL will collate outcome data and create a database to store processed data. Data will be stored on a data safe-haven compliant with a Data Safety Protection Toolkit and ISO27001.

There may be a requirement to transfer information to countries outside the European Economic Area (for example, to a research partner). Where this information contains personal data, Imperial College London will ensure that it is transferred in accordance with data protection legislation. If the data is transferred to a country which is not subject to a European Commission (EC) adequacy decision in respect of its data protection standards, Imperial College London will enter into a data sharing agreement with the recipient organisation that incorporates EC approved standard contractual clauses that safeguard how your personal data is processed.

11.12. Data Protection and Participant Confidentiality

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

The site investigator will preserve the confidentiality of all participants taking part in the trial, which will be conducted in accordance with the General Data Protection Regulation (GDPR).

The Sponsor will be using information from participants and their medical records in order to undertake this study and will act as the data controller for this study. This means that the Sponsor is responsible for looking after participant information and using it properly. Imperial College London will keep unidentifiable information about participants for 30 years after the study has finished.

Participants' rights to access, change or move their information are limited, as information needs to be managed in specific ways in order for the research to be reliable and accurate. If participants withdraw from the study, the information about them already obtained will be kept. To safeguard participant rights, the minimum personally-identifiable information possible will be used.

When participants agree to take part in a research study, the information about their health and care may be provided to researchers running other research studies in the organisation

and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Their information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research.

11.13. End of Trial

Last participant alive who completes 30 years of follow-up from randomisation.

11.14. Study Documentation and Data Storage

The investigator must retain essential documents until notified by the Sponsor, and for at least ten years after study completion. Subject files and other source data (including copies of protocols, CRFs, original reports of test results, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) must be retained. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks. No study document will be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

12. DATA MANAGEMENT

12.1. Source Data

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

12.2. Language

CRFs will be in English. All written material to be used by participants must use vocabulary that is clearly understood and be in the language appropriate for the study site.

12.3. Database

We will use the OpenClinica database application for electronic data capture (EDC) to record case report form data for participants in the study. OpenClinica is a regulatory compliant database and is Sponsor-approved for non-CTIMP studies. Study staff at each participating site will enter baseline and follow-up data into the online database. The database is password-protected and users will have passwords to access, enter and use the data for the full study duration. All members of the research team will receive training appropriate to their role and duties and will respect and comply with participant confidentiality.

12.4. Data Collection

eCRFs will be based on relevant data collection tools tested in previous studies that we have undertaken and will undergo review by the study team, relevant clinical staff and the statistician prior to use. Participant level data collection will include baseline factors, Prostate Health Check results, adverse events, biopsy recommendations, biopsy details and results, post-biopsy complications, staging scans and treatments. Self-reported, validated questionnaires will be used to assess health-related quality of life. Details of procedures for CRF/eCRF completion will be provided in a study manual. Health related outcome data from national databases will also be collated and stored in the eCRF.

12.5. Archiving

All trial documentation, including that held at participating sites and the trial coordinating centre, will be archived for a minimum of 30 years following the end of the study as defined in 9.13.

13. STUDY MANAGEMENT STRUCTURE

13.1. Trial Steering Committee

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

13.2. Trial Management Group

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

13.3. Data Monitoring Committee

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

13.4. Early Discontinuation of the Study

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

13.5. Risk Assessment

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

13.6. Monitoring

The study will be monitored periodically by trial monitors to assess the progress of the study, verify adherence to the protocol, ICH GCP E6 guidelines[67] and other national/international

requirements and to review the completeness, accuracy and consistency of the data. Monitoring procedures and requirements will be documented in a Monitoring Plan, in accordance with the risk assessment.

13.7. Quality Control and Quality Assurance

Quality Control will be performed according to ICTU internal procedures. The study may be audited by a Quality Assurance representative of the Sponsor and/or ICTU. All necessary data and documents will be made available for inspection. The study may be subject to inspection and audit by regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd Edition)[68.]

13.8. Peer Review

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

Patient and Public Involvement

PPIE during study development

First, lay members with a lived experience of prostate cancer and who attended our NCRI group meeting are fully committed to helping with the conduct of the study. They have significant experience with previous ethics committees and Trial Management Groups. Second, several lay groups for ReIMAGINE, IP1-PROSTAGRAM and Barcode1, were involved in providing feedback to the rationale and design for the screening studies. A number of PPI representatives were fully involved in the NCRI/PCUK Screening study development group.

13.9. Ongoing Involvement

PPI representatives will be co-researchers, attend research meetings and lead the regular focus groups. We will provide training and mentoring through our Patient Experience Research Centre. Focus groups will be asked whether in future some of them might be willing to be part of the research team so that during the study there will be ongoing representation. Our PPI co-applicants and focus groups will lead work throughout the study to share the trial's concept and conduct, and at study end, the results. Final results will be shared with trial participants. Throughout the study, social media platforms will be used to communicate about the trial through accessible written, visual and video/Vlog formats. Findings will be presented at international conferences and published in high impact journals. Stakeholders such as patient support groups, charities, NHS policy makers and professional organisations (representing urologists, oncologists, radiologists, radiographers) will be informed. Press releases will be used to widely disseminate to online, print and TV media. Results will be shared early with NICE so guidelines can be informed.

PPI focus groups will meet to review participant material and recruitment strategies before Stage 1 starts and then every 6-12 months to help make changes if required. We will use written, visual and video material which are accessible to different ethnic and socio-economic groups using our existing links to community and patient and carer support groups. In order to ensure active representation of vulnerable groups, such as people with learning disability, who are often excluded for screening studies and trials, we will convene separate PPI groups comprising individuals with mild learning disabilities and a group for carers. They will review information and consent forms to ensure that they are accessible, advise on recruitment and compliance strategies and develop dissemination materials (including videos and newsletters)

targeting people with learning disabilities, carers, charities and advocacy groups. Professor Chauhan and Dr Ali have links to carer and patient advocacy and support groups through her previous research, such as Mencap[69] and the Foundation for People with Learning Disabilities[70], who will assist in identifying suitable members and co-facilitation of the groups. All PPI members will be given gift vouchers for their time, and travel costs will be reimbursed.

13.10. Publication and Dissemination Policy

Information concerning the study, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of the Sponsor. The investigator may use this information for the purposes of the study only. It is understood by the investigator that the Sponsor will use information developed in this clinical study and, therefore, may disclose it as required to other clinical investigators. In order to allow the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to the Sponsor. Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from the Funder.

Therefore, all information obtained as a result of the study will be regarded as CONFIDENTIAL, at least until appropriate analysis and review by the investigator(s) are completed. Permission from the TMG is necessary prior to disclosing any information relative to this study. Any request by site investigators or other collaborators to access the study dataset must be formally reviewed by the TMG. The results may be published or presented by the investigator(s), but the Funder will be given the opportunity to review and comment on any such results before any presentations or publications are produced as laid out in the funding contract. Lay summaries of the results for public and patient engagement, webinars/podcasts to publicise the result to patients and public, and a Clinical Study Report summarising the study results will be prepared and the latter submitted to the REC within a year of the end of study.

We will publish the protocol and have it available on our institutional website. This publication will be in line with ICMJE requirements and therefore explicitly state our conditions on: data types; additional available documentation; window of availability [dates indicating opening and closure of access]; eligibility of requests; types of analysis permitted; method of access. We will post the data sharing opportunity on our university websites. We will also take queries from interested third parties to assist and guide them to the opportunity. All subsequent publications of primary and secondary outcomes will be compliant with the NIHR Open Access Policy[71.]

During the period of funding, our datasets will be collected and completed in the manner described above. We anticipate opening access to data beyond the existing research. There will be a lock-out period to enable the key outcomes of the studies to report first after which data access will be through application to the study group. All participants will provide written informed consent for involvement in this study and permission for use of their data in scientific research (including sharing with the wider research community). We will ensure they have read and have a readily available copy of the latest version of our sponsor-approved privacy notice at the time of reading the Participant Information Sheet and before providing consent. All external users will be bound by a data sharing agreement. This will be drawn up and ratified by Imperial Research Contracts Office and form part of the contract with NIHR[72]. Professor Ahmed will act as the data custodian on behalf of Imperial College London and hold overall responsibility for data management. The persons responsible for data security and quality assurance will be Professor Ahmed and Professor Gabe.

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REVISION HISTORY

Version	Date	Summary of changes

SIGNATURE PAGE 1 (Chief Investigator)

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

Study Title: TRANSFORM

Protocol Number:

Signed: _____

Name of Chief Investigator: Hashim U. Ahmed

Title: Professor

Date: _____

SIGNATURE PAGE 2 (SPONSOR)

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

Study Title: TRANSFORM

Protocol Number:

Signed: _____

Name of Sponsor's Representative
Imperial College London

Date: _____

SIGNATURE PAGE 3 (LEAD STATISTICIAN)

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

Study Title: TRANSFORM

Protocol Number:

Signed: _____

Name of Statistician: Professor Rhian Gabe
Title: Professor
Organisation/Company: Queen Mary – University of London

Date: _____

SIGNATURE PAGE 4 (PRINCIPAL INVESTIGATOR)

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

Study Title: TRANSFORM

Protocol Number:

Address of Institution: _____

_____

_____

Signed: _____

Print Name and Title: _____

Date: _____